Uniform Medical Plan (UMP) coverage limits for drugs covered under UMP's prescription drug benefit

Updates effective June 01, 2024

These coverage limits apply to all UMP Plans that the Public Employees Benefits Board (PEBB) and the School Employees Benefits Board (SEBB) offer.

As a state-sponsored health plan, UMP follows the Washington State Pharmacy and Therapeutics (P&T) Committee's coverage recommendations. The committee consists of Washington health care professionals, including physicians and pharmacists. The UMP Preferred Drug List (PDL) aligns with the committee's coverage recommendations and contains useful information such as a drug's coverage limits. The UMP PDL is the same for both Public Employees Benefits Board (PEBB) and School Employees Benefits Board (SEBB) members.

The Washington State P&T committee does not review all drug classes. For all other prescription drug classes, the Washington State Rx Services P&T Committee makes coverage recommendations for UMP to consider. UMP then determines a drug's coverage, including any coverage limits. These drugs are also included on the UMP PDL.

Some prescription drugs require preauthorization to determine whether they are medically necessary and meet UMP coverage criteria. If you do not receive approval for your preauthorization, UMP will not cover these drugs. **To request a preauthorization, a member, pharmacy, or prescribing provider can call Washington State Rx Services at 1-888-361-1611 (TRS: 711).**

Some drugs may only be covered under UMP medical benefits and have different rules for preauthorization. To request a preauthorization for a drug covered under UMP medical benefits, call UMP Customer Service at:

- PEBB Members: 1-888-849-3681 (TRS: 711)
- SEBB Members: 1-800-628-3481 (TRS: 711)

For more information:

- Refer to your plan's current certificate of coverage by visiting **Forms and publications at hca.wa.gov/ump-coc**
- Call Washington State Rx Services at 1-888-361-1611 (TRS: 711)
- Refer to the **UMP Preferred Drug List by visiting hca.wa.gov/assets/pebb/ump-preferred-drug-list-2024.pdf**

Policy Type: PA/SP Pharmacy Coverage Policy: UMP108

Split Fill Management*

Description

Acalabrutinib (Calquence) and its active metabolite inhibit Bruton tyrosine kinase (BTK) by irreversibly bonding to the active BTK site. This prevents activation of the signaling proteins CD86 and CD69, as well as inhibits proliferation and survival of malignant B cells.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
acalabrutinib (Calquence)	100 mg capsule	Mantle cell lymphoma (previously treated); Chronic lymphocytic leukemia (CLL); small lymphocytic lymphoma (SLL)	60 capsules/30 days
	100 mg tablets		60 tablets/30 days

Initial Evaluation

I. **Acalabrutinib (Calquence)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. Member has not experienced disease progression while on a BTK inhibitor [e.g. zanubrutinib (Brukinsa®), ibrutinib (Imbruvica®)]; **AND**
   D. A diagnosis of one of the following:
      1. **Chronic Lymphocytic Leukemia (CLL) or small lymphocytic lymphoma (SLL)**; **AND**
         i. Medication is used in **one** of the following settings:
            a. Previously untreated CLL/SLL; **AND**
               i. Medication will be used as monotherapy or in combination with obinutuzumab (Gazyva); **OR**
            b. Relapsed or refractory after at least one prior systemic therapy; **AND**
               i. Member has **not** experienced disease progression while on venetoclax (Vencelxta) or a phosphoinositide-3 kinase inhibitor [e.g. duvelisib (Copiktra), idelalisib (Zydelig)]; **AND**

ii. Medication will **not** be used in combination with other oncologic medications (i.e., will be used as monotherapy)

II. Acalabrutinib (Calquence) is considered investigational when used for all other conditions, including but not limited to:
   A. Mantle cell lymphoma (MCL)
   B. Diffuse Large B-Cell Lymphoma
   C. Head and neck squamous cell carcinoma
   D. Ovarian cancer
   E. Non-small cell lung cancer (NSCLC)
   F. Severe Chronic Graft Versus Host Disease
   G. Waldenström's macroglobulinemia (WM)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication will **not** be used in combination with other oncologic medications (i.e., will be used as monotherapy); **OR**
   A. Acalabrutinib (Calquence) will be used in combination with obinutuzumab (Gazyva) in the setting of previously untreated CLL/SLL; **AND**
IV. Documentation is provided indicating disease response to therapy, as defined by stabilization of disease, decrease in the size of the tumor, or tumor spread.

Supporting Evidence

I. Safety and efficacy of acalabrutinib (Calquence) has not been established in the pediatric population.
II. CLL and SLL are difficult, life threatening diseases, accordingly treatment with acalabrutinib (Calquence) requires consultation with an oncologist or hematologist.
III. There is no published data from a head-to-head studies between acalabrutinib (Calquence) and other BTK inhibitors [zanubrutinib (Brukinsa), ibrutinib (Imbruvica)] to show superiority of one BTK inhibitor over another. There is also no published data in the use of BTK inhibitors in patients diagnosed with MCL or CLL/SLL that have relapsed or are refractory to other BTK inhibitors. Additionally, no data is available to show one BTK inhibitor could overcome common mechanisms of resistance of BTK inhibitors.
IV. The efficacy of acalabrutinib (Calquence) in patients with CLL was demonstrated in two randomized, controlled trials which included patients with SLL because it is the same disease. In the ELEVATE-TN trial, a randomized, multicenter, open-label, actively controlled, three-arm trial of acalabrutinib (Calquence) in combination with obinutuzumab, acalabrutinib (Calquence)

monotherapy, and obinutuzumab in combination with chlorambucil in patients with previously untreated chronic lymphocytic leukemia, both the acalabrutinib (Calquence) monotherapy arm and acalabrutinib (Calquence) in combination with obinutuzumab arm significantly prolonged progression free survival (PFS) when compared to obinutuzumab plus chlorambucil.

V. The efficacy of acalabrutinib (Calquence) in patients with relapsed or refractory CLL was based on a multicenter, randomized, open-label trial (ASCEND). The trial enrolled patients with relapsed or refractory CLL after at least one prior systemic therapy, while excluding those with transformed disease, prolymphocytic leukemia, or who had previous treatment with venetoclax, a Bruton tyrosine kinase inhibitor, or a phosphoinositide-3 kinase inhibitor. Interim analysis results indicate acalabrutinib (Calquence) significantly prolonged PFS when compared to rituximab combined with idelalisib or bendamustine.

Investigational or Not Medically Necessary Uses

I. Acalabrutinib (Calquence) has not been sufficiently evaluated outside CLL/SLL. Limited evidence is available consisting of early phase studies evaluating use in other cancers; however, safety and efficacy have not been established in these conditions:
   A. Mantle cell lymphoma (MCL)
      i. For the treatment of MCL, acalabrutinib (Calquence) was FDA-approved under the accelerated approval pathway based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
      ii. Acalabrutinib (Calquence) was studied in an open-label, phase 2 study in 124 patients with relapsed or refractory mantle cell lymphoma. Oral acalabrutinib (100 mg twice per day) was given until disease progression or unacceptable toxicity. At a median follow-up of 15.2 months, 100 (81%) patients achieved an overall response. The most common prior therapies in clinical trials included rituximab, bendamustine + rituximab, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) - based regimen, Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), bortezomib or carfilzomib, stem-cell transplant and lenalidomide.
      iii. Treatment of MCL with acalabrutinib (Calquence) remains experimental and investigational. The quality of evidence is considered low due to observational nature of clinical trial (single-arm, open-label study design) with unknown clinical impact on the overall survival rate, health-related quality of life, or symptom improvement in treated patients. Confirmatory trials are needed to definitively establish benefit and value of this agent in MCL.
   B. Diffuse Large B-Cell Lymphoma
   C. Head and neck squamous cell carcinoma
   D. Ovarian cancer
   E. Non-small cell lung cancer (NSCLC)
   F. Severe Chronic Graft Versus Host Disease
   G. Waldenström's macroglobulinemia (WM)

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Calquence [Prescribing Information]. Wilmington, DE: AstraZeneca; November 2019.
2. Wang M, Rule S, Zinzani PL, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet. 2018;391(10121):659-667.
3. ClinicalTrials.gov. Elevate CLL TN: Study of Obinutuzumab + Chlorambucil, Acalabrutinib (ACP-196) + Obinutuzumab, and Acalabrutinib in Subjects With Previously Untreated CLL. NCT02475681
4. ClinicalTrials.gov. A Study of Acalabrutinib vs Investigator's Choice of Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in R/R CLL. NCT02970318.
5. AstraZeneca (2019). ELEVATE-TN: Phase 3 Study of Acalabrutinib Combined with Obinutuzumab or Alone vs Obinutuzumab plus Chlorambucil in Patients with Treatment-Naïve Chronic Lymphocytic Leukemia [PowerPoint slides]. Retrieved from AstraZeneca.
6. AstraZeneca (2019). Acalabrutinib vs Rituximab plus Idelalisib or Bendamustine by Investigator's Choice in Relapsed/Refractory Chronic Lymphocytic Leukemia: Results from a Pre-Planed Interim Analysis of Phase 3 Ascend Study [PowerPoint slides]. Retrieved from AstraZeneca.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 100mg tablet formulation to the policy	08/2022
Removed initial criteria and moved MCL indication to investigational or not medically necessary uses section	01/2022
Updated criteria to policy format. Addition of age requirement to ages 18 and older. Require member has not experienced disease progression while on a BTK inhibitor. Added new indication of CLL/SLL.	12/2019
Previous Reviews	02/2018
Criteria created	01/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP265

Split Fill Management*

Description

adagrasib (Krazati®) is an orally administered selective inhibitor of Kirsten Rat Sarcoma viral oncogene homologue (KRAS) and targets tumors harboring KRAS G12C mutation.

Length of Authorization

- N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
adagrasib (Krazati®)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation	600 mg tablets	60 tablets/30 days

Initial Evaluation

I. **Adagrasib (Krazati)** is considered investigational when used for all conditions, including but not limited to Non-Small Cell Lung cancer (NSCLC).

Renewal Evaluation

I. N/A

Supporting Evidence

I. Adagrasib (Krazati) is the second therapy FDA-approved for advanced or metastatic NSCLC that harbors a KRAS G12C mutation. It follows sotorasib (Lumakras), which received accelerated FDA approval in this setting, in 2021.

II. KRAS mutations account for up to 25% of mutations in NSCLC and are often associated with resistance to targeted therapies and generally poor patient outcomes in patients with cancer. KRAS G12C, a subset of KRAS mutations, accounts for about 13% of mutations in NSCLC.

III. Most patients with NSCLC including *KRAS*-mutated tumors are treated with systemic chemotherapy, which includes carboplatin, pemetrexed, cisplatin, and paclitaxel. Additionally, targeted immunotherapy such as inhibitors of programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) (e.g., pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo)) are also recommended. Vascular Endothelial Growth Factor (VEGF) inhibitor

ramucirumab (Cyramza) in combination with docetaxel (Taxotere) has shown success as a subsequent-line therapy in refractory disease.

IV. Adagrasib (Krazati) is a subsequent-line therapy in the advanced or metastatic NSCLC, after progression on or after at least one prior systemic chemotherapy and is indicated for patients 18 years of age and older.

V. The New Drug Application (NDA) for adagrasib (Krazati) for the treatment of NSCLC was based on results from a subset of participants (cohort A) in an open-label, Phase 1/2, single-arm trial (KRYSTAL-1). Patients (N=116) with KRAS G12C mutated NSCLC, who had disease progression after platinum-based chemotherapy and/ or immunotherapy received adagrasib (Krazati) 600 mg orally twice daily for a median 15.7 months. The primary efficacy outcome was Objective Response Rate (ORR). Key secondary outcomes were Progression-free Survival (PFS), duration of response (DoR), and Overall Survival (OS). Adagrasib (Krazati) showed an ORR of 42.9% (95% CI; 33.5, 52.6), which included one patient (0.9%) complete response (CR) with remainder (n= 47) exhibiting partial responses. Additionally, participants in this cohort showed DoR of 8.5 months (95% CI; 6.2, 13.8), PFS 6.5 months (95% CI; 4.7, 8.4), and OS 12.6 months (95% CI; 9.2, 19.2).

VI. Based on the data from KRYSTAL-1 trial, the quality of the evidence to support efficacy of adagrasib (Krazati) is considered low at this time. Given the lack of comparator and single-arm open-label trial design, as well as lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy remains uncertain.

VII. The safety of adagrasib (Krazati) was based on drug exposure during the clinical trial (N=116). All participants reported any grade adverse reactions (AE) with 81.9% suffering a grade ≥ 3 AE. The most common AE included diarrhea, nausea and vomiting, fatigue, dyspnea, and increased creatinine and aspartate aminotransferase (AST). Anemia, hyponatremia, and dyspnea were reported as serious (grade ≥ 3) AE. Adagrasib (Krazati) led to 82.8% dose reduction or therapy interruptions, with 15.5% of patients requiring permanent discontinuation. Twenty (17.2%) patient deaths were reported during the trial, of which, two (1.7%) were ascribed as treatment-emergent (cardiac failure and pulmonary hemorrhage). Current patient exposure to adagrasib (Krazati) is limited to clinical trial participants; thus, the real-world safety profile and patient experience with this drug remain undefined. Based on a single-arm, open-label clinical trial in a small patient population, the overall safety profile of adagrasib (Krazati) is largely unknown.

VIII. Currently, there are multiple clinical trials (Phase 1b / 2) ongoing for adagrasib (Krazati) in the settings of NSCLC, colorectal cancer, and other solid tumors harboring KRAS G12C mutation. Additionally, adagrasib (Krazati) is being studied as a combination regimen with other targeted therapies (e.g., MEK inhibitor, EGFR inhibitor, SHP2 inhibitor) for the treatment of NSCLC. These clinical trials are in early phases and as of October 2022, data is not available for review.

IX. Single-arm, open-label clinical trial may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.

X. Targeted therapies for treatment of NSCLC have garnered interest in recent years and may be considered part of a paradigm shift in the management of NSCLC based on histology and actionable driver mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Acquired resistance to current molecularly targeted therapies in lung cancer presents a major clinical challenge. Additionally, targeted therapy approach is also susceptible to failure due to escape mutations.

XI. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents (e.g., docetaxel, pemetrexed) and immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab) remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Additionally, combination regimens containing angiogenesis inhibitors with conventional chemotherapy agents (e.g., ramucirumab and docetaxel) have been successful treatment options based on a Phase 3 clinical trial reporting OS of 10.5 months versus docetaxel monotherapy 9.1 months (HR 0.86; 95% CI 0.75, 0.98; p 0.023). The efficacy and safety of targeted agents such as adagrasib (Krazati) in comparison with, or in combination with, currently established regimens, have not been studied and remain unknown.

XII. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for NSCLC note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, continued approval of adagrasib (Krazati) as a subsequent-line treatment of NSCLC, remains contingent upon verification of clinical benefit in confirmatory trials. Additionally, an expanded access program via manufacturer, as part of the ongoing clinical studies of adagrasib (Krazati), remains a practical option and an alternative path to treatment for qualifying patients.

Investigational or Not Medically Necessary Uses

I. Adagrasib (Krazati) has not been sufficiently studied for safety and efficacy for any condition to date.

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References

1. Jänne PA, Riely GJ, et al. Adagrasib in Non-Small-Cell Lung Cancer Harboring a *KRASG12C* Mutation. N Engl J Med. 2022 Jul 14;387(2):120-131.
2. Takamasa K, Suda K, et al. KRAS Secondary Mutations That Confer Acquired Resistance to KRAS G12C Inhibitors, Sotorasib and Adagrasib, and Overcoming Strategies: Insights From In Vitro Experiments. J Thor Oncol. 2021 16 (8): 1321-1332.
3. Black RC, Khurshid H. NSCLC: an update of driver mutations, their role in pathogenesis and clinical significance. R I Med J. (2013). 2015; 98: 25-8.
4. Aggarwal S, Whipple S, Hsu H, et al. 1339P: Clinicopathological characteristics and treatment patterns observed in real-world care in patients with advanced non-small cell lung cancer (NSCLC) and KRAS G12C mutations in the Flatiron Health (FH)-Foundation Medicine (FMI) Clinico-Genomic Database (CGDB). *Ann Oncol*. 2020;31: S860.
5. Hayashi H, Okamoto I, Taguri M, Morita S, & Nakagawa K. Post-progression survival in patients with advanced non-small-cell lung cancer who receive second-line or third-line chemotherapy. *Clin Lung Cancer*. 2013; 14:261-266.

6. National comprehensive Cancer Network. NCCN Guidelines: Non-small Cell Lung Cancer V3.2022. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated March 16, 2022.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
sotorasib (Lumakras)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP002

Split Fill Management* (applies to lorlatinib [Lorbrena], crizotinib [Xalkori], ceritinib [Zykadia] and brigatinib [Alunbrig] only)

Description
Crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena) are orally administered anaplastic lymphoma kinase-positive (ALK+) tyrosine kinase inhibitors (TKI).

Length of Authorization
- Initial: Six months; first three months split fill for lorlatinib (Lorbrena), crizotinib (Xalkori), ceritinib (Zykadia), and brigatinib (Alunbrig).
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
crizotinib (Xalkori)	200 mg capsules	ALK+ NSCLC, metastatic; ROS1+ NSCLC, metastatic; ALK+ IMT, unresectable, recurrent, refractory	60 capsules/30 days
	250 mg capsules		60 capsules/30 days
	200 mg capsules	ALK+ systemic ALCL, relapsed/refractory; ALK+ IMT, unresectable, recurrent, refractory	120 capsules/30 days
	250 mg capsules		120 capsules/30 days
ceritinib (Zykadia)	150 mg capsules	ALK+ NSCLC, metastatic	84 capsules/28 days
	150 mg tablets		84 tablets/28 days
alectinib (Alecensa)	150 mg capsules		240 capsules/30 days
brigatinib (Alunbrig)	30 mg tablets		180 tablets/30 days
	90 mg tablets		30 tablets/30 days
	90 mg and 180 mg tablet titration pack		30 tablets/30 days
	180 mg tablets		30 tablets/30 days
lorlatinib (Lorbrena)	25 mg tablets		90 tablets/30 days
	100 mg tablets		30 tablets/30 days

Initial Evaluation

I. **Crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena)** may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. The medication will not be used in combination with other agents and will be used as monotherapy for the diagnosis submitted; **AND**
   C. The member has metastatic (stage IV) disease; **AND**
   D. A diagnosis of one of the following:
      1. **ALK+ Non-Small Cell Lung Cancer as detected by an FDA-approved test**; **AND**
         i. Alectinib (Alecensa) is prescribed unless contraindicated or not tolerated; **AND**
            a. For alectinib (Alecensa);
               i. The member has not progressed on any other agent listed in this policy; **OR**
               ii. The member has progressed on or after use of crizotinib (Xalkori)
            b. For crizotinib (Xalkori);
               i. The member has not progressed on any other agent listed in this policy
            c. For ceritinib (Zykadia);
               i. The member has not progressed on any other therapy listed in this policy; **OR**
               ii. The member has progressed on crizotinib (Xalkori)
            d. For brigatinib (Alunbrig)
               i. The member has not progressed on any other therapy listed in this policy; **OR**
               ii. The member has progressed on crizotinib (Xalkori)
            e. For lorlatinib (Lorbrena);
               i. The member has not progressed on any other therapy listed in this policy; **OR**
               ii. The member has progressed on alectinib (Alecensa); **OR**
               iii. The member has progressed on ceritinib (Zykadia); **OR**
               iv. The member has progressed on crizotinib (Xalkori) AND one other agent in this policy;**OR**
      2. **ROS1+ Non-Small Cell Lung Cancer as detected by an FDA-approved test**; **AND**
         i. The request is for crizotinib (Xalkori)

II. Crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena) are considered investigational when used for all other conditions, including but not limited to:
   A. ALK+ systemic ALCL in patients one year of age and older
   B. Inflammatory myofibroblastic tumors (IMT)
   C. ROS1+ NSCLC for any agent in this policy except for crizotinib (Xalkori)

D. NSCLC prior to the metastatic setting, or outside of the ROS1+ or ALK mutation (e.g., RET-rearranged NSCLC)
E. NSCLC in combination with other therapies
F. Thyroid cancer
G. Melanoma
H. Gastrointestinal cancer
I. Prostate cancer
J. Leukemias or lymphomas
K. Urothelial cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication is prescribed by, or in consultation with, an oncologist; **AND**
IV. The medication continues to be used as monotherapy for ALK+ or ROS1+ NSCLC; **AND**
V. There is documentation of disease response with treatment, defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

I. There is currently no evidence for safety and efficacy of any of these agents in combination with another ALK inhibitor, or in combination with any other therapies for the treatment of non-small-cell lung cancer (NSCLC). Any open prior authorizations for other ALK-inhibitors will be closed if coverage is approved for an agent in this policy. These agents have only been studied in the metastatic and adult populations with NSCLC in clinical trials.
II. Alectinib (Alecensa) has been evaluated in the first-line setting for metastatic ALK+ NSCLC, or after progression on crizotinib (Xalkori). A class review was done in 2018 which revealed advantages with alectinib (Alecensa) including superior head-to-head progression-free survival (PFS), intracranial response compared to crizotinib, and a more favorable safety profile via indirect comparison. As of 2021, lorlatinib (Lorbrena) was added to NCCN guideline for NSCLC as the 1st-line therapy for ALK-positive NSCLC (category 1) along with alectinib (Alecensa),brigatinib (Alunbrig), and ceritinib (Zykadia) (all category 1).
III. Notably, alectinib (Alecensa) remains the preferred agent for first-line treatment. A review of clinical data indicates that all ALK+ tyrosine kinase inhibitors indicated in the first-line treatment setting have comparable evidence with no agent standing out as superior to others (based on efficacy analysis supported by improvement in PFS, comparable toxicity profiles, and no clear survival advantage reported for any of the agents). Alectinib was recommended as the preferred first-line therapy of ALK-positive NSCLC by National Comprehensive Cancer Network (NCCN) NSCLC panel (V7.2021) (based on clinical trial data from ALEX and J-ALEX trials). As of September 2022, this recommendation remains unchanged. Additionally, alectinib (Alecensa) has been evaluated after progression on crizotinib (Xalkori) or lorlatinib (Lorbrena); however,

safety and efficacy after progression on ceritinib (Zykadia) and/or brigatinib (Alunbrig) are unknown.

IV. In the second line setting, several agents have been evaluated after progression on crizotinib (Xalkori). Lorlatinib (Lorbrena) is the only agent at this time that has been evaluated in the third line setting following progression on crizotinib (Xalkori) and one other ALK+ TKI for NSCLC.

V. Lorlatinib (Lorbrena) received its FDA-approval for second or greater line therapy in the metastatic setting of NSCLC. As of July 2019, a phase III clinical trial was in the enrollment stage to determine the comparative efficacy against crizotinib (Xalkori).

VI. In March 2021, lorlatinib (Lorbrena) received expanded approval in the first-line setting for metastatic ALK+ NSCLC based on the data from a phase 3, open-label, randomized clinical trial (CROWN study). In 296 previously untreated patients with advanced metastatic ALK+ NSCLC, lorlatinib (Lorbrena) showed higher efficacy as compared to crizotinib (Xalkori) based on a 12 month PFS rate of 78% (95% CI; 70, 84) versus that of 39% (95% CI, 30 to 48) in crizotinib arm [HR 0.28; (95% CI, 0.19 to 0.41) *; P*<0.001]. Median PFS for lorlatinib (Lorbrena) was not reached while that for crizotinib (Xalkori) was 9.3 months (95% CI; 7.6, 11.1).

VII. Crizotinib (Xalkori) is currently FDA-approved for ROS1+ NSCLC and ALK+ systemic ALCL. Several other agents are being evaluated in clinical trials; however, safety and efficacy data was not available as of July 2019.

VIII. Brigatinib (Alunbrig) was evaluated in an open-label, Phase 3, randomized trial against crizotinib (Xalkori) in metastatic ALK+ NSCLC. The study included 275 subjects, and those receiving brigatinib (Alunbrig) had a greater PFS (12-month PFS was 67% versus 43%; HR 0.49, p<0.001). The intracranial response was 78% for brigatinib (Alunbrig) and 29% for crizotinib (Xalkori). The data is not considered of high quality due to open label trial design, and lack of clinically significant outcomes such as overall survival and quality of life parameters.

IX. There is currently no evidence that ALK-inhibitors improve clinical outcomes (e.g., overall survival, quality of life) in patients with NSCLC. Quality of life parameter improvements were reported in CROWN study for lorlatinib (Lorbrena). However, this improvement was not clinically significant. Although PFS data is promising, PFS is a surrogate endpoint in NSCLC that has not been correlated with improved outcomes.

X. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Investigational or Not Medically Necessary Uses

I. The agents in this policy have not been sufficiently evaluated in the following settings. There may be NCCN recommendations or low-quality data available; however, safety and efficacy have not been established for:
   A. ALK+ systemic ALCL in patients one year of age and older
      i. In January 2021, crizotinib (Xalkori) received expanded approval in patients aged one and older with ALK+ relapsed or refractory systemic anaplastic large cell lymphoma (ALCL) based on a phase 2, open-label, single-arm study in 26 patients aged one to ≤ 21 years with ALK+ ALCL. All enrolled patients were refractory to

systemic chemotherapy, two patients were refractory to a monoclonal antibody, and one patient was refractory to brentuximab. Primary outcome studied was objective response rate (ORR), which was 88% [95% CI 71-96]. There were 21 (81%) and 2 (8%) of patients who achieved complete response (CR) and partial response (PR), respectively. The median time to first response was 3.9 weeks (range: 3.5-9.1 weeks). Progression free survival and overall survival were not evaluated.

ii. There is currently no evidence that crizotinib (Xalkori) improves clinically meaningful outcomes (e.g., overall survival, quality of life) in patients with ALCL. Improvement in ORR has not been correlated with improved clinically meaningful outcomes. Crizotinib (Xalkori) remains an investigational treatment in all patients with ALCL.

B. Inflammatory myofibroblastic tumors (IMT)
   i. In July 2022, crizotinib (Xalkori) received FDA approval for the treatment of adult and pediatric patients one year and older with unresectable, recurrent, or refractory ALK+ IMT. The medication received the approval based on two clinical trials, one in the pediatric space and one in adults.
   ii. The efficacy of crizotinib (Xalkori) in pediatrics was evaluated in a multicenter, single-arm, open-label Phase 2 study in fourteen patients aged 1 to 21 with unresectable, recurrent, or refractory ALK+ IMT. Twelve patients had undergone prior therapy, most commonly surgery, but also chemotherapy and radiation. Twelve of the fourteen patients received 280mg/m^2 twice daily until disease progression or unacceptable toxicity; two patients received a lower dose. The primary endpoint was objective response rate (ORR); five patients attained a complete response and seven had a partial response.
   iii. The efficacy of crizotinib (Xalkori) in adults was evaluated in a multicenter, single-arm, open-label phase 1b study of seven patients with unresectable, recurrent, or refractory ALK+IMT. Patients received 250 mg twice daily in evaluation of the primary outcome of ORR. Of the seven patients, one patient had a complete response, five patients had a partial response, and the median duration of treatment was nearly three years in 67% of these patients.
   iv. Currently, there is no evidence that crizotinib (Xalkori) improves clinically meaningful outcomes (e.g., overall survival, quality of life) in patients with ALK+IMT. Improvement in ORR has not been correlated with improved clinically meaningful outcomes. Crizotinib (Xalkori) remains an investigational treatment in all patients with ALK+IMT.
C. ROS1+ NSCLC for any agent in this policy except for crizotinib (Xalkori)
D. NSCLC prior to the metastatic setting, or outside of the ROS1+ or ALK mutation (e.g., RET-rearranged NSCLC)
E. NSCLC in combination with other therapies
F. Thyroid cancer
G. Melanoma
H. Gastrointestinal cancer
I. Prostate cancer
J. Leukemias or lymphomas
K. Urothelial cancer

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
entrectinib (Rozlytrek)	NSCLC- metastatic, ROS1+

Policy Implementation/Update:

Action and Summary of Changes	Date
Added expanded indication for crizotinib (Xalkori) for ALK+ IMT as investigational and updated quantity limit table to include this indication	4/2023
Updated supporting evidence around alectinib being the preferred first-line therapy	11/2021
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Added expanded indication for lorlatinib (Lorbrena) in the first-line treatment setting; added indication of ALK+ systemic ALCL for crizotinib (Xalkori) as investigational, updated quantity level limits for crizotinib (Xalkori), updated the supporting evidence section to include crizotinib (Xalkori) in the setting of ALK+ systemic ALCL	04/2021
Criteria update: Transitioned prior authorization criteria to policy format and consolidated all agents into one policy. Brigatinib now allowed for first-line setting if member has CI or intolerance to preferred therapy. Quantity level limits updated to reflect currently available products and package sizes. Addition of Zykadia tablets that are available in addition to the capsules.	07/2019
Criteria updates: Crizotinib updated criteria to new format, moved new start versus continuation question up. Updated prescriber question to fit current format, updated and added a question regarding both of the FDA-approved indications. Added a question regarding other therapies tried and failed or contraindicated. Zykadia updated to new format, deleted try and fail crizotinib question as this agent can now be used first line, added try and fail alectinib question, as per class review this is Moda Health's preferred agent. Removed age question, removed LFT question, QT prolongation question, and placed new versus continuation question up front. Alecensa criteria updated criteria to new format, deleted try and fail crizotinib question as this agent can now be used first line, removed age question. Alunbrig criteria updated to add question regarding prescribed and preferred therapy.	01/2018
Past criteria reviews	12/2012, 09/2014, 12/2015, 06/2017
Criteria created	12/2011

Policy Type: PA/SP Pharmacy Coverage Policy: UMP003

Split Fill Management* [Applies to alpelisib (Piqray) ONLY]

Description

Alpelisib (Piqray, Vijoice) is an orally administered kinase inhibitor with predominant activity against PIK3CA gene.

Length of Authorization

- Initial: Six months (first three months split fill for alpelisib [Piqray] only)
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit*
alpelisib (Piqray)	Advanced or metastatic breast cancer, PIK3CA mutation positive, HR+, HER2-	150 mg tablets (300 mg daily dose pack)	56 tablets/28 days
		200 mg tablets (200 mg daily dose pack)	28 tablets/28 days
		200 mg and 50 mg tablets (250 mg daily dose pack)	56 tablets/28 days
alpelisib (Vijoice)	PIK3CA-Related Overgrowth Spectrum (PROS)[Ŧ, **]	50 mg tablets (50 mg daily dose pack)	28 tablets/28 days
		125 mg tablets (125 mg daily dose pack)	28 tablets/28 days
		200 mg and 50 mg tablets (250 mg daily dose pack)	56 tablets/28 days

***Quantity limit exceptions not allowed, except for dose reductions.**

[Ŧ]Experimental/ Investigational indication.

*****Disclaimer: In the event an exception is granted for alpelisib (Vijoice) for any condition, a trial of a comparable, cost-effective formulation of alpelisib will be required [i.e., alpelisib (Piqray)].***

Initial Evaluation

I. **Alpelisib (Piqray)** may be considered medically necessary when the following criteria are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. A diagnosis of **advanced or metastatic breast cancer; AND**
      1. The request is for alpelisib (Piqray); **AND**
      2. The breast cancer is HR-positive, HER2-negative; **AND**
      3. PIK3CA mutation has been tested and confirmed; **AND**
      4. Provider attestation that the member is endocrine resistant or refractory; **AND**
      5. The medication will be used in combination with fulvestrant (Faslodex) only; AND

6. Alpelisib (Piqray) will not be used in combination with any other oncolytic medication including but not limited to CDK4/6 inhibitors (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.]

II. Alpelisib (Piqray) is considered not medically necessary when the criteria above are not met and/or when used for:
   A. Breast cancer that is not PIK3CA mutated.

III. Alpelisib (Piqray, Vijoice) is considered investigational when used for all other conditions, including but not limited to:
   A. PIK3CA- Related Overgrowth Spectrum (PROS)
   B. Overgrowth Spectrum disorders without PIK3CA mutation
   C. Breast cancer that is not HR+, HER2-, PIK3CA mutated, and/or advanced or metastatic
   D. Meningioma
   E. Oropharyngeal cancer
   F. Melanoma
   G. Renal cell cancer
   H. Pancreatic cancer
   I. Head and neck cancers
   J. Ovarian cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Alpelisib (Piqray) will be used in combination with fulvestrant (Faslodex); **AND**
   A. Alpelisib (Piqray) will not be used in combination with any other oncolytic medication including but not limited to CDK4/6 inhibitors (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.]; **AND**
IV. Member has exhibited a positive response to treatment or stability of disease symptoms (e.g., stabilization of disease, a decrease in tumor size or tumor spread)

Supporting Evidence

I. Alpelisib (Piqray, Vijoice) is an orally administered kinase inhibitor with predominant activity against PIK3CA gene. It is FDA-approved for the treatment of advanced or metastatic breast cancer with PIK3CA mutation, and for PIK3CA-Related Overgrowth Spectrum (PROS). The FDA approvals for these indications are specific to the respective formulation of alpelisib as well as recommended dosing. Alpelisib (Piqray) is indicated for the treatment of breast cancer, and alpelisib (Vijoice) is indicated for the treatment of PROS. Of note, use of alpelisib (Vijoice) for the treatment of PROS is considered experimental and investigational (please see the experimental and investigational section below).

II. Given the complexities involved with the diagnosis, treatment approaches and management of therapy for the indicated population, the treatment with alpelisib (Piqray) should be initiated by or in consultation with an oncologist.

III. Alpelisib (Piqray) was evaluated in one double-blind, Phase 3, placebo-controlled randomized trial (SOLAR-1). Both arms were in combination with fulvestrant. The trial evaluated adult subjects with and without the PIK3CA mutation; however, those without the mutation did not show favorable outcomes; thus, the efficacy information stated here is specific to those with the PIK3CA mutation. Safety information was pulled from the entirety of the population.

IV. Subjects in the pivotal trial had HR+, HER2-, advanced or metastatic breast cancer; 98% of which had received prior endocrine therapy and were deemed to be endocrine resistant. The trial focused on the endocrine-refractory population. The primary efficacy outcome was progression free survival (PFS), and secondary outcomes included PFS per a blinded review committee, overall response (OR) and clinical benefit (CB) (i.e., complete or partial response or stable disease). The primary outcome, PFS, was 11 months versus 5.7 months for alpelisib (Piqray) plus fulvestrant versus placebo plus fulvestrant (HR 0.65, $p<0.001$). Overall response was 26.6% versus 12.8% respectively, and CB was 61.5% versus 45.3% respectively.

V. There is a high risk of serious adverse events with alpelisib (Piqray). Serious adverse events occurred in 34.9% versus 16.7% for the placebo group. Adverse events of serious grade that occurred more often in the alpelisib (Piqray) arm versus placebo included: hyperglycemia, diarrhea, abdominal pain, acute kidney injury, anemia, nausea, osteonecrosis of the jaw, rash, stomatitis, erythema multiforme, hypokalemia, mucosal inflammation, maculopapular rash, creatinine increased, brain edema, renal failure, bacteremia, Steven's Johnson Syndrome, and many other cases of serious safety concerns. Common adverse reactions occurring in more than 20% of subjects included laboratory abnormalities (glucose, creatinine, lymphocyte, GGT, ALT, lipase, calcium, hemoglobin), fatigue, decrease appetite, stomatitis, vomiting, weight loss, aPTT prolongation, and alopecia. Tolerability of alpelisib (Piqray) is of concern; 74% of subjects from the treatment arm in SOLAR-1 required a dose-interruption and 64% required a dose-reduction versus 32% and 9% for the placebo arm respectively. Permanent discontinuation of drug due to adverse events occurred in 25% of alpelisib (Piqray) subjects versus 4.2% for subjects in the placebo group.

VI. The safety and efficacy of alpelisib (Piqray) in patients with HR+, HER2-, advanced or metastatic breast cancer with PIK3CA mutation and prior CDK4/6 inhibitor use has not been extensively studied due to evolving standard of care to include front-line use of CDK4/6 inhibitors. Nevertheless, the use of alpelisib (Piqray) may be supported in this setting by a small number of patients included in the SOLAR-1 trial, a Phase 2, open-label trial, BYLieve, as well as several non-interventional, retrospective studies which demonstrate modest efficacy and comparable safety in the real-world setting.

Investigational or Not Medically Necessary Uses

I. PIK3CA-Related Overgrowth Spectrum (PROS):
*** Disclaimer: In the event an exception is granted for alpelisib (Vijoice) for any condition, a trial of a comparable, cost-effective formulation of alpelisib will be required [i.e., alpelisib (Piqray)].*

A. Alpelisib (Vijoice) received accelerated FDA-approval and a breakthrough therapy designation for the treatment of PIK3CA-related overgrowth spectrum (PROS) in patients two years of age and older, who require systemic therapy. This approval was based on the data of an open-label, retrospective chart review study, and continued approval remains contingent upon confirmatory trials.

B. Alpelisib (Vijoice) is available as monthly therapy packs consisting of 50 mg, 125 mg and 200 mg tablets. The recommended dose of alpelisib (Vijoice) is 250 mg once daily for adults. For pediatric patients, the dose is age dependent. For children 2 to 6 years of age: 50 mg once a day; and for children ≥6 years of age and adolescents <18 years of age: initial dose of 50 mg daily for 6 months, followed by dose titration to 125 mg once a day to optimize clinical response.
C. As of September 2022, the monthly cost of alpelisib (Vijoice) remains significantly higher (>2 fold) than that of comparable formulations (therapy packs) of alpelisib (Piqray). In the event an exception is granted for alpelisib (Vijoice) for the treatment of PROS, alpelisib (Piqray) may serve as a comparable cost-effective formulation.
D. According to the prescribing information for alpelisib (Piqray, Vijoice), there is no well-established maximum dose for the approved indications. It is expected that alpelisib (Vijoice) may be utilized at higher doses in order to optimize clinical response. Availability of alpelisib (Piqray) therapy packs consisting of alpelisib (Piqray) 50 mg, 150 mg, and 200 mg tablets, may provide an avenue for dose escalations and optimizations. As an example, for an adult member requiring 250 mg daily dose of alpelisib (Vijoice), a 250 mg daily dose pack of alpelisib (Piqray) may be considered as an alternative. Similarly, a provider outreach may be needed in order to achieve optimized dosing for adolescent members, for whom the recommended daily dose of alpelisib (Vijoice) is 125 mg. It is estimated that these members may see dose escalations to 150 mg or beyond. In absence of concerns regarding drug toxicity, a daily dose of 150 mg may be efficacious alternative to a 125 mg daily dose.
E. PIK3CA-related overgrowth spectrum (PROS) is a heterogeneous group of rare, asymmetric overgrowth disorders caused by postzygotic variants in the PIK3CA gene. One PIK3CA encodes the p110α catalytic subunit of phosphoinositide 3-kinase (PI3K), which transduces activation of tyrosine kinase growth factor and hormone receptors into activation of AKT and mTOR signaling to promote tissue growth.
F. Overgrowth includes adipose tissue, muscle, skin, bone, blood or lymph vessels, or neural tissue, among others. Adipose and vascular components are particularly striking, reflecting the inherent plasticity and postnatal growth potential of these tissues. Complications of PROS depend on the anatomical site and extent of overgrowth, but may include functional impairment (e.g., of walking or swallowing), pain, recurrent superficial infections, thromboembolism, and/or hemorrhage, all of which may be debilitating, and cause early mortality. Based on the organ system involvement and the types of lesions, PROS may present as heterogeneous segmental overgrowth phenotypes - with or without vascular anomalies. Some of the prominent anomalies classified under PROS include CLOVES Syndrome, Klippel-Trenaunay Syndrome (KTS), Fibroadipose Infiltrating Lipomatosis (FIL), and Megalencephaly-Capillary Malformation (MCAP, or M-CM).
G. Current standard of care for PROS involves regular monitoring, debulking surgery, amputation, and/or endovascular occlusive procedures. Regrowth following surgery occurs frequently and repeated surgery is common.
H. Allosteric mTOR inhibitors such as sirolimus, which is approved for posttransplant immunosuppression, have been utilized for PROS treatment. Sirolimus may potently attenuate pathological AKT signaling and reduces cell proliferation in dermal fibroblasts derived from people with PROS, which suggests that it could be an effective treatment of PROS. However, it is important to note that the use of sirolimus may only be applicable to the patient population, whose PROS involves vascular and lymphatic malformations with predominant adipose overgrowth. These lesions are typically seen in CLOVES syndrome,

FIL, and MCAP, and manifest as visible lesions on the contralateral limb, truncal region, and/or face. In absence of these anomalies, the use of sirolimus may be deemed inappropriate by the treating provider.

I. A non-randomized, single-arm, open-label clinical trial (N=39) assessed the efficacy and safety of low-dose sirolimus (median target plasma levels of 3.3 ng/mL). Patients aged from three years to 65 years were included. For the primary outcome, tissue volumes at affected and unaffected sites were measured by dual-energy X-ray absorptiometry during 26 weeks of untreated run-in and 26 weeks of sirolimus therapy. Among the 30 participants, who completed the study, sirolimus led to a change in mean percentage total tissue volume of –7.2% (SD 16.0, p 0.04) at affected sites, but not at unaffected sites (+1.7%, SD 11.5, p 0.48) (n = 23 evaluable). No differences were detected in QOL scores before and after sirolimus treatment among adults or children. During run-in, five hospitalizations in five participants and two surgical interventions in two participants were recorded. In the treatment phase 15 hospitalizations in 9 participants and no surgical interventions arose. This difference was not significant (p = 0.24). Twenty-eight of 39 (72%) participants had ≥1 adverse event related to sirolimus of which 37% were grade 3 or 4 in severity and 7/39 (18%) participants were withdrawn consequently.

J. Efficacy of alpelisib (Vijoice) was evaluated using real-world data from EPIK-P1, a single-arm, open-label retrospective chart review study in patients, who received alpelisib (Vijoice) as part of an expanded access program for compassionate use. Eligible patients had clinical manifestations of PROS that were assessed by the treating physicians as severe or life-threatening and necessitating systemic treatment and had documented evidence of mutation in the PIK3CA gene. The efficacy of alpelisib (Vijoice) was evaluated in a total of 37 patients with at least one target lesion identified on imaging performed within 24 weeks prior to receipt of the first dose. The major efficacy outcome measure was the proportion of patients with a radiological response at week 24 as determined by blinded independent central radiology review, defined as a ≥20% reduction from baseline in the sum of measurable target lesion volume in up to 3 lesions confirmed by at least 1 subsequent imaging assessment. Duration of response was an additional efficacy outcome measure. Of the 37 patients included in the efficacy population, 27% (95% CI: 14, 44) had a radiological response at week 24. The most common (≥10%) adverse reactions occurring in patients were diarrhea, stomatitis, and hyperglycemia. Additionally, improvements in functionality were observed as determined by Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale and Lansky and Karnofsky scales: at baseline, the performance status was recorded for 47 patients: at the 24 weeks follow-up, 30% of patients showed ECOG PS improvement of at least 1 point and Karnofsky scale at least 20 points.

K. Despite accelerated approval and orphan designation, continued approval of alpelisib (Vijoice) remains contingent upon the verification of clinical benefit in confirmatory trials. Although FDA-approved for the treatment of PROS, efficacy data for alpelisib (Vijoice) is based on a retrospective chart review of a small patient population. The quality of data is considered low and the true clinical value of alpelisib (Vijoice) for the treatment of PROS remains undetermined.

L. Given the lack of curative therapy options and paucity of clinical data supporting the use of currently approved therapies, enrollment in a clinical trial may remain a practical management approach for patients with PROS. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field, while participating in important medical research and further advancements in treatment, with

close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced diseases with limited or no treatment options. As of September 2022, alpelisib (Vijoice) is available to patients via ongoing clinical trial and an expanded access program across the US and other countries.

II. Breast cancer without PIK3CA mutation.
    A. Alpelisib (Piqray) was evaluated in breast cancer patients that did not have the PIK3CA mutation and statistical significance over placebo was not reached.
III. Aleplisib (Piqray, Vijoice) is currently being investigated for safety and efficacy in many oncolytic disease states and potentially other non-oncolytic conditions. Safety and efficacy have not yet been determined in the following:
    A. Breast cancer that is not HR+, HER2-, PIK3CA mutated, and/or advanced or metastatic
    B. Meningioma
    C. Oropharyngeal cancer
    D. Melanoma
    E. Renal cell cancer
    F. Pancreatic cancer
    G. Head and neck cancers
    H. Ovarian cancer

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state

Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors	Breast cancer, HER2-negative, HR-positive, advanced, or metastatic

Policy Implementation/Update:

Action and Summary of Changes	Date
Removal of criterion requiring CDK4/6 inhibitor naïve patient population from the metastatic breast cancer indication	08/2023
Inclusion of new indication for PROS in the QL table; added PROS as E/I indication; added supporting evidence for PROS; format changes to align with current policy format	11/2022
Updated supporting evidence section to include data from BYLieve clinical trial	09/2020
Policy created	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP030

Description

Amifampridine (Firdapse, Ruzurgi) are orally administered, broad-spectrum potassium channel blockers.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
amifampridine (Firdapse)	Lambert-Eaton myasthenic syndrome	10 mg tablets	240 tablets/30 days
amifampridine (Ruzurgi)*		10 mg tablets	240 tablets/30 days

**In a January 2022 court ruling, the FDA converted the final approval of the Ruzurgi new drug application to a tentative approval. Therefore, Ruzurgi may not be legally marketed or distributed in the United States at this time*

Initial Evaluation

I. Amifampridine (Firdapse, Ruzurgi) may be considered medically necessary when the following criteria are met:
   A. Prescribed by, or in consultation with, a neurologist; **AND**
   B. A diagnosis of **Lambert-Eaton Myasthenic Syndrome (LEMS)**; **AND**
      a. Documentation of a confirmatory diagnostic test:
         i. Repetitive Nerve Stimulation (RNS); **OR**
         ii. Positive anti-P/Q type voltage-gated calcium channel (VGCC) antibody test; **AND**
      b. Member is experiencing moderate to severe weakness that interferes with function

II. Amifampridine (Firdapse, Ruzurgi) is considered investigational when used for all other conditions, including but not limited to the diagnosis of:
   A. Inflammatory muscle disease
   B. Limb-girdle muscular dystrophy
   C. Myasthenia gravis
   D. Congenital myasthenic syndrome
   E. Motor neuron disease (i.e. amyotrophic lateral sclerosis, multifocal motor neuropathy)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g., improved muscle strength

Supporting Evidence

I. LEMS is a rare presynaptic disorder of neuromuscular transmission in which the release of acetylcholine is impaired. Disruption of a subset of P/Q-type CA2+ channels causes proximal muscle weakness, depressed tendon reflexes, post-tetanic potentiation, and autonomic dysfunction. Major clinical presentation is progressive proximal muscle weakness. Forty to 60% of LEMs cases are paraneoplastic, involving and correlated with a [usually new] cancer diagnosis. Remaining patients with autonomic LEMS and without cancer, expect normal longevity.
II. Patients with LEMS who have mild weakness that does not interfere with function can be monitored without the use of symptomatic or immunologic therapy. Amifampridine (also known as 3,4-diaminopyridine) is the recommended therapy in patients with moderate or severe weakness that interferes with functions of daily living. Guanidine is approved for the treatment of LEMS, however, is associated with a high-level of toxicity and adverse effects, limiting its use. Pyridostigmine is known to be less toxic overall and is sometimes taken as in conjunction with guanidine. Use of pyridostigmine is generally accepted if amifampridine is not accessible, however its use is not supported by high-quality data. When used as monotherapy it has been shown to be only mildly effective with no effect on muscle strength. Immunoglobulin is often used in patients specifically for refractory weakness, which may or may not be associated with the underlying cancer in paraneoplastic LEMS. Alternative immunotherapies used include prednisone, azathioprine, plasma exchange, mycophenolate, rituximab.
III. In trials LMS-002, LMS-003, and DAPPER, subjects were confirmed of diagnosis of LEMS by nerve conduction findings OR positive anti-P/Q type voltage-gated calcium channel (VGCC) antibody test. This appears to be aligned with practice as the diagnosis is made via clinical features (e.g., muscle weakness, autonomic dysfunction, ptosis and diplopia) and electrodiagnostic studies (e.g., VGCC or repetitive nerve stimulation) as confirmatory evidence.
IV. The clinical presentation of LEMS that of slowly progressive, symmetric and proximal weakness, among other clinical symptoms, indicates a need of specific diagnosis by an experienced specialist.
V. There is a lack of strong scientific evidence to support the safety and efficacy for an increased dosing frequency or doses above the recommended. Trials were too small to indicate a dose-related trend of improvement or indicate a variation in effectiveness among subgroup populations.

Investigational or Not Medically Necessary Uses

I. Diagnosis of LEMS is largely based on clinical assessment and rule-out of other symptomatically similar disease. The following disease states have a similar presentation or relatedness to LEMS, however, randomized controlled trials to support the efficacy and safety of amifampridine (Firdapse, Ruzurgi) have yet to be completed.
   A. Inflammatory muscle disease
   B. Limb-girdle muscular dystrophy
   C. Myasthenia gravis
   D. Congenital myasthenic syndrome
   E. Motor neuron disease (i.e. amyotrophic lateral sclerosis, multifocal motor neuropathy)

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Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Removal of requirement to trail Ruzurgi prior to Firdapse due to removal of Ruzurgi from market. In a January 2022 court ruling, the FDA converted the final approval of the Ruzurgi new drug application to a tentative approval. Therefore, Ruzurgi may not be legally marketed or distributed in the United States at this time. Addition of criteria requiring symptomatic disease. Removal of initial criteria requiring trial of pyridostigmine or IVIG. Updated renewal section to include samples language and previous approvals.	04/2022
Addition of Ruzurgi to policy	07/2019
Policy created	02/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP201

Description

Amikacin liposomal (Arikayce) is an aminoglycoside antibiotic administered via nebulizer with the Lamira™ Nebulizer System

Length of Authorization

- Initial: Six months
- Renewal: Twelve months

Quantity limits

amikacin liposomal (Arikayce)	Indication	Quantity Limit	*DDID*
590 mg/8.4 mL suspension	*Mycobacterium avium* complex	252 mL/30 day	204273

Initial Evaluation

I. Amikacin liposomal (Arikayce) may be considered medically necessary when the following criteria are met:
   A. Prescribed by an infectious disease specialist; **AND**
   B. Patient is ≥ 18 years of age; **AND**
   C. A diagnosis of refractory *Mycobacterium avium* complex (MAC) lung disease as confirmed by a MAC-positive sputum culture when the following are met:
      1. Positive sputum culture obtained after at least six months of compliant use of a multi-drug regimen for MAC lung disease such as clarithromycin (or azithromycin), rifampin, and ethambutol within the past 12 months; **AND**
      2. Will be used as part of a multi-drug regimen; **AND**
      3. HIV negative

II. Amikacin liposomal (Arikayce) is considered investigational when used for all other conditions, including but not limited to:
   A. Cystic fibrosis patients with *Pseudomonas aeruginosa*
   B. Non-refractory MAC lung disease
   C. Use of amikacin liposomal (Arikayce) alone

Renewal Evaluation

I. Received therapy with amikacin liposomal (Arikayce) as part of a multi-drug regimen; **AND**
II. Has not received or will not receive 18 months or more of therapy with amikacin liposomal (Arikayce); **AND**
III. Negative sputum culture obtained within the last 30 days; **AND**

IV. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. Amikacin liposomal (Arikayce)is FDA-approved as part of a combination regimen for the treatment of treatment of MAC lung disease in adults who do not achieve negative sputum cultures after 6 months of a multidrug background regimen therapy.
II. As per the package insert: Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Clinical benefit has not yet been established due to uncertainties with sputum culture conversion predicting clinical benefit in this patient population. As only limited clinical safety and effectiveness data for Arikayce is currently available, use should be reserved to adults who have limited or no alternative treatment options.
III. In the pivotal trial leading to approval, patients with a diagnosis of cystic fibrosis or HIV were excluded. The study met the primary efficacy outcome of culture conversion (three consecutive monthly negative sputum cultures) by month six.
IV. Per ATS/ISDA guidelines, the goals of therapy include symptomatic, radiographic, and microbiologic improvement. The primary microbiologic goal of therapy is 12 months of negative sputum cultures while on therapy; therefore, sputum must be collected from patients throughout treatment. Patients should show clinical improvement within 3 to 6 months and should convert their sputum to negative within 12 months on macrolide-containing regimens. Failure to respond in these time periods should prompt investigation for possible noncompliance (perhaps due to drug intolerance) or macrolide resistance or the presence of anatomic limitations to successful therapy (e.g., focal cystic or cavitary disease).
V. Recent genotyping studies support 12 months of culture-negative sputum as a reasonable treatment endpoint because new positive sputum cultures for MAC after initial sputum conversion and culture negativity for 10 to 12 months are usually due to reinfection (new MAC genotype) rather than disease relapse.
VI. The ATS/IDSA guidelines state that patients should continue to be treated until they have negative cultures for one year. Patients that have had negative cultures for 1 year will not be approved for continued treatment.
VII. Treatment beyond the first renewal approval (after 18 months) will not be approved as amikacin liposomal (Arikayce) has not been studied beyond 18 moths nor in the reinfection or disease relapse setting.

Investigational or Not Medically Necessary Uses

I. Cystic fibrosis patients with *Pseudomonas aeruginosa*
    A. Use in cystic fibrosis patients with *Pseudomonas aeruginosa* was evaluated in a phase 3 study (NCT01315678), comparing amikacin liposomal (Arikayce) to inhaled tobramycin (Tobi). Results from the study are not yet available.

II. Non-refractory MAC lung disease

A. Per FDA label, the use of Arikayce is not recommended for patients with non-refractory MAC lung disease. Arikayce has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy.

III. Use of amikacin liposomal (Arikayce) alone

A. In the pivotal trial leading to approval amikacin liposomal (Arikayce) was studied as part of a multi-drug regimen for treatment of refractory MAC. Monotherapy treatment with amikacin liposomal (Arikayce) is not supported by clinical evidence.

References

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Policy Implementation/Update:

Date Created	January 2019
Date Effective	February 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

Policy Type: PA Pharmacy Coverage Policy: UMP109

Description

Oxymetholone (Androl-50) enhances production of erythropoietin in patients with anemias due to bone marrow failure. It stimulates erythropoiesis in anemias due to deficient red cell production. Oxandrolone is a synthetic testosterone derivative with similar androgenic and anabolic actions.

Length of Authorization

- **Oxymetholone (Anadrol-50)**
    i. Anemias
        1. Initial: Six months
        2. Renewal: 12 months
    ii. Cachexia associated with AIDS:
        1. Initial: Three months
        2. Renewal: Three months

- **Generic oxandrolone**
    i. Initial: Three months
    ii. Renewal: Not eligible. If additional treatment courses are requested, please see initial criteria.

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
oxymetholone (Anadrol-50)	50 mg tablets	Anemias caused by deficient red cell production; Cachexia associated with AIDS	Anemias: 1 to 5 mg/kg/day Cachexia: 90 tablets/30 days
oxandrolone	2.5 mg tablets	Weight gain associated with surgery, infections, trauma; Catabolism with prolonged corticosteroid use; Bone pain associated with osteoporosis; Cachexia associated with AIDS	Adults: 60 tablets/30 days Pediatrics: ≤0.1 mg/kg/day
	10 mg tablets		

Initial Evaluation

I. **Oxymetholone (Anadrol-50)** may be considered medically necessary when the following criteria below are met:
    A. Member has a diagnosis of **anemia caused by deficient red cell production** associated with one of the following conditions:
        1. Acquired aplastic anemia; **OR**

2. Congenital aplastic anemia; **OR**
3. Fanconi's anemia; **OR**
4. Hypoplastic anemias caused by the administration of myelotoxic drugs, or myelosuppression due to chemotherapy; **OR**
5. Myelofibrosis; **OR**

B. Member has a diagnosis of **cachexia associated with AIDS**; **AND**
   1. Medication is prescribed by, or in consultation with, a specialist in gastroenterology, nutritional support, or infectious disease; **AND**
      i. Member has ≥ 10% unintentional weight loss over a 12 month period; **OR**
      ii. Member has ≥ 7.5% unintentional weight loss over a 6 month period; **OR**
      iii. Member has ≥ 5% body cell mass (BCM) loss within 6 months; **OR**
      iv. For males, BCM < 35% and body mass index (BMI) < 27 kg/m^2; **OR**
      v. For females, BCM < 23% and BMI < 27 kg/m^2; **OR**
      vi. BMI < 18 kg/m^2; **AND**
      vii. Weight loss is not attributable to other causes

II. **Generic oxandrolone** may be considered medically necessary when the following criteria below are met:
   A. Medication will be used as adjunctive therapy to promote weight gain; **AND**
      1. Weight loss is due to one of the following conditions:
         i. Extensive surgery; **OR**
         ii. Chronic infections; **OR**
         iii. Severe trauma; **OR**
         iv. Member fails to gain or maintain normal weight without definite pathophysiological reasons; **OR**
   B. Medication will be used to offset the protein catabolism associated with prolonged administration of corticosteroids; **OR**
   C. Medication will be used for the treatment of bone pain associated with osteoporosis; **OR**
   D. Member has a diagnosis of **cachexia associated with AIDS**; **AND**
      1. Medication is prescribed by, or in consultation with, a specialist in gastroenterology, nutritional support, or infectious disease; **AND**
         i. Member has ≥ 10% unintentional weight loss over a 12 month period; **OR**
         ii. Member has ≥ 7.5% unintentional weight loss over a 6 month period; **OR**
         iii. Member has ≥ 5% body cell mass (BCM) loss within 6 months; **OR**
         iv. For males, BCM < 35% and body mass index (BMI) < 27 kg/m^2; **OR**
         v. For females, BCM < 23% and BMI < 27 kg/m^2; **OR**
         vi. BMI < 18 kg/m^2; **AND**
         vii. Weight loss is not attributable to other causes; **OR**
   E. Member has a diagnosis of Turner Syndrome

III. Oxymetholone (Anadrol-50) and oxandrolone are considered investigational when used for all other conditions.

Renewal Evaluation

I. **Oxymetholone (Anadrol-50)**
- Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- Member has exhibited improvement or stability of disease symptoms (e.g. weight gain, reduction in pain, resolution of symptoms)

II. **Oxandrolone**: If an additional treatment course is requested, please see initial criteria.

Supporting Evidence

I. Oxymetholone (Anadrol-50) is FDA-approved for the treatment of anemias caused by deficient red blood cells. Common conditions associated with this include acquired and congenital aplastic anemia, myelofibrosis, and hypoplastic anemias due to the administration of myelotoxic drugs. Other supportive measures for these anemias include transfusion, correction of iron, folic acid, vitamin B12 or pyridoxine deficiency, antibacterial therapy, and the appropriate use of corticosteroids.
    - Oxymetholone (Anadrol-50) is the most commonly used androgen in Fanconi's anemia, but danazol and oxandrolone have also been used. The efficacy of androgens in Fanconi's anemia was evaluated in a retrospective series that included 37 patients with available medication records. Of these patients, 68% had an improvement in hemoglobin level, and 32% showed improvements in hemoglobin, white blood cell count, and platelet count. In most cases, the responses were sufficient enough to convert the patient from transfusion-dependent to transfusion-independent. The median time to response was 12 to 14 weeks.
    - Although FDA-approved for myelofibrosis-associated anemia, oxymetholone (Anadrol-50) is not routinely recommended for use. Danazol, another oral anabolic steroid, is considered an NCCN Category 2A option in patients with anemia associated with myelofibrosis when serum EPO remains above 500 mU/mL despite treating coexisting causes. Other options include lenalidomide (Revlimid) and thalidomide.

II. For treatment of anemias caused by deficient red blood cells, if there is no response seen after three to six months, therapy should be discontinued. If blood counts stabilize or improve, the daily dose may be tapered to the minimum effective dose to avoid non-hematologic toxicity.

III. Oxandrolone is FDA-approved as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiological reasons, fail to gain or maintain normal weight. It is also indicated to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of bone pain that may accompany osteoporosis.

- Current osteoporosis guidelines do not make recommendations regarding use of oxandrolone for osteoporosis related pain.

IV. A two to four week course of oxandrolone is usually adequate depending on clinical response and tolerance. Therapy should be intermittent (vs chronic).

V. Testosterone and its derivatives, such as oxandrolone, have been studied in patients with HIV/AIDS. A 2004 review concluded that improvements in body composition and muscle strength were significant with oxandrolone in the majority of well-designed trails, although long-term safety and optimal dose were yet to be determined. Historically, weight loss and tissue wasting were common in HIV/AIDS; however, the incidence of wasting has declined since the introduction of effective antiretroviral treatment.

VI. Anabolic steroids, such as oxandrolone may be used as an adjunct to growth hormone (GH) in patients with Turner Syndrome. It is well established that GH therapy is effective in increasing final adult height. For those less than nine years of age, growth-promoting therapy is generally initiated with GH alone. However, in older patients, or those with extreme short stature, consideration can be given to adding an agent such as oxandrolone.

- Therapy should be continued until a satisfactory height has been attained or until little growth potential remains (e.g. bone age ≥ 14 years and growth velocity < 2 cm/year)

VII. Androgen therapy can be associated with a number of side effects, including virilization, growth abnormalities, behavioral changes, and hypertension. Serious side effects involve the liver, and include transaminitis, cholestasis, peliosis hepatitis, and liver tumors. Given these concerning risks, patients receiving androgen therapy should have liver chemistry profiles monitored every one to two months, and liver ultrasounds performed every six to 12 months.

Investigational or Not Medically Necessary Uses

IV. Due to a lack of high-quality, prospective clinical trials, oxymetholone (Anadrol-50) and oxandrolone are considered investigational for all other conditions.

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Policy Implementation/Update:

Date Created	December 2019
Date Effective	December 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date
New policy created	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP087

Description

Apomorphine (Apokyn, Kynmobi), a non-ergoline dopamine agonist, is administered as a subcutaneous injection. It possesses an unknown mechanism in the treatment of Parkinson's disease but is suggested that its effects are attributed to stimulation of post-synaptic D(2)-type receptors within the brain.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
apomorphine (Apokyn)	10 mg/mL Subcutaneous Injection	Parkinson's Disease	54 mL/30 days
apomorphine (Kynmobi)	10 mg sublingual film	Parkinson's Disease	150 films/30 days
	15 mg sublingual film		150 films/30 days
	20 mg sublingual film		150 films/30 days
	25 mg sublingual film		150 films/30 days
	30 mg sublingual film		150 films/30 days
	10/15/20/25/30mg titration kit		1 kit/30 days

Initial Evaluation

I. Apomorphine (Apokyn, Kynmobi) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Must be prescribed by, or in consultation with, a neurologist; **AND**
   C. Not used in combination with a 5-HT_3 receptor antagonist (e.g. ondansetron, granisetron, dolasetron, etc.); **AND**
   D. A diagnosis of **Parkinson's disease** when the following are met:
      1. Member experiences predictable acute, intermittent hypomobility "off" episodes; **AND**

2. Provider must attest that the first dose will be done in office and the member will be monitored; **AND**
3. Member will be taking carbidopa/levodopa concurrently with apomorphine (Apokyn, Kynmobi); **AND**
4. Treatment with ONE of the following has been ineffective, contraindicated, or not tolerated:
    i. Dopamine agonist (e.g. pramipexole, ropinirole, rotigotine)
    ii. Monoamine oxide-B (MAO-B) inhibitor (e.g. selegiline, rasagiline)
    iii. Catechol-O-methyl transferase (COMT) inhibitors (e.g. entacapone, tolcapone)

II. Apomorphine (Apokyn) is considered investigational when used for all other conditions, including but not limited to:
    A. Erectile dysfunction

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has demonstrated benefit through reduction of "off" episodes/hypomobility

Supporting Evidence

I. Apomorphine subcutaneous injection (Apokyn) was studied in three randomized controlled trials. All patients in the studies were on L-dopa, 86% of patients were on oral dopaminergic agonists, 31% were on catechol-ortho-methyl transferase inhibitors, and 10% were on monoamine B oxidase inhibitors.
    - Study one was a randomized, double-blind, placebo-controlled, parallel-group trial evaluating 29 patients with advanced Parkinson's disease who had at least two hours of "off" time per day. Apomorphine (Apokyn) demonstrated a statistically significant decrease in the Unified Parkinson's Disease Rating Scale (UPDRS) compared to placebo, with a mean change from baseline of -23.9 and -0.1 (p<0.001) respectively.
    - Study two was a randomized, placebo-controlled crossover trial evaluating 17 patients with Parkinson's disease who had been using apomorphine (Apokyn) for at least three months. Apomorphine (Apokyn) demonstrated a statistically significant decrease in UPDRS compared to placebo, with a mean change from baseline of -20 and -3 respectively.
    - Study three was a randomized, double-blind, placebo-controlled, trial evaluating 62 patients with Parkinson's disease who had been using apomorphine (Apokyn) for at least three months. Apomorphine (Apokyn) demonstrated a statistically significant decrease in UPDRS at 20 minutes compared to placebo, with a mean change from baseline of -24.2 vs -7.4 (p<0.0001) respectively.

II. Apomorphine sublingual tablet (Kynmobi) was studied in one phase 3 clinical trial that consisted of an open label dose-titration phase followed by a 12 week randomized, double-blind, placebo-controlled trial in 109 patients who had diagnosis of Parkinson's Disease and had at least two hours of 'off' time per day with predictable morning 'off' periods. Patients continued concomitant Parkinson's Disease medications including levodopa-containing agents (100% apomorphine and placebo group), dopamine agonists (56% apomorphine and placebo group), monoamine oxidase-B inhibitors (41% apomorphine, 44% placebo), amantadine (15% apomorphine, 29% placebo) and catechol-O-methyltransferase inhibitors (9% apomorphine and placebo groups).
    - The primary efficacy endpoint, mean change from pre-dose to 30 minutes post-dose in MDS-UPDRS Part 3 score at week 12, was significantly greater in the apomorphine group compared to placebo (change -11.1, SE 1.46, 95% CI -14.0 to -8.2, with apomorphine sublingual film VS -3.5, 1.29, -6.1 to -0.9, with placebo) with a least squares mean difference of -7.6 (SE 1.96, 95% CI -11.5 to -3.7; p=0.0002).
    - The key secondary endpoint, percentage of patients with a self-rated full on response within 30 minutes at the 12-week visit, was significantly greater in the apomorphine group (35%, SE 21 to 35) compared to placebo (16%, SE 8 to 30) (OR 2.81, 1.04 to 7.64; p=0.043).

III. Use of apomorphine (Apokyn, Kynmobi) with 5-HT_3 antagonists (e.g. ondansetron, granisetron, dolasetron, or alosetron) is contraindicated. There have been reports of profound hypotension and loss of consciousness when administered together.

IV. Adverse events are similar between both the sublingual and subcutaneous formulations of apomorphine (Apokyn, Kynmobi), including syncope, hypotension, orthostatic hypotension, nausea, vomiting, falling asleep during activities of daily living, somnolence, and hallucinations or psychotic-like behavior. Oral mucosal irritation was common during the clinical trials for apomorphine sublingual films (Kynmobi) with approximately 20% of patients developing mild to moderate oral mucosal ulcerations or stomatitis, oral soft tissue pain or paresthesia, oral/pharyngeal soft tissue swelling or oral mucosal erythema.

V. Because of the high incidence of nausea and vomiting with apomorphine (Apokyn, Kynmobi) at recommended doses, a non 5HT-3 antagonist antiemetic (e.g. trimethobenzamide) should be initiated beginning three days prior to starting apomorphine (Apokyn, Kynmobi). Treatment with the antiemetic should be continued only as long as necessary to control nausea and vomiting symptoms, and ideally is discontinued no longer than two months after initiation of apomorphine (Apokyn, Kynmobi).

VI. Due to high incidence of syncope/hypotension/orthostatic hypotension with apomorphine (Apokyn, Kynmobi), dose initiation should occur under the supervision of a healthcare provider where blood pressure and pulse can be monitored according to the package insert.

VII. According to the prescribing information for apomorphine subcutaneous injection (Apokyn), there is no evidence from controlled trials that doses greater than 0.6mL (6mg) gave an increased effect and therefore, individual doses exceeding 0.6mL (6mg) are not recommended. The average frequency of dosing in the developmental program is 3 times per day. Additionally, there is limited experience with single doses greater than 0.6 mL (6mg), dosing more than five times per day, and with total daily doses greater than 2mL (20mg).

VIII. According to the prescribing information for apomorphine sublingual tablets (Kynmobi), the dose range is 10mg to 30mg per dose. The maximum single dose should not exceed 30mg; do not administer more than five doses per day.

Investigational or Not Medically Necessary Uses

I. Apomorphine (Apokyn) has not been adequately studied in patients with erectile dysfunction.

References

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5. Orlanow CW et al. Apomorphine sublingual film for off episodes in Parkinson's disease: a randomized, double-blind, placebo-controlled phase 3 study. *Lancet Neurol* 2020; 19:135-44.
6. Kynmobi [prescribing information]. Sunovion Pharmaceuticals, Inc.: Marlborough, MA; May 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
• Added apomorphine sublingual films (Kynmobi) to policy • Added requirement of member is experiencing predictable acute, intermittent hypomobility "off" episodes • Updated renewal criteria to require prior approval through this OR prior health plan (not established via samples) • Removed renal criteria requirement confirming lack of toxicity to therapy • Updated apomorphine subcutaneous injection (Apokyn) QLL to align with FDA label and package size of 3mL/cartridge	03/2021
Criteria transitioned to policy	10/2019
Previous reviews	11/2014 12/2008 09/2008
Criteria created	09/2005

Policy Type: PA/SP Pharmacy Coverage Policy: UMP251

Split Fill Management*

Description

Asciminib (Scemblix) is an orally administered BCR-ABL1 tyrosine kinase inhibitor (TKI) specifically targeting the ABL myristoyl pocket (STAMP) of BCR-ABL protein.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
asciminib (Scemblix)	20 mg tablets	Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CP-CML) with resistance or intolerance to two prior tyrosine kinase inhibitors	60 tablets/30 days*
	40 mg tablets		60 tablets/30 days*
asciminib (Scemblix)	20 mg tablets	Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia in chronic phase (CP-CML) with T315I mutation	60 tablets/30 days*
	40 mg tablets		300 tablets/30 days*

**Quantity exceptions are not allowed.*

Initial Evaluation

I. **Asciminib (Scemblix)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. Medication will not be used in combination with any other BCR-ABL1 tyrosine kinase inhibitor (e.g., imatinib [Gleevec], dasatinib [Sprycel], bosutinib [Bosulif]); **AND**
   D. A diagnosis of **Chronic Myeloid Leukemia (CML)** when the following are met:
      i. The member has chronic phase Philadelphia chromosome-positive CML (Ph+ CP-CML); **AND**
         a. Documented resistance, or intolerance to, two prior BCR-ABL1 tyrosine kinase inhibitors (TKIs) (e.g., imatinib (Gleevec), dasatinib

(Sprycel), nilotinib (Tasigna), bosutinib (Bosulif), ponatinib (Iclusig)); **AND**

b. Requested total daily dose of asciminib (Scemblix) does not exceed 80 mg per day (40 mg twice a day); **OR**

ii. The member has chronic phase Philadelphia chromosome-positive CML (Ph+ CP-CML) with T315I mutation; **AND**

a. Ponatinib (Iclusig) has been ineffective, or not tolerated; **OR**

i. Documentation that the member has pre-existing cardiovascular and/ or hepatic comorbidity that precludes the use of ponatinib (Iclusig); **AND**

b. Requested total daily dose of asciminib (Scemblix) does not exceed 400 mg per day (200 mg twice a day)

II. Asciminib (Scemblix) is considered investigational when used for all other conditions, including but not limited to:

A. Newly diagnosed CP-CML not previously treated with a TKI

B. CML in accelerated phase (AP-CML) or blast phase (BP-CML)

C. Any myeloproliferative neoplasm other than CP-CML (e.g., acute myeloid leukemia (AML), chronic lymphocytic l CLL)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Medication will not be used in combination with any other BCR-ABL1 tyrosine kinase inhibitor [e.g., imatinib (Gleevec), dasatinib (Sprycel), bosutinib (Bosulif)]; **AND**

IV. Member has exhibited improvement or stability of disease symptoms [e.g., complete cytogenic response (CCyR), major molecular response (MMR)]

Supporting Evidence

I. Asciminib (Scemblix) is a BCR-ABL1 tyrosine kinase inhibitor (TKI). Unlike previous generation TKIs, which bind to the ATP binding pocket on BCR-ABL1 protein, asciminib (Scemblix) is purported to specifically target the ABL myristoyl pocket (STAMP), thus named a STAMP-inhibitor. Asciminib (Scemblix) is the first BCR-ABL1 STAMP inhibitor, FDA-approved as a third-line treatment option after resistance or intolerance to two or more prior TKIs for the treatment of Philadelphia chromosome positive chronic phase Chronic Myeloid Leukemia (Ph+ CP-CML). Additionally, it may be a treatment option for PH+ CP-CML with T315I mutation. The NCCN guideline for CML has included asciminib (Scemblix) as a Category 2A recommendation in these settings.

II. Given the complexities involved in diagnosis and management of CML, therapy decisions regarding initiation of asciminib (Scemblix) must be made by, or under the supervision of, a specialist practicing in this setting, (e.g., an oncologist, hematologist).

III. Asciminib (Scemblix) has ongoing clinical trials in the setting of treatment of CML in combination with another TKI (e.g., imatinib). However, such combination therapy has not been sufficiently supported by available clinical data and/or FDA approval.

IV. CML is classified into three groups that help predict its outlook. The phases are based mainly on the number of immature white blood cells (blasts) in the blood or bone marrow. Different groups of experts have suggested different cutoffs to define the phases, but a common system (proposed by the World Health Organization (WHO)) is widely accepted, described below:

- Chronic Phase (CP-CML): Less than 10% blasts in their blood or bone marrow samples. Generally mild symptoms (if any) and usually respond to standard treatments. Most patients are diagnosed in the chronic phase.
- Accelerated Phase (AP-CML): If any of the following are true: Blood samples have > 15% but < 30% blasts; plasma basophils ≥ 20%; ≥ 30% plasma (peripheral) blasts and promyelocytes combined; Very low platelet counts (100 x 1,000/mm^3 or less); or new chromosome changes in the leukemia cells with the Philadelphia chromosome.
- Blast phase (acute phase or blast crisis): Bone marrow and/or blood samples have ≥ 20% blasts. Large clusters of blasts are seen in the bone marrow. The blast cells have spread to tissues and organs beyond the bone marrow. CML acts like an AML in this phase.

V. Asciminib (Scemblix) is an oral tablet taken once or twice a day (dose based on indication) and is available as a 20 mg and 40 mg formulation. The dose for CP-CML refractory to ≥ 2 TKI is up to 80 mg per day (40 mg BID), while in the setting of CP-CML with T315I mutation, recommended dose of asciminib (Scemblix) is 200 mg twice a day. Dose reductions may be necessary due to drug related adverse reactions. Consequently, 20 mg tablet may be necessary to achieve dose modification for members requiring a lower dose. However, it should be noted that any increments of dosing up to 200 mg (each dose) may be achievable by use of a maximum 60 tablets of asciminib (Scemblix) 20 mg tabs. Similarly, in the setting of CP-CML refractory to ≥ 2 TKI, based on the maximum recommended dose (80 mg per day), quantity limit exceptions to asciminib (Scemblix) 40 mg tablet are not advised given excessive additional cost.

VI. More than 95% cases of CML are caused by the BCR-ABL1 fusion gene (Ph chromosome) and are usually diagnosed in its chronic phase when the treatment is very effective for most patients. Current standard of care for the treatment of CP-CML involves use of BCR-ABL1 TKI and allogenic hematopoietic cell transplant (HCT). First-generation TKI (imatinib) is the preferred initial therapy for patients with low-risk scores, while second-generation TKI (e.g., bosutinib, dasatinib, nilotinib) are the preferred regimens for intermediate or high-risk cases of CP-CML. The NCCN treatment guideline for CML recommends use of an alternative second-generation TKI for CP-CML refractory to first-generation TKI. Ponatinib (Iclusig) is a third-line therapy option for CP-CML resistant to at least two prior TKIs, or for patients with T315I mutation. Additionally, omacetaxine (Synribo) is recommended in cases with T315I mutation and on progression from CP-CML to accelerated phase CML (AP-CML).

VII. Clinical Trials: Asciminib (Scemblix) was evaluated in two open-label clinical trials, one for each FDA-approved indication, a Phase 3 randomized trial (ASCEMBL) and a Phase 1, single-arm trial (X2101).

- Phase 3: A randomized (2:1), open-label trial of asciminib (Scemblix) (40 mg BID) versus bosutinib (Bosulif) (500 mg QD) as active comparator. This trial was designed for the treatment of CP-CML in adult patients (N=233) refractory to ≥ 2 TKIs or

intolerance to the most recent TKI therapy. The rate of major molecular response (MMR) at week 24 was the primary endpoint along with MMR and rate of complete cytogenic response (CCyR) at 96 weeks, as key secondary endpoints. Known T315I mutations were excluded. At Week 24, the MMR rate was 25.5% for patients receiving asciminib (Scemblix) and 13.2% for those receiving bosutinib (Bosulif). The between-arm common treatment difference was 12.2% (95% CI: 2.19, 22.30; p=0.029). Additionally, asciminib arm reported a deep molecular response (MMR4.5; BCR-ABL1 < 0.0032%) in 10.8% (n=17) versus 5.3% (n=4) for those in bosutinib (Bosulif) arm.

- Phase 1: A single-arm dose exploration trial (N= 150), which was expanded for assessing asciminib (Scemblix) in Ph+ CP-CML patients (n=52) with T315I mutation. Majority of patients were refractory to ≥ 2 prior TKI therapies, however patients with T315I mutation were enrolled if refractory to one prior TKI. Although the primary endpoint was determination of maximum tolerated dose of asciminib (Scemblix), MMR was used as an objective measure of efficacy. At week 24, four out of 17 evaluable patients (24%) in the T315I+ CML cohort, who did not have MMR at baseline, achieved MMR (BCR-ABL ≤0.1%).

VIII. Asciminib (Scemblix) received accelerated FDA-approval as a third-line treatment for Ph+ CP-CML, refractory to two or more TKI therapies, and a full FDA-approval for treatment of CP-CML with T315I mutation. Continued approval in the third-line treatment setting remains contingent upon verification of clinical benefits in confirmatory trials.

IX. The safety data of asciminib (Scemblix) was based on all participants exposed to therapy. The most common adverse events (AE) included: Phase 1 trial: fatigue, increased lipase, thrombocytopenia, and hypertension. Phase 3 trial: 89.7% of patients in the asciminib arm and 96.1% of patients in the bosutinib arm experienced an AE with most common AE: diarrhea, increased ALT, and AST. Participants in the asciminib (Scemblix) arm reported significantly higher neutropenia (21.8% versus 21.1%) and thrombocytopenia (28.8% versus 18.4%) compared to bosutinib (Bosulif). During the Phase 3 clinical trial, asciminib (Scemblix) led to 36% dose reductions and 52% therapy interruptions, majority due to AE.

X. Asciminib (Scemblix) has not been compared with ponatinib (Iclusig) in head-to-head clinical trials. The majority of the safety and efficacy data for the use of TKIs in the setting of T315+ CP-CML are rooted in the previous clinical trials and established real-world efficacy and safety data of ponatinib (Iclusig). Additionally, omacetaxine (Synribo), a protein synthesis inhibitor, is indicated for the treatment of CP-CML with T315I mutation. Prescribing information for ponatinib (Iclusig) includes warnings and precautions related to cardiovascular toxicities, hepatic impairment, pancreatitis, hypertension, neuropathy, among others. It should be noted that proposed benefit of asciminib (Scemblix) over ponatinib (Iclusig) may be based on purported safety profile and lack of severe adverse events in the clinical trial population. The real-world long-term safety of asciminib (Scemblix) remains unknown. Weighing the safety, efficacy, cost, and clinical experience, ponatinib (Iclusig) may be considered an appropriate high-value treatment option in this space. Coverage of asciminib (Scemblix) in ponatinib-naïve population may be considered based on medical necessity (e.g., history of cardiovascular disorders, un-controlled hypertension etc.).

Investigational or Not Medically Necessary Uses

I. There are several clinical trials underway for assessing efficacy of asciminib (Scemblix) in the first-line treatment setting for CML as well as in combination with other TKIs. Trials have not been completed, and safety and efficacy in this setting and/or as a combination therapy remain unknown.
II. Asciminib (Scemblix) has not been FDA-approved, or sufficiently studied for safety and efficacy for the treatment of other conditions or settings, including CML in accelerated phase (AP-CML) or blast phase (BP-CML).

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Rea D, Mauro MJ et al. A Phase 3, Open-Label, Randomized Study of Asciminib, a STAMP Inhibitor, vs Bosutinib in CML After ≥2 Prior TKIs. Blood. 2021 Aug 18: blood.2020009984. doi: 10.1182/blood.2020009984. PMID: 34407542.
2. Hughes TP, Mauro MJ, et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. N Engl J Med. 2019 Dec 12;381(24):2315-2326.
3. NCCN Clinical practice Guidelines in Oncology for chronic myeloid leukemia; V2.2022; updated November 15th, 2021.
4. Novartis. Scemblix (asciminib) [Prescribing Information]. 2021. Novartis Pharmaceutical Corp.; East Hanover, NJ.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2022

Policy Type: PA Pharmacy Coverage Policy: UMP006

Description

Asfotase alfa (Strensiq™) is a tissue nonspecific alkaline phosphatase fusion protein considered a form of enzyme replacement therapy.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
asfotase alfa (Strensiq)	18mg/0.45mL vial	infantile, pediatric, or juvenile onset hypophosphatasia	24 vials/28 days
	28mg/ 0.7mL		24 vials/ 28 days
	40mg/ 1 mL vial		24 vials/ 28 days
	80mg/ 0.8 mL vial		24 vials/ 28 days

*See appendix A for dose recommendations

Initial Evaluation

I. Asfotase alfa (Strensiq) may be considered medically necessary when the following criteria below are met:
   A. Diagnosis is made by, or in consultation with, a geneticist, metabolic specialist, endocrinologist, or bone and mineral specialist; **AND**
   B. A diagnosis of **perinatal/infantile-onset and juvenile-onset hypophosphatasia (HPP)** when the following are met:
      1. Documented tissue-non-specified alkaline phosphatase (TNSALP) gene mutation status; **OR**
      2. Documented serum alkaline phosphatase (ALP) level below the age and gender-adjusted normal range; **AND**
         i. Elevated TNSALP substrate levels as determined by age and gender specific reference range of one of the following:
            a. Plasma pyridoxal-5'-phosphate (PLP); **OR**
            b. Urine concentration of phosphoethanolamine (PEA); **OR**
            c. Urinary inorganic pyrophosphate level (PPi); **AND**
      3. Onset of perinatal/infantile or juvenile-onset HPP occurring prior to the age of 18, as documented by signs and/or symptoms (e.g., respiratory insufficiency, vitamin B6 responsive seizures, failure to thrive, delayed walking, waddling gait, dental abnormalities, low trauma fracture, etc.); **OR**
         i. Radiographic evidence supporting the diagnosis of HPP prior to the age of 18 (e.g. craniosynostosis, infantile rickets, non-traumatic fracture); **AND**
         ii. Provider attestation member will be monitored for ectopic calcification

II. Asfotase alfa (Strensiq) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Adult-onset HPP
   B. Odontohypophosphatasia
   C. Pseudophypophosphatasia
   D. Other forms or causes of osteomalacia: X-linked hypophosphatemia, low bone mass, inappropriate treatment with bisphosphonates, osteoporosis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Diagnosis is made by, or in consultation with, a geneticist, metabolic specialist, endocrinologist, or bone and mineral specialist; **AND**
IV. A diagnosis of **perinatal/infantile-onset and juvenile-onset hypophosphatasia (HPP)**; **AND**
V. Documentation of a positive response to therapy with asfotase alfa, which includes improvement and/or stabilization in the clinical signs and symptoms of hypophosphatasia (e.g. improvement in ALP/PLP/PEA/PPi levels, improvement in respiratory function/breathing, weight gain, improvement in milestones, absence of new fractures/reduction in fracture occurrence, radiographic evidence of improvement, etc).

Supporting Evidence

I. Perinatal/infantile and juvenile-onset HPP are the pediatric variants of hypophosphatasia, which is a rare genetic disorder that impairs bone metabolism. HPP is associated with a high mortality rate, with survival rate estimated at less than 50% by one year of age in infancy due to rachitic deformities developed by six months of age; the diagnosis is lethal in the perinatal setting. Juvenile HPP is associated with premature loss of deciduous teeth, delayed walking, and waddling gait. Due to the risk of fractures, bone deformities and failure to thrive, there is risk for abnormal growth and development in pediatric patients diagnosed with perinatal/infantile or juvenile-onset HPP.
   - Approval by the FDA was based on three pivotal trials (ENB-002-08/ENB-003-08, ENB-010-10, and ENB-006-09/ENB-008-10) conducted in 13 pediatric patients (five subjects with perinatal/infantile-onset HPP; eight subjects with juvenile-onset HPP).
      i. A Kaplan-Meier analysis of pooled overall survival data (n=68) was compared with a natural history group (n=48). This analysis showed an overall survival rate of 91% (n=68) of treated subjects when compared with 27% (n=48) of the historical control group.
      ii. In the juvenile-onset population, efficacy was assessed based on the Tinetti Modified Performance Oriented Mobility Assessment – Gait (mPOMA-G) scale. It was agreed by the FDA that change in gait is considered a surrogate marker and is not interpreted as an improvement in clinical outcomes. Radiographic analysis showed improvement in all subjects with treatment; however, using change in rickets severity and assessed by the Radiographic Global Impression of Change (RGI-C) scale, when compared to control group.

- HPP is a broadly expressed disorder ranging from death to arthropathy without bone disease. Prognosis is largely based on skeletal complications, with the most severe disease affecting patients with perinatal/infantile or juvenile-onset of HPP.
- Adult-onset hypophosphatasia is characterized by poor healing, bone pain, recurrent fracture, and increased incidence of pyrophosphate arthropathy and chondrocalcinosis. As onset presents during middle-age, the benefit of enzyme replacement in the adult population is unknown.
- The presence of a defective TNSALP allele without sign or symptoms of dental or arthritic complications helps determine the patient is a carrier only.
- As ectopic calcification has been reported, monitoring for ectopic calcification by means of ophthalmic examination and renal ultrasound is recommended by label at baseline and periodically throughout treatment.

Investigational or Not Medically Necessary Uses

I. Adult-onset HPP
   A. Asfotase alfa (Strensiq) is FDA-indicated for the treatment of members with perinatal/infantile- and juvenile-onset HPP; these populations are known to have the most severe disease and the benefit of enzyme replacement therapy is supported by data.
   B. There are limited to no research studies to support the efficacy of asfotase alfa (Strensiq) in the setting of adult-onset HPP without history of infantile and/or juvenile onset HPP. Evidence is currently limited to case-reports only.
   C. Adult-onset HPP treatment is currently limited to supportive therapy.

II. Odontohypophosphatasia
   A. Odontohypophosphatasia, expressed in dental complications alone, is the mildest and most prevalent form of hypophosphatasia. This diagnosis is typically associated with otherwise normal and/or good health condition.

III. Pseudohypophosphatasia
   A. Resembles infantile hypophosphatasia, however, without low serum alkaline phosphatase. Use of age-dependent reference range is important to differentiate between infantile-onset and pseudohypophosphatasia, or simply a transient elevation in TNSALP substrate.
   B. Causes of pseudohypophosphatasia can include, but are not limited to: cardiac bypass surgery, Celiac disease, Cushing syndrome, hypothyroidism, multiple myeloma, starvation, certain vitamin or mineral deficiencies or intoxications, or improperly collected blood sampling.

IV. Other forms or causes of osteomalacia: X-linked hypophosphatemia, low bone mass, inappropriate treatment with bisphosphonates, osteoporosis.

Appendix

Weight-Based Dosing for Administration of **2 mg/kg** three times per week

Body Weight (kg)	Dose to Inject	Volume to Inject	Vial Configuration	Number of Vials per 28 days
3	6 mg	0.15 mL	18mg/0.45mL	12
4	8 mg	0.2 mL	18mg/0.45mL	12
5	10 mg	0.25 mL	18mg/0.45mL	12
6	12 mg	0.3 mL	18mg/0.45mL	12
7	14 mg	0.35 mL	18mg/0.45mL	12
8	16 mg	0.4 mL	18mg/0.45mL	12

9	18 mg	0.45 mL	18mg/0.45mL	12
10	20 mg	0.5 mL	28mg/0.7kmL	12
15	30 mg	0.75 mL	40mg/mL	12
20	40 mg	1 mL	40mg/mL	12
25	50 mg	1.25 mL	Two 28mg/0.7mL	24
30	60 mg	1.5 mL	Two 40mg/mL	24
35	70 mg	1.75 mL	Two 40mg/mL	24
40	80 mg	0.8 mL	80mg/0.8mL	12
50	100 mg	1 mL	Two 80mg/0.8mL	24
60	120 mg	1.2 mL	Two 80mg/0.8mL	24
70	140 mg	1.4 mL	Two 80mg/0.8mL	24
80	160 mg	1.6 mL	Two 80mg/0.8mL	24

Weight-Based Dosing for Administration of **1 mg/kg** six times per week

Body Weight (kg)	Dose to Inject	Volume to Inject	Vial Configuration	Number of Vials per 28 days
3	3 mg	0.08 mL	18mg/0.45mL	24
4	4 mg	0.1 mL	18mg/0.45mL	24
5	5 mg	0.13 mL	18mg/0.45mL	24
6	6 mg	0.15 mL	18mg/0.45mL	24
7	7 mg	0.18 mL	18mg/0.45mL	24
8	8 mg	0.2 mL	18mg/0.45mL	24
9	9 mg	0.23 mL	18mg/0.45mL	24
10	10 mg	0.25 mL	18mg/0.45mL	24
15	15 mg	0.38 mL	18mg/0.45mL	24
20	20 mg	5 mL	28mg/0.7mL	24
25	25 mg	1.63 mL	28mg/0.7mL	24
30	30 mg	0.75 mL	40mg/mL	24
35	35 mg	0.88 mL	40mg/mL	24
40	40 mg	1 mL	40mg/mL	24
50	50 mg	0.5 mL	80mg/0.8mL	24
60	60 mg	1.6 mL	80mg/0.8mL	24
70	70 mg	0.7 mL	80mg/0.8mL	24
80	80 mg	0.8 mL	80mg/0.8mL	24

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated the age of onset of symptoms from 12 years of age to 18 years of age. Updated renewal criteria to be limited to requirements around being prescribed by a specialist, confirmation of indication, and documented improvements in signs/symptoms rather than repetition of all initial criteria.	12/2020
Transfer to policy format. Added NMC and Supportive Evidence sections. Addition of criterion for appropriate diagnosis, as is recommended by compendia and medical literature. Addition of requirement of diagnosis by a specialist: diagnosis requires assessment of multiple laboratory levels, and combined/compared with clinical presentation. Potential for differential diagnosis is high. Change to initial approval of six months and renewal at 12 months from 3 month initial approval and 6 month renewal. As the overall benefit of Strensiq is seen over the course of pediatric development, a longer renewal period was implemented.	09/2019
Previous reviews	8/2017
Policy created	11/2015

Policy Type: PA/SP Pharmacy Coverage Policy: UMP237

Description

Avacopan (Tavneos) is a complement C5a receptor antagonist for the treatment of antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
avacopan (Tavneos)	10 mg capsules	Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis	180 capsules/30 days

Initial Evaluation

I. **Avacopan (Tavneos)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a nephrologist, rheumatologist, pulmonologist, or a specialist in the treatment of vasculitis associated disorders; **AND**
   C. A diagnosis of **antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV)** when the following are met:
      1. Diagnosis is classified as **granulomatosis with polyangiitis (GPA)** or **microscopic polyangiitis (MPA)**; **AND**
      2. Presence of organ-threatening manifestations (e.g., severe and progressive kidney involvement, severe lung or nervous system involvement); **AND**
      3. Treatment with high dose glucocorticoids in combination with standard of care agents (e.g., cyclophosphamide, rituximab) has been ineffective, contraindicated, or not tolerated; **AND**
      4. INDUCTION: Medication will be used in combination with cyclophosphamide or rituximab (e.g., Rituxan, Ruxience); **AND**
      5. MAINTENANCE: Medication will **NOT** be used in combination with rituximab (e.g., Rituxan, Ruxience)

II. Avacopan (Tavneos) is considered investigational when used for all other conditions, including but not limited to:
   A. MPA or GPA in patients less than 12 years of age
   B. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
   C. Systemic lupus erythematosus

D. IgA vasculitis
E. Rheumatoid vasculitis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. For maintenance treatment, medication will **NOT** be used in combination with rituximab (e.g., Rituxan, Ruxience); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., achievement of long-standing remission, decrease in rates of relapse); **OR**
V. Medication will be used for induction treatment in combination with cyclophosphamide or rituximab (e.g., Rituxan, Ruxience)

Supporting Evidence

I. ANCA-associated vasculitis (AAV) are a group of rare autoimmune disorders characterized by inflammation and destruction of small to medium-sized blood vessels and presence of circulating ANCA. Specific subtypes include GPA, MPA, renal-limited vasculitis, and eosinophilic granulomatosis with polyangiitis (EGPA). The presentation of AAV is highly variable and spectrum of disease may range from relatively mild and localized to the upper respiratory tract to life-threatening involvement of multiple organ systems. If left untreated AAV is a fatal disorder, with the main cause of death due to respiratory or renal failure.
II. Assessment of AAV requires expert guidance to differentiate activity from damage or infection and to consider differential diagnoses. Patients may require interventions by multiple different specialists depending on organ involvement and disease severity and may require services such as immunological monitoring, specialized radiography, assessment of eye involvement, and renal transplantation. The 2015 European League Against Rheumatism (EULAR) clinical guidelines recommend that all AAV patients should be managed in close collaboration with, or at, centers of expertise (Grade of recommendation: C).
III. The diagnosis of GPA or MPA is suspected in patients presenting with constitutional symptoms (e.g., fever, weight loss, arthralgias) with clinical evidence of renal or respiratory tract involvement. Testing for ANCA should be performed using assays for proteins within neutrophils called proteinase 3 (PR3) and myeloperoxidase (MPO). Approximately 82 to 94 percent of patients with either GPA or MPA have a positive ANCA, depending on severity of disease. GPA is primarily associated with PR3-ANCA (65 to 75 percent of cases), while MPA is primarily associated with MPO-ANCA (55 to 65 percent of cases). A negative assay does not exclude the diagnosis of GPA or MPA and ANCA status may change over time. Tissue biopsies should be considered in cases of suspected AAV to confirm diagnosis. Tissue biopsy is particularly important in patients who are ANCA-negative or in whom there is a degree of diagnostic uncertainty. A negative or “nondiagnostic” biopsy does not exclude a diagnosis of AAV as diagnostic sensitivities vary depending on the organ biopsied.

IV. Disease severity is characterized as either organ or life threatening or non-organ threatening. Examples of non-organ threatening disease include skin involvement without ulceration, myositis, nasal, and paranasal disease without bony involvement or cartilage collapse. For non-organ threatening disease treatment with methotrexate or mycophenolate is preferred. For organ or life threatening disease, treatment with cyclophosphamide or rituximab is indicated.

V. Treatment of patients with AAV is comprised of two phases: induction and maintenance. Induction treatment typically lasts for three-to-six months with the goal of establishing remission. For some induction may extend for longer than 6 months, however this is not common. The optimal duration of maintenance is unknown. Therapy for induction and maintenance is chosen based on the severity of disease. The 2015 EULAR clinical guidelines recommend induction treatment based on severity of the disease:

Induction/relapse

- New onset organ-threatening or life threatening AAV – combination of high-dose glucocorticoids and either cyclophosphamide OR rituximab (Grade of recommendation: A)
- Non-organ threatening AAV – combination of high-dose glucocorticoids and either methotrexate or mycophenolate mofetil (Grade of recommendation: B for methotrexate, C for mycophenolate mofetil)

Maintenance: Combination of low-dose glucocorticoids initially and either azathioprine, rituximab, methotrexate or mycophenolate mofetil for at least 24 months following sustained remission (Grade of recommendation: A)

VI. Avacopan (Tavneos) was studied in one 52-week, randomized, double-blind, double-dummy, Phase 3 clinical trial in 331 patients with newly diagnosed or relapsed GPA or MPA, in whom treatment with cyclophosphamide or rituximab was indicated. Enrolled patients were 12 years of age or older, with median patient age of 61 years. Avacopan (Tavneos) was studied at an oral dose of 30 mg twice daily against oral prednisone taper over a 21-week period (6 0mg, 45 mg for patients <55 kg and 30 mg for patients <37 kg per day starting dose). All patients received cyclophosphamide followed by azathioprine (or mycophenolate mofetil) or rituximab. Patients were allowed to receive glucocorticoid rescue therapy and to continue glucocorticoids for non-vasculitis reasons. The primary efficacy outcomes were clinical remission at week 26 and sustained remission at week 52 and no receipt of glucocorticoids for 4 weeks before evaluation of efficacy endpoints.

Primary Endpoints	Avacopan (n=166)	Prednisone (n=164)	Difference (95% CI)	p-value
Remission at wk 26, no %	120 (72.3)	115 (70.1)	3.4 (-6.0-12.8)	**Noninferiority: p<0.001** Superiority: p=0.24
Sustained remission at wk 52, no %	109 (65.7)	90 (54.9)	12.5 (2.6-22.3)	**Noninferiority: p<0.001 Superiority: p=0.007**

VII. Safety profile of avacopan (Tavneos) is still developing and is limited to a small population, 166 patients who received at least one dose of avacopan (Tavneos) and 134 who received it for more than six months. Overall a similar proportion of patients in both treatment arms experienced adverse events (AEs), including serious adverse events (SAEs) and AEs leading to discontinuation. SAEs occurred in 42.2% vs 45.1% of the avacopan (Tavneos) and prednisone arms, respectively. Common SAEs included ANCA-positive vasculitis, 7.2% vs 12.2%; pneumonia, 4.8% vs 3.7%; GPA, 3% vs 0.6%; acute kidney injury 1.2% vs 0.6%; and urinary tract infection

1.8% vs 1.2% in the avacopan (Tavneos) and prednisone arms, respectively. There were more patients in the avacopan (Tavneos) group than in the prednisone group that experienced SAEs of abnormality on liver-function testing, 5.4% vs 3.7%, respectively. More patients experienced AEs related to glucocorticoids in the prednisone group than in the avacopan (Tavneos) group, 80.5% vs 66.3%, respectively.

VIII. The place in therapy for avacopan's (Tavneos) is evolving; however, it is currently limited by evidence gathered from one Phase 3 clinical trial with a small safety database. High dose glucocorticoids have a known safety profile and remain highly effective when used in combination with the standard of care (e.g., cyclophosphamide, rituximab) to induce remission. This coupled with absence of significant differences in the observed adverse events seen in patients treated with avacopan (Tavneos), makes high dose glucocorticoids an appropriate first-line treatment option. Though there were fewer steroid related adverse events noted in the avacopan (Tavneos) arm during the pivotal clinical trial, the majority of adverse events expected with a prednisone taper when starting with a high dose are predictable, manageable, and transient. At this time, insight to the safety profile and cost-effectiveness of glucocorticoids are favorable to avacopan (Tavneos).

IX. Maintenance therapy is initiated after successful induction of remission. Avacopan (Tavneos) has not been studied in combination with rituximab as maintenance therapy. Further studies are needed to establish safety and efficacy of this combination therapy. At this time it is unknown whether efficacy may be additive if these therapies are used in combination, and safety of this combination is unknown.

Investigational or Not Medically Necessary Uses

I. Avacopan (Tavneos) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. MPA or GPA in patients less than 12 years of age
   B. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
   C. Systemic lupus erythematosus
   D. IgA vasculitis
   E. Rheumatoid vasculitis

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria in the renewal section which ensures medication will not be used in combination with rituximab for maintenance and if used for induction treatment, medication will be used in combination with cyclophosphamide or rituximab and does not require attestation of achieved remission.	01/2022

Policy created	08/2021

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Policy Type: PA/SP Pharmacy Coverage Policy: UMP181

Split Fill Management*

Description

Avapritinib (Ayvakit) is an orally administered tyrosine kinase inhibitor that acts on platelet-derived growth factor receptor alpha (PDGFRA) and v-kit Hardy Zukerman 4 feline sarcoma viral oncogene homolog (KIT) mutants.

Length of Authorization

- N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
avapritinib (Ayvakit)	Unresectable or metastatic Gastrointestinal Stromal Tumor with a PDGFRA exon 18 mutation Advanced Systemic Mastocytosis, including aggressive systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm and mast cell leukemia	300 mg tablets	30 tablets/30 days
		200 mg tablets	
		100 mg tablets	
		50 mg tablets	
		25 mg tablets	
	Indolent Systemic Mastocytosis	25 mg tablets	30 tablets/30 days

Initial Evaluation

I. **Avapritinib (Ayvakit)** is considered investigational when used for all conditions, including but not limited to gastrointestinal stromal tumor (GIST), advanced systemic mastocytosis (AdvSM) [e.g., aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), mast cell leukemia (MCL)], and indolent systemic mastocytosis (ISM).

Renewal Evaluation

I. N/A

Supporting Evidence

I. Avapritinib (Ayvakit) is FDA-approved for the treatment of adults with unresectable or metastatic GIST harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations, adult patients with advanced systemic mastocytosis (AdvSM), including patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), and mast cell leukemia (MCL), and adults with indolent systemic mastocytosis (ISM) whose symptoms are not adequately controlled by best supportive care (BSC).

II. Avapritinib (Ayvakit) has not been evaluated in patients under the age of 18; therefore, its safety and efficacy in the pediatric population is unknown.

III. Avapritinib (Ayvakit) has not been sufficiently evaluated for safety and/or efficacy in combination with any other oncolytic medication. Avapritinib (Ayvakit) has been studied when used in combination with BSC therapies (e.g., antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc.) in patients with systemic mastocytosis.

IV. Due to the complex nature of treating any of the diagnoses listed above, treatment with avapritinib (Ayvakit) should be prescribed by, or in consultation with, an oncologist. When being requested for systemic mastocytosis, treatment may be prescribed by, an oncologist, allergist, immunologist gastroenterologist, or dermatologist.

V. **Gastrointestinal Stromal Tumors (GIST)**

   a. The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology guidelines state most PDGFRA mutations respond to imatinib (Gleevec), with the exception of PDGFRA D842V mutants, which do not respond to current TKI therapies [e.g. imatinib (Gleevec), sunitinib (Sutent), regorafenib (Stivarga)]. Avapritinib (Ayvakit) carries a category 2A recommendation as a preferred first line regimen for patients with unresectable, progressive, or metastatic GIST with a PDGFRA exon 18 mutations that are insensitive to imatinib (including PDGFRA D842V). Avapritinib (Ayvakit) is also listed under “useful in certain circumstances” as an additional treatment option after progression on approved therapies.

   b. GIST tumors have the following mutation prevalence: 75%-80% are KIT mutated, 5%-10% are PDGFRA mutated, and 10%-15% do not express KIT or PDGFRA. PDGFRA D842V mutants make up 60% of all PDGFRA mutations.

   c. In an international survey, imatinib (Gleevec) had a median progression free survival (PFS) of 2.8 months for patients with a D842V substitution and 28.5 months for patients with other PDGFRA mutations. In 46 months of follow-up, median overall survival was 14.7 months for patients with D842V substitutions and was not reached for patients with other PDGFRA mutations.

   d. Avapritinib (Ayvakit) was FDA-approved off interim analysis of one Phase 1, open-label, single-arm trial (NAVIGATOR) in 43 patients with unresectable or metastatic GIST that is PDGFRA positive. Patients included had previously tried and failed one or more previous TKIs. The primary efficacy outcome was overall response rate (ORR), and at interim analysis, it was 84% (95% CI 69, 93), and 89% (95% CI 75, 97) for the PDGFRA exon 18 group, and PDGFRA D842V group, respectively. Secondary outcomes included duration of response (DOR), and PFS, which were only reported for the PDGFRA D842V group.

DOR was 27.6 months (95% CI 14.3, 27.6), and median PFS was 29.5 months (95% CI not reported).

1. At trial completion, the ORR in the *PDGFRA* D842V population (n = 56), 91% (51/56 patients). The DOR was 27.6 months (95% CI: 17.6 – not reached [NR]); the median PFS was 34.0 months (95% CI: 22.9 – NR); median OS was not reached.

e. Single-arm, open-label clinical trials may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between drug use and patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.
f. The quality of the current evidence for avapritinib (Ayvakit) is considered low. The primary outcome, ORR, has not yet been correlated to clinically meaningful outcomes such as overall survival or quality of life parameters in GIST. The PFS result has unknown value due to the small sample size as well as the single arm, open-label design, and the medications significant safety profile. There is a lack of evidence indicated that avapritinib (Ayvakit) would provide a net health benefit for members.
g. Clinical trials initially started avapritinib (Ayvakit) at 400 mg daily but reduced the dose to 300 mg due to toxicity. Of the patients receiving 400 mg and 300 mg, 97% and 72% experienced AEs of grade ≥3 severity, respectively. There was no noted difference in efficacy between the 400 mg and 300 mg doses.
h. Avapritinib (Ayvakit) showed a 49% dose reduction rate, a 57% dose interruption rate, and a 22% permanent discontinuation rate due to intolerable adverse events.
i. Avapritinib (Ayvakit) has notable serious side effects for anemia (9%), abdominal pain (3%), pleural effusion (3%), sepsis (3%), gastrointestinal hemorrhage (2%), vomiting (2%), acute kidney injury (2%), pneumonia (1%), and tumor hemorrhage (1%). Almost all patients experienced one AE (99%), with the most common AEs (>20%) being: edema, nausea, fatigue, cognitive impairment, vomiting, decreased appetite, diarrhea, increased lacrimation, abdominal pain, constipation, rash, dizziness, and hair color changes. There are no specific contraindications to using avapritinib (Ayvakit); however, warnings and precautions include: intracranial hemorrhage, central nervous system effects (e.g., cognitive impairment, dizziness, sleep disorders), and embryo-fetal toxicity.
j. The VOYAGER trial was a randomized, open-label, phase 3 clinical trial evaluating PFS, ORR, and OS of avapritinib (Ayvakit) against regorafenib (Stivarga) in patients with locally advanced unresectable or metastatic GIST. There was no significant difference in median PFS between avapritinib and regorafenib in patients with molecularly unselected, late-line GIST. In May 2020, the FDA issued a complete response letter stating that it will not approve a new drug application for avapritinib for use in the treatment of adult patients with unresectable or metastatic fourth-line GIST based on data from VOYAGER.

VI. **Advanced Systemic Mastocytosis (AdvSM)**

a. Systemic mastocytosis (SM) is a rare, clonal neoplastic proliferation of mast cells driven by the *KIT*D816V mutation, resulting in uncontrolled proliferation and activation of abnormal mast cells in various tissues, including skin, bone marrow, gastrointestinal tract, liver, spleen, and lymph nodes. Advanced systemic mastocytosis (AdvSM) accounts for approximately 5% of all SM cases and includes the following disease variants: aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).
b. According to NCCN guidelines for systemic mastocytosis, as of May 2022, treatment options for AdvSM include cytoreductive therapy, allogenic HCT, and enrollment in clinical trials. Cytoreductive therapies include avapritinib, midostaurin, cladribine, imatinib, and peginterferon alfa-2a ± prednisone. The guidelines note the following treatment considerations for AdvSM, all with category 2A recommendations:
    1. Preferred regimens: Avapritinib and midostaurin
    2. Other recommended regimens: Cladribine for patients that may require when rapid debulking of disease. Peginterferon alfa-2a, has a cytostatic mechanism of action and may be more suitable for patients with slowly progressive disease without the need for rapid cytoreduction
    3. Useful in certain circumstance: Imatinib is FDA-approved for adult patients with ASM without the KIT D816V mutation (including wild-type) or with unknown mutational status. Imatinib included as a treatment option for patients with ASM (for KIT D816V mutation negative or unknown, WDSM, or if eosinophilia is present with FIP1L1-PDGFRA fusion gene may also be considered as another treatment option for patients diagnosed with ASM or SM-ANH.
c. Avapritinib (Ayvakit) was FDA-approved based on the data from one phase 1 (EXPLORER) and a prespecified interim analysis of the phase 2 (PATHFINDER) multicenter, single-arm, open-label clinical trials. Patients were considered evaluable if they had a confirmed diagnosis of AdvSM per World Health Organization (WHO) and met modified international working group-myeloproliferative neoplasms research and treatment-European competence network on mastocytosis (IWG-MRT-ECNM) criteria at baseline. There were 48 evaluable patients in the EXPLORER trial and 32 patients in the PATHFINDER trial at interim analysis. The primary efficacy endpoint in the PATHFINDER trial was overall response rate (ORR), which was 75%. A favorable ORR was observed in the EXPLORER trial, which was 75% (95% CI, 62 – 86). Additional efficacy outcome measures included duration of response (DOR) and time to response; the median DOR for all evaluable patients was 38.3 months (95% CI, 19, not estimable) and time to response was 2.1 months.
d. A pooled efficacy and safety analysis from the EXPLORER and PATHFINDER trials compared avapritinib and best available therapy in patients with AdvSM who received ≥1 systemic therapy prior to avapritinib. The ORR in n=31 evaluable patients was 71% (95% CI: 52 – 86), including 19% with complete remission (CR)/CR with partial recovery of peripheral blood counts (CRh). Median OS was not reached (median follow-up 17.7 months). Median time to response was 2.3 months, median time to CR/CRh was 7.4

months. The median duration of response (DOR) was not reached. Median OS was significantly improved in patients treated with avapritinib (49.0 months [95% CI, 46.9 months–not estimable] vs. 26.8 months [95% CI, 18.2–39.7 months]; adjusted HR, 0.48; 95% CI, 0.29–0.79; P = .004). Data further demonstrated that avapritinib treatment was associated with improved OS compared to midostaurin (HR, 0.59; 95% CI, 0.36–0.97; P < .001) and cladribine (HR, 0.32; 95% CI, 0.15–0.67; P = .003). OS was also improved in patients with SM-AHN treated with avapritinib compared to best available therapy. The efficacy of avapritinib in patients with AdvSM was established irrespective of prior therapies or S/A/R mutation status.

e. Single-arm, open-label clinical trials may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.
f. Based on information from the EXPLORER and PATHFINDER trials, the quality of evidence is considered low at this time given the single-arm, open-label trial design and use of surrogate marker as the primary efficacy outcome. At this time, there is no correlation between ORR and clinically meaningful outcomes of morbidity and mortality or quality of life parameters. Therefore, the true efficacy of the medication remains unknown. The medication also has a significant safety profile that is under post-marketing review by the FDA. There is a lack of evidence indicating that avapritinib (Ayvakit) would provide a net health benefit for members.
g. Avapritinib (Ayvakit) is associated with notable serious side effects, including anemia (5%), subdural hematoma (4%), pleural effusion, ascites and pneumonia (3% each), acute kidney injury, gastrointestinal hemorrhage, intracranial hemorrhage, encephalopathy, gastric hemorrhage, large intestine perforation, pyrexia, and vomiting (2% each). Grade ≥3 cytopenias occurred in up to one-quarter of patients and facial/periorbital edema (any grade) in one-half (3 percent grade ≥3 facial/periorbital edema). No new safety signals were observed during the clinical trials for AdvSM.
h. In patients with AdvSM, a platelet count must be performed prior to initiating therapy and every 2 weeks first the first 8 weeks of starting therapy. Thrombocytopenia is listed as a warning/precaution for therapy when used in patients with AdvSM. Avapritinib (Ayvakit) is not recommended for the treatment of patients with AdvSM with platelet counts of less than 50 X 10^9/L.
i. The FDA has issued a post-marketing requirement to provide additional evaluation of the safety signals of intracranial hemorrhage and cognitive adverse reactions associated with avapritinib (Ayvakit), which can only be adequately assessed in clinical trials. This trial is anticipated to be submitted by 12/2021. The FDA has also issued a second post-marketing requirement to submit the completed phase 2 PATHFINDER trial data, which is anticipated to be completed 1/2026.

VII. **Non-advanced, indolent systemic mastocytosis (ISM)**

a. Indolent systemic mastocytosis (ISM) is defined as a rare, usually benign, chronic, form of systemic mastocytosis characterized by an abnormal accumulation of neoplastic mast cells mainly in the bone marrow, but also in other organs or tissues such as the skin. ISM accounts for more than 70% of all SM cases in published literature. One of the key diagnostic determinants that differentiates ISM from other SM subtypes includes absence of C-findings (are indicative of organ damage produced by mast cell infiltration via biopdy), no evidence of an associated hematologic neoplasm, low mast cell burden, and higher prevalence of skin lesions. Patients with ISM have a near-normal life expectancy, and ISM carries a low risk of progression with < 3% of patients progressing to a more severe form of systemic mastocytosis. The most common cause of death is disability or anaphylaxis.
b. Avapritinib (Ayvakit) is the first FDA-approved therapy for ISM. Approval was based on data from the randomized, double-blind, placebo-controlled part of the PIONEER trial, 141 patients received avapritinib (Ayvakit) 25 mg once daily + best supportive care (BSC) and 71 patients received placebo + BSC. The study included adults with an indolent SM diagnosis confirmed by central pathology review, and moderate-to-severe symptom burden despite an optimized regimen of BSC, which may include antihistamines, cromolyn, anti-IgE antibody, leukotriene receptor antagonists, corticosteroids, etc. All patients were able to continue symptom-directed therapy throughout the trial and, following completion of the 24-week treatment period, had the option to receive avapritinib (Ayvakit) in an open-label extension study (HARBOR trial). The primary endpoint was the change in patient-reported disease symptoms as assessed by the ISM Symptom Assessment Form (ISM-SAF) total symptom score (TSS) Key secondary endpoints include mean change in individual symptom scores of ISM-SAF, change in most severe symptom score, QoL, and several biomarkers of mast cell burden. Avapritinib (Ayvakit) achieved a statistically significant improvement in TSS compared to placebo at 24 weeks (p=0.003) and demonstrated statistically significant differences all key secondary endpoints, observed with improvements in severe symptoms and across all symptoms measured by the ISM-SAF that deepened over time.
c. The most common treatment-related AEs were headache (8 %), nausea (6%), peripheral edema (6%), periorbital edema (6%), and dizziness (3%). Across treatment arms, most adverse events were mild to moderate in severity, and treatment-related AEs leading to discontinuations were low for both arms (< 2% each). No new safety signals were observed during the clinical trials for ISM.
d. Data from this trial are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. It is unclear whether avapritinib (Ayvakit) provides a clinically meaningful improvement in a condition that is already indolent. Furthermore, the NCCN guideline acknowledges that the IWG-MRT-ECNM response criteria were developed mainly for use in clinical trials and may not be widely used in clinical practice. There is a lack of evidence indicating that avapritinib (Ayvakit) would provide a net health benefit for members with an already indolent form of SM.
e. The NCCN guidelines recommend observation or treating mast cell activation symptoms with best supportive care in patients with symptomatic ISM. The guidelines do not have

any pharmacotherapies listed in their treatment algorithm for ISM nor have avapritinib (Ayvakit) noted as a potential therapy option for ISM. Furthermore, the NCCN guidelines encourages enrollment in well-designed clinical trials investigating novel therapeutic strategies regardless of SM type. As of May 2023, an expanded access program (EAP) (NCT04714086) for avapritinib for patients with ISM is available, which may provide access to therapy in lieu of clinical trial enrollment.

Investigational or Not Medically Necessary Uses

I. Avapritinib (Ayvakit) has not been FDA-approved, OR sufficiently studied for safety and efficacy for any condition or setting to date, including those listed below:
   A. Gastrointestinal Stromal Tumor (GIST)
   B. Advanced systemic mastocytosis (AdvSM, ASM, SM-ANH, MCL)
   C. Non-advanced, indolent systemic mastocytosis (ISM)
   D. Non-advance, smoldering systemic mastocytosis (SMM)
   E. Soft tissue sarcoma
   F. Solid tumors with or without CKIT or PDGFRA mutations
   G. Acute myeloid leukemia (AML) with or without CKIT or PDGFRA mutations

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
regorafenib (Stivarga)	Gastrointestinal Stromal Tumors (GIST)
dasatinib (Sprycel)	Gastrointestinal Stromal Tumors (GIST)
ripretinib (Qinlock)	Gastrointestinal Stromal Tumors (GIST)
sunitinib (Sutent)	Gastrointestinal stromal tumors (GIST)
imatinib (Gleevec)	Gastrointestinal stromal tumors (GIST) Systemic mast cell disease (systemic mastocytosis)
midostaurin (Rydapt)	Systemic mast cell disease (aggressive systemic mastocytosis, systemic mastocytosis with hematological neoplasm, mast cell leukemia)
omalizumab (Xolair)	Systemic mastocytosis

Policy Implementation/Update

Action and Summary of Changes	Date
Added new indication of indolent systemic mastocytosis (ISM). Updated supporting evidence, E/I section, references for all indications. Added solid tumors and AML to E/I section. Added related policies section.	05/2023
Addition of new indication advanced systemic mastocytosis (AdvSM) and updated trial information for gastrointestinal stromal tumors (GIST)	10/2021
Policy created	05/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP169

Description

Avatrombopag (Doptelet®), eltrombopag olamine (Promacta®), eltrombopag choline (Alvaiz®), lusutrombopag (Mulpleta®) are thrombopoietin (TPO) receptor agonists that induce the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation, thus resulting in an increased production of platelets.

Fostamatinib (Tavalisse™) is a tyrosine kinase inhibitor (TKI) with activity against spleen tyrosine kinase (SYK). Fostamatinib metabolite, R406, inhibits signal transduction of Fc-activating receptors, B-cell receptors, and reduces antibody-mediated destruction of platelets.

Length of Authorization

- Initial:
  - **Avatrombopag (Doptelet)**
    - Thrombocytopenia associated with chronic liver disease, prior to planned procedure: one month
    - Chronic immune thrombocytopenia (ITP): Three months
  - **Eltrombopag olamime (Promacta)**
    - Chronic thrombocytopenia due to chronic hepatitis C: three months
    - Chronic Immune Thrombocytopenia (ITP): three months
    - First-line treatment severe aplastic anemia: six months
    - Severe aplastic anemia, refractory: four months
  - **Eltrombopag choline (Alvaiz)**
    - Chronic thrombocytopennia due to chronic hepatitis C: three months
    - Persistent or Chronic thrombocytopenia (ITP): Three months
    - Severe aplastic anemia, refractory: four months
  - **Lusutrombopag (Mulpleta)**
    - Thrombocytopenia associated with chronic liver disease, prior to planned procedure: one month
  - **Fostamatinib (Tavalisse)**
    - Chronic Immune Thrombocytopenia (ITP): three months

- Renewal:
  - **i. Avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse)**
    - Chronic Immune Thrombocytopenia (ITP), refractory severe aplastic anemia, chronic thrombocytopenia due to chronic hepatitis C: six months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
avatrombopag (Doptelet)	Thrombocytopenia associated with chronic liver disease, prior to planned procedure	20 mg tablet	15 tablets/ 30 days
	Chronic Immune Thrombocytopenia (ITP)		60 tablets/30 days
eltrombopag (Promacta)	Severe aplastic anemia	12.5 mg/1 packet	***[2 to 5 Years of age]*** 2.5mg/kg/day ***[6 to 11 Years of age]*** 30 packets/30 days (3 kits/30 days) ***[12 years and older]*** 30 packets/30 days (6 kits/30 days)
		25 mg/1 packet	***[2 to 5 Years of age]*** 2.5mg/kg/day ***[6 to 11 Years of age]*** 90 packets/30 days (3 kits/30 days) ***[12 years and older]*** 180 packets/30 days (6 kits/30 days)
		12.5 mg tablet	30 tablets/ 30 days
		25 mg tablet	30 tablets/ 30 days
		50 mg tablet	30 tablets/ 30 days
		75 mg tablet	60 tablets/ 30 days
	Chronic thrombocytopenia due to chronic Hepatitis C	12.5 mg/1 packet	30 packets/ 30 days (4 kits/30 days)
		25 mg/1 packet	120 packets/30 days (4 kits/30 days)
		12.5 mg tablet	30 tablets/ 30 days
		25 mg tablet	30 tablets/ 30 days
		50 mg tablet	60 tablets/ 30 days
		75 mg tablet	30 tablets/ 30 days
	Chronic immune thrombocytopenia (ITP)	12.5 mg/1 packet	30 packets/30 days (3 kits/30 days)
		25 mg/1 packet	90 packets/30 days (3 kits/30 days)
		12.5 mg tablet	30 tablets/ 30 days
		25 mg tablet	
		50 mg tablet	

		75 mg tablet	
lusutrombopag (Mulpleta)	Thrombocytopenia associated with chronic liver disease, prior to planned procedure	3 mg tablet	7 tablets/ 365 days
fostamatinib (Tavalisse)	Chronic Immune Thrombocytopenia	100 mg tablets	60 tablets/30 days
		150 mg tablets	
Eltrombopag Choline (Alvaiz)	Persistent or Chronic Immune Thrombocytopenia	9 mg tablet	30 tablets/30 days
		18 mg tablet	30 tablets/30 days
		36 mg tablet	30 tablets/30 days
		54 mg tablet	30 tablets/30 days
	Chronic Hepatitis C Thrombocytopenia	9 mg tablet	60 tablets/30 days
		18 mg tablet	60 tablets/30 days
		36 mg tablet	30 tablets/30 days
		54 mg tablet	30 tablets/30 days
	Severe Aplastic Anemia (refractory)	9 mg tablet	60 tablets/30 days
		18 mg tablet	60 tablets/30 days
		36 mg tablet	60 tablets/30 days
		54 mg tablet	60 tablets/30 days

Initial Evaluation

I. Avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), lusutrombopag (Mulpleta) and fostamatinib (Tavalisse) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a hematologist or gastroenterologist; **AND**
   B. Medication is not used in combination with another thrombopoietin (TPO) receptor agonists (e.g. avatrombopag, eltrombopag, lusutrombopag); **AND**
   C. A diagnosis of one of the following:
      1. **Chronic liver disease (CLD)-associated thrombocytopenia**; **AND**
         i. Member is 18 years of age or older; **AND**
         ii. Documentation of platelet count less than 50 x 10^9/L; **AND**
         iii. Request is for *avatrombopag (Doptelet) OR lusutrombopag (Mulpleta);* **AND**
            a. Member is scheduled to undergo an invasive procedure that carries an intermediate-to-high risk of bleeding (e.g. spinal surgery, cardiac surgery, large polypectomy, or liver biopsy); **OR**
         iv. Member has a documented diagnosis of **chronic Hepatitis C infection**; **AND**
            a. Member is unable to initiate or maintain interferon-based treatment [eg. pegylated interferon (Pegasys®) and ribavirin]; **AND**
            b. Request is for *eltrombopag olamine (Promacta)* tablets; **OR**
            c. Request is for *eltrombopag olamine (Promacta)* packets; **AND**

1. Member is unable to swallow tablets; **OR**

d. Request is for *eltrombopag choline (Alvaiz)* tablets; **AND**

i. The member has trialed and failed, had intolerance, or contraindication to using eltrombopag olamine (Promacta); **OR**

2. **Chronic Immune Thrombocytopenia; AND**

i. Treatment with first-line therapies (e.g corticosteroids, immunoglobulins, or splenectomy) have been ineffective, contraindicated, or not tolerated; **AND**

ii. Documentation of platelet count that is less than 30 x 10^9/L with symptoms of bleeding; **AND**

iii. Member is one year of age or older; **AND**

a. Request is for *eltrombopag olamine (Promacta)* tablet formulation; **OR**

b. Request is for *eltrombopag olamine (Promacta)* packets; **AND**

i. Member is unable to swallow tablets; **OR**

iv. Member is six years of age or older; **AND**

a. Request is for *eltrombopag choline (Alvaiz)* tablets; **AND**

i. The member has trialed and failed, had intolerance, or contraindication to using eltrombopag olamine (Promacta); **OR**

v. Member is 18 years of age or older; **AND**

a. Request is for *avatrombopag (Doptelet)*; **OR**

b. Request is for *fostamatinib (Tavalisse);* **OR**

i. **Severe aplastic anemia; AND**

i. Member has met at least two of the following three criteria:

1. Absolute neutrophil count (ANC) less than 500/microL; **OR**
2. Platelet count less than 20,000/microL; **OR**
3. Absolute reticulocyte count (ARC) less than 60,000/microL; **AND**

ii. Member has NOT received prior immunosuppressive therapy (IST) (e.g., request as first-line); **AND**

a. Member is two years of age or older; **AND**

b. *Eltrombopag olamine (Promacta)* will be initiated concurrently with immunosuppressive therapy (e.g., horse antithymocyte globulin (h-ATG) and cyclosporine); **OR**

iii. Member has severe aplastic anemia with refractory thrombocytopenia; **AND**

a. Treatment with at least one course of horse or rabbit anti-thymocyte globulin (ATG) and cyclosporine A (CSA) has been ineffective, contraindicated or not tolerated; **AND**

b. Request is for *eltrombopag olamine (Promacta)* tablet formulation; **OR**

c. Request is for *eltrombopag olamine (Promacta)* packets; **AND**

a. Member is unable to swallow tablets; **OR**

d. Request is for eltrombopag choline (Alvaiz) tablets; **AND**
    a. The member has trialed and failed, had intolerance, or contraindication to using eltrombopag olamine (Promacta)

II. Avatrombopag (Doptelet) is considered investigational when used for all other conditions, including but not limited to:
    A. Chemotherapy-induced thrombocytopenia in adults with active non-hematological cancers

III. Eltrombopag olamine (Promacta) is considered investigational when used for all other conditions, including but not limited to:
    A. Elderly patients with Acute Myeloid Leukemia receiving induction chemotherapy
    B. Prevention of chemotherapy induced thrombocytopenia
    C. Thrombocytopenia with chronic HBV infection
    D. Thrombocytopenia after consolidation therapy in acute myeloid leukemia (AML)
    E. Thrombocytopenia associated with myelodysplastic syndrome

IV. Eltrombopag choline (Alvaiz) is considered investigational when used for all other conditions, including but not limited to:
    A. Myelodysplastic syndromes: thrombocytopenia, monotherapy in adult patients
    B. Acute Myeloid Leukemia in adults

V. Lusutrombopag (Mulpleta) is considered investigational when used for all other conditions.

VI. Fostamatinib (Tavalisse) is considered investigational when used for all other conditions, including but not limited to:
    A. Malignancies:
        1. Advanced colorectal, non-small cell lung, head and neck hepatocellular and renal cell carcinomas, and pheochromocytoma and thyroid tumors
        2. B-cell Lymphoma
        3. Large B-Cell Lymphoma
        4. Ovarian Cancer
        5. T-Cell Lymphoma
    B. Rheumatoid Arthritis (RA)
    C. Renal Transplant Rejection (antibody mediated rejection)
    D. Chronic Graft vs. Host Disease

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms; **AND**

A. **Chronic thrombocytopenia due to chronic Hepatitis C**; **AND**

1. Member is unable to initiate or maintain interferon-based treatment [e.g. pegylated interferon (Pegasys®) and ribavirin]; **OR**

B. **Chronic Immune Thrombocytopenia**; **AND**

1. Platelet count has increased to greater than or equal to 50 x10^9/L; **OR**

C. **Severe aplastic anemia; AND**

1. Absolute neutrophil count (ANC) less than 500/microL at baseline; **AND**
   i. ANC has increased 100%; **OR**
   ii. An ANC increase greater than or equal to 500/microL; **OR**
2. Platelet count was less than 20,000/microL at baseline; **AND**
   i. Increase in platelet count has been greater than or equal to 20,000/microL from baseline; **OR**
   ii. Stable platelet counts with transfusion independence for ≥ 8 weeks; **OR**
3. Absolute reticulocyte count (ARC) less than 60,000/microL at baseline; **AND**
   i. There has been an increase in hemoglobin by 1.5 g/dL; **OR**
   ii. In patients receiving transfusions, there has been a reduction in red blood cell transfusions.

Supporting Evidence

I. The clinical trials for avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), lusutrombopag (Mulpleta), and fostamatinib (Tavalisse) did not include patients who were concomitantly using another TPO receptor agonists. Due to this, there is no data to assess the safety and efficacy of these agents when used concomitantly.

II. Considering the complexity of the indications and agents, they must be prescribed by, or in consultation with, a hematologist or gastroenterologist.

III. The safety and efficacy clinical trials of avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), and lusutrombopag (Mulpleta) for chronic liver disease (CLD)-associated thrombocytopenia, did not include patients younger than 18 years of age. Therefore, there is no clinical trial data to support the use of these agents in pediatric patients.

IV. Avatrombopag (Doptelet), eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz), and lusutrombopag (Mulpleta), for chronic liver disease (CLD)-associated thrombocytopenia, were studied in patients with a platelet count less than 50 x 10^9/L. This is because the risk for serious bleeding does not occur until the platelet count becomes very low–less than 10 x 10^9/L or 20 x 10^9/L, with the risk for mild bleeding occurring when the platelet count is less than 50 x 10^9/L. These agents should not be administered to patients with chronic liver disease, without associated thrombocytopenia or risk of surgical bleed, in an effort to normalize platelet counts (normal platelet count in adults ranges from 150 x 10^9/L to 450 x 10^9/L).

V. Avatrombopag (Doptelet) and lusutrombopag (Mulpleta) are indicated for the treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure that carries an intermediate-to-high risk of bleeding (e.g. spinal surgery, cardiac surgery, large polypectomy, liver biopsy). They should not be administered to patients with chronic liver disease, without associated thrombocytopenia or risk of surgical bleed, in an effort

to normalize platelet counts (normal platelet count in adults ranges from 150 x 10^9/L to 450 x 10^9/L).

VI. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) are indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. It should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. It should not be used to normalize platelet counts outside of this indication (normal platelet count in adults ranges from 150 x 10^9/L to 450 x 10^9/L).

VII. There is no safety and efficacy data to show superiority of one formulation over the other. The effectiveness of eltrombopag choline (Alvaiz) has been established based on adequate and well-controlled studies of eltrombopag olamine (Promacta) in adult and pediatric patients 6 years and older with persistent or chronic ITP, adult patients with chronic hepatitis C-associated thrombocytopenia, and adults patients with refractory severe aplastic anemia. In November 2023, Alvaiz was approved under the FDA accelerated approval 505(b)(2) process. The fundamental differences between the two salt forms: choline and olamine, respectively are the cost-effectiveness, dosage formulations, and differences of indications in both adult and patient populations. Eltrombopag choline (Alvaiz) has a reduced food effect therefore influencing the overall bioavailability for a patient in comparison to Eltrombopag olamine (Promacta). Per the package insert Alvaiz cannot be substituted with another eltrombopag product on a milligrams per milligrams basis. Although Alvaiz has reduced food effect, and therefore slightly increased bioavailability, the overall therapeutic effect remains similar to Promacta. This is reinforced by the package insert guidance to retain the same strict reduction of calcium intake (<50mg) and to refrain from administering Alvaiz 2 hours prior to and/or 4 hours post consumption of calcium and/or supplements containing polyvalent cations.

VIII. Avatrombopag (Doptelet), eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse) are indicated for the treatment of patients with chronic immune thrombocytopenia who have had an insufficient response to a first-line treatment (e.g. corticosteroids, immunoglobulins, or splenectomy).

IX. According to American Society of Hematology 2019 clinical guidelines thrombopoietin receptor agonists such as Eltrombopag olamine (Promacta) are considered second line therapy for management of immune thrombocytopenia.

X. Patients with platelet counts less than 30 x 10^9/L were included in clinical trials for avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse).

XI. The efficacy and safety of eltrombopag olamine (Promacta) in pediatric patients one year and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials. The trials differed in time since ITP diagnosis: at least 6 months versus at least 12 months. The primary endpoint was participants who achieved a platelet count greater than, or equal to, 50 x 10^9/L for at least six out of eight weeks, generally seen between weeks five and 12. Pediatric patients (75%) treated with eltrombopag olamine (Promacta), compared with placebo (21%), saw an increased value with at least one platelet count greater than, or equal to, 50 x 10^9/L during the first 12 weeks of randomized treatment in absence of rescue therapy. Platelet response to eltrombopag olamine (Promacta) was consistent across the age cohorts. Fewer pediatric

patients treated required rescue treatment during the randomized, double blind period compared with placebo-treated patients (13% [6/45] versus 50% [11/22]).

a. The safety and effectiveness of eltrombopag choline (Alvaiz) has not been established in pediatric patients less than 6 years of age with persistent or chronic ITP. Pediatric patients must be able to swallow eltrombopag choline (Alvaiz) tablets whole.

XII. The safety and efficacy clinical trials of avatrombopag (Doptelet) and fostamatinib (Tavalisse), for chronic ITP, did not include patients younger than 18 years of age.

- Fostamatinib (Tavalisse) is not recommended for use in patients less than 18 years of age because adverse effects on actively growing bones were observed in nonclinical studies. In subchronic, chronic, and carcinogenicity studies, chondrodystrophy of the femoral head was seen in rodents.

XIII. Eltrombopag olamine (Promacta) is indicated in combination with standard immunosuppressive therapy for the first-line treatment of severe aplastic anemia and of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. Eltrombopag choline (Alvaiz) does not share this indication with eltrombopag olamine (Promacta).

XIV. According to aplastic anemia & MDS international foundation (AAMDS) for a confirmed diagnosis of aplastic anemia the patient has to have met at least two of the following cell counts: absolute neutrophil count (ANC) less than 500/microL, platelet count less than 20,000/microL, or absolute reticulocyte count (ARC) less than 60,000/microL.

XV. Thirty-four patients, two to 16 years of age, were enrolled in Study US01T. The primary outcome was rate of complete hematologic response at six months. In the D1-M6 cohort, 7 and 17 out of 25 pediatric patients achieved a complete and overall response, respectively, at six months.

XVI. Ninety-two patients were enrolled in a prospective phase 1-2 study of immunosuppressive therapy plus eltrombopag olamine (Promacta). The three consecutively enrolled cohorts differed regarding the timing of initiation and the duration of the eltrombopag olamine (Promacta) regimen (cohort 1 received eltrombopag olamine (Promacta) from day 14 to six months, cohort 2 from day 14 to three months, and cohort 3 from day one to six months). The primary outcome was complete hematologic response at 6 months. Secondary end points included overall response, survival, relapse, and clonal evolution to myeloid cancer. The rate of complete response at 6 months was 33% in cohort 1, 26% in cohort 2, and 58% in cohort 3. The overall response rates at 6 months was 80% cohort 1, 87% cohort 2, and 94% cohort 3. The addition of eltrombopag olamine (Promacta) to immunosuppressive therapy (e.g. horse antithymocyte globulin (h-ATG) and cyclosporine) was associated with higher rates of hematologic response among patients with severe aplastic anemia than in a historical cohort.

XVII. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) was studied in a single-arm, single-center, open-label trial in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy.

XVIII. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. It should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. It should not be used to

normalize platelet counts (normal platelet count in adults ranges from 150 x 10^9/L to 450 x 10^9/L).

XIX. Treatment with avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse) should be discontinued after 12 weeks (three months) of treatment if platelet counts do not increase to a level sufficient to avoid clinically important bleeding (greater than or equal to 50 x10^9 /L – risk for serious bleeding doesn't occur until the count becomes very low—less than 10 x 10^9/L or 20 x 10^9/L, and for mild bleeding when the count is less than 50 x 10^9/L). These agents should not be administered to patients with chronic liver disease, that do not meet this criterion, in an effort to normalize platelet counts (normal platelet count in adults ranges from 150 x 10^9/L to 450 x 10^9/L).

XX. In the clinical trial, the primary end point was hematologic response at three to four months and defined as uni- or multilineage recovery by one or more of the following criteria: (1) platelet response (increase to 20 × 10^3/μL above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks in those who were transfusion dependent on entry into the protocol); (2) erythroid response (when pretreatment hemoglobin was <9 g/dL, defined as an increase in hemoglobin by 1.5 g/dL or, in transfused patients, a reduction in the units of packed red blood cell transfusions by an absolute number of at least 4 transfusions for 8 consecutive weeks, compared with the pretreatment transfusion number in the previous 8 weeks); and (3) neutrophil response (when pretreatment absolute neutrophil count [ANC] of <0.5 × 10^3/μL as at least a 100% increase in ANC, or an ANC increase >0.5 × 10^3/μL, and the toxicity profile as measured using Common Terminology Criteria for Adverse Events).

Investigational or Not Medically Necessary Uses

I. Avatrombopag (Doptelet)
   A. Chemotherapy-Induced Thrombocytopenia in adults with active non-hematological cancers
      i. A randomized, double-blind, placebo-controlled study with an open-label extension to evaluate the efficacy and safety of avatrombopag (Doptelet) for the treatment of chemotherapy-induced thrombocytopenia in subjects with active non-hematological cancers is still recruiting.
   B. There is limited or no published clinical trial data to support the use of avatrombopag (Doptelet) in conditions other than thrombocytopenia associated with chronic liver disease prior to planned procedure and chronic immune thrombocytopenia (ITP).

II. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz)
   A. Elderly Patients with Acute Myeloid Leukemia receiving induction chemotherapy (EPAG2015)
      i. A Phase II, randomized, placebo-controlled study to assess the impact on outcome of eltrombopag (Promacta) administered to elderly patients with acute myeloid leukemia receiving induction chemotherapy in 110 participants and is still recruiting.
   B. Prevention of chemotherapy induced thrombocytopenia
      i. A phase I/II open-label study of eltrombopag for the prevention of chemotherapy induced thrombocytopenia (CIT) in subjects with advanced soft tissue and bone sarcomas receiving gemcitabine and docetaxel chemotherapy was terminated.
   C. Thrombocytopenia with chronic HBV infection

i. A multicenter, single-arm, open-label study in 58 participants to evaluate the efficacy and safety of eltrombopag for thrombocytopenia in Chinese patients with chronic HBV infection is still recruiting.

D. Thrombocytopenia after consolidation therapy in acute myeloid leukemia (AML)
   i. Randomized, single arm, single-blind study in 220 participants of eltrombopag (Promacta) and eltrombopag choline (Alvaiz) in thrombocytopenia after consolidation therapy in acute myeloid leukemia (AML) is in recruiting stage.

E. Thrombocytopenia associated with myelodysplastic syndrome
   i. In a three-part study of eltrombopag in thrombocytopenic subjects with myelodysplastic syndromes or acute myeloid leukemia.
      1. Part 1 was an open-label with 17 patients receiving eltrombopag and 11 patients completing treatment. Primary endpoint was number of participants with platelet response up to week 8 and four experienced significantly increased platelet counts, and ten had reduced platelet transfusion requirements.
      2. Part 2 was a randomized, double-blind with 145 patients who received supportive care plus eltrombopag (n=98) or placebo (n=47). Primary outcome was clinically relevant thrombocytopenic events (CRTE) from week 5 up to week 12. Average weekly CRTE were significantly lower with eltrombopag (54% [95% CI 43-64]) than with placebo (69% [57-80], odds ratio [OR] 0·20, 95% CI 0·05-0·87; p=0·032) although the difference between treatment groups was less than 30%. Serious adverse events were reported in 56 (58%) eltrombopag-treated patients and 32 (68%) placebo-treated patients. Seven eltrombopag recipients and two placebo recipients had serious adverse events that were suspected to be study drug-related (acute kidney injury, arterial thrombosis, bone pain, diarrhea, myocardial infarction, pyrexia, retinal vein occlusion, n=1 each; placebo: vomiting, white blood cell count increased, n=1 each). Two eltrombopag recipients had arterial thrombosis n=1 and myocardial infarction n=1. No placebo recipients experienced fatal or serious adverse events suspected to be study drug related.
      3. Part 3 is an extension ongoing study.
      4. Overall the clinical trial had a small patient population, showed limited efficacy and had questionable safety.
   ii. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukemia was completed in a multicenter, randomized, placebo-controlled, double-blind, phase 1/2 trial.
      1. Primary outcome was safety and tolerability parameters including non-hematological laboratory Grade 3/Grade 4 toxicities, change in bone marrow blast counts from baseline, and adverse events reporting. [Time Frame: Approximately 46 months].
      2. Ninety-eight patients were randomized to receive either eltrombopag (n=64) or placebo (n=34). Sixty-three (98%) patients in the eltrombopag

group and 32 (94%) patients in the placebo group had adverse events. The most common adverse events were pyrexia (27 [42%] vs 11 [32%]), nausea (20 [31%] vs 7 [21%]), diarrhea (19 [30%] vs 6 [18%]), fatigue (16 [25%] vs 6 [18%]), decreased appetite (15 [23%] vs 5 [15%]), and pneumonia (14 [22%] vs 8 [24%]). Drug-related adverse events of grade 3 or higher were reported in six (9%) patients in the eltrombopag group and four (12%) patients in the placebo group.

3. In this clinical trial efficacy was not assessed.

F. There is limited or no published clinical trial data to support the use of eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) in conditions other than severe aplastic anemia, chronic thrombocytopenia due to chronic hepatitis C, and chronic immune thrombocytopenia (ITP).

III. Lusutrombopag (Mulpleta)

A. There is limited or no published clinical trial data to support the use of lusutrombopag (Mulpleta) in conditions other than thrombocytopenia associated with chronic liver disease prior to a planned procedure.

IV. Fostamatinib (Tavalisse)

A. Malignancies

i. Advanced colorectal, non-small cell lung, head, and neck, hepatocellular and renal cell carcinomas, pheochromocytoma, and thyroid tumors

1. A broad, multi-histology, single group assignment, open label, phase II study of the multi-kinase inhibitor R935788 (fostamatinib disodium) in advanced colorectal, non-small cell lung, head and neck, hepatocellular and renal cell carcinomas, pheochromocytoma, and thyroid tumors in in 37 participants.
2. Fostamatinib had limited anti-tumor activity in this first clinical trial in patients with advanced refractory solid tumors; reduction in CECs and CEPs was indicative of anti-angiogenic effects. Abnormal liver testing at baseline appeared to influence drug tolerability.

B. B-cell Lymphoma

i. A Phase I/II, multi-Center, single group assignment, open label trial of the safety and efficacy of fostamatinib in 81 patients with relapsed/refractory B-cell lymphoma. The clinical trial showed limited efficacy and considering it is an open label, single group trial, further clinical research is necessary to show efficacy and safety.

C. Large B-cell lymphoma, relapsed or refractory

i. Phase II, single group assignment, open label trial with 101 participants to evaluate the efficacy of fostamatinib in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The clinical trial showed limited efficacy and considering it is an open label, single group trial, further clinical research is necessary to show efficacy and safety.

D. Ovarian cancer

i. Phase I, single group assignment, open label clinical trial of combined fostamatinib and paclitaxel in ovarian cancer with 18 participants and still recruiting.

E. T-cell lymphoma
    i. Phase II, multicenter, open label, single assessment group, simon two-stage study of fostamatinib disodium in patients with relapsed or refractory T-cell lymphoma in 18 participants. The clinical trial was not blinded or randomized. It wasn't powered enough to show efficacy or safety of fostamatinib (Tavalisse) in T-cell lymphoma.
F. Rheumatoid arthritis (RA)
    i. A Long-term, open label, single assignment study to assess the safety of fostamatinib in the treatment of rheumatoid arthritis in Asia was terminated.
    ii. A Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of two dosing regimens of fostamatinib in patients with rheumatoid arthritis with an inadequate response to a tumor necrosis factor-α antagonist.
    iii. Adult patients were randomized (1:1:1) to fostamatinib [100 mg bid for 24 weeks (n=105; Group A)], or 100 mg bid for 4 weeks, then 150 mg qd (n=108; Group B), or to placebo (n=110; Group C) for 24 weeks. Nonresponders at Week 12 could enter a long-term extension study. The primary endpoint was the proportion of patients achieving an American College of Rheumatology 20% (ACR20) response at Week 24.
    iv. Due to efficacy and safety results from the clinical trial, the companies developing fostamatinib have decided not to study it further in RA at this time.
G. Renal Transplant Rejection (antibody mediated rejection)
    i. Fostamatinib is being studied in a phase 2, single center, not randomized, open label, pilot study to assess the safety and efficacy of fostamatinib in the treatment of chronic active antibody mediated rejection in renal transplantation is still recruiting.
H. Chronic Graft vs. Host Disease
    i. A phase I, open label, single group assignment trial of fostamatinib and chronic graft vs. host disease development after allogeneic stem cell transplantation with 18 participants is still recruiting.
I. There is limited or no published clinical trial data to support the use of fostamatinib (Tavalisse) in conditions other than chronic immune thrombocytopenia (ITP).

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Policy Implementation/Update

Action and Summary of Changes	Date
Added eltrombopag choline (Alvaiz) for the treatment of persistent or chronic immune thrombocytopenia in adult and pediatric patients 6 years of age and older, chronic Hepatitis C-associated thrombocytopenia, and severe aplastic anemia (refractory). Updated supporting evidence, references, and formatting.	03/2024
Added new strength of 25mg eltrombopag (Promacta) packet for oral suspension	05/2020
• Added investigational indications for avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) • Added age limits to eltrombopag (Promacta) for immunosuppressive naive Severe aplastic anemia at two years of age or older, and relapsed or refractory severe aplastic anemia at 18 years of age or older. • Added criteria for Severe aplastic anemia; [Member has to meet at least two of the following three criteria are met: 1) Absolute neutrophil count (ANC) less than 500/microL, or 2) Platelet count less than 20,000/microL, or 3) Absolute reticulocyte count (ARC) less than 60,000/microL • Added member is 18 years of age or older if request is for avatrombopag (Doptelet), fostamatinib (Tavalisse) and fostamatinib (Tavalisse) [for chronic ITP] • Added criteria if request is for eltrombopag (Promacta) packets, member has demonstrated inability to swallow tablets • Changed QL for eltrombopag (Promacta) packets • Changed QL for avatrombopag (Doptelet) for chronic immune thrombocytopenia (ITP) • Changed initial and renewal length of authorization for all agents • Combined as one policy: avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) with fostamatinib (Tavalisse)	02/2020
Previous reviews fostamatinib (Tavalisse)	06/2018, 11/2019,
Conversion to policy format fostamatinib (Tavalisse)	11/2019
Avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) combined as policy: TPO-Receptor Agonists	10/2019
Previous reviews avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)	10/2019,
Policy created avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)	10/2019
Policy created fostamatinib (Tavalisse)	06/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP007

Split Fill Management*

Description

Axitinib (Inlyta) is an orally administered tyrosine kinase inhibitor, including vascular endothelial growth factor receptors (VEGFR) that are responsible for tumor growth, angiogenesis, and disease progression.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
axitinib (Inlyta)	1 mg tablets	Advance renal cell carcinoma	180 tablets/30 days
	5 mg tablets		60 tablets/30 days

Initial Evaluation

I. Axitinib (Inlyta) may be considered medically necessary when the following criteria below are met:
   A. Axitinib (Inlyta) is prescribed by, or in consultation with, an oncologist or urologist; **AND**
   B. A diagnosis of **Advanced Renal Cell Carcinoma (Relapsed or Stage IV)** when the following are met**:**
      1. Axitinib (Inlyta) will be used as monotherapy; **AND**
      2. Prior treatment with one of the following has been ineffective or not tolerated, unless ALL are contraindicated.
         i. sunitinib (Sutent)
         ii. temsirolimus (Torisel)
         iii. bevacizumab (Avastin)
         iv. pazopanib (Votrient)
         v. sorafenib (Nexavar)
         vi. everolimus (Afinitor); **OR**
      3. Axitinib (Inlyta) will be used in combination with pembrolizumab (Keytruda) as first-line therapy; **OR**
      4. Axitinib (Inlyta) will be used in combination with avelumab (Bavencio) as first-line therapy

II. Axitinib (Inlyta) is considered investigational when used for all other conditions, including but not limited to:

A. Non-metastatic Stage I-III Renal Cell Carcinoma

Renewal Evaluation

I. Tumor response is documented with stabilization of disease or decrease in size of tumor or tumor spread; **AND**
II. The member has an absence of unacceptable toxicity from the medication

Supporting Evidence

I. Axitinib (Inlyta) is indicated for advance renal cell carcinoma (RCC) after failure of one prior systemic therapy; or as first-line therapy when used in combination with pembrolizumab (Keytuda); or as first-line therapy when used in combination with avelumab (Bavencio).
II. The FDA approval of axitinib (Inlyta) in the setting of advanced RCC after failure of one prior systemic therapy was based on the results of a phase 3 trial (AXIS). In the AXIS trial, the primary end point was progression free survival in the intention-to-treat population. The median PFS was 6·7 months with axitinib compared to 4·7 months with sorafenib (hazard ratio 0·665; 95% CI 0·544-0·812; one-sided p<0·0001).
    - Note: Sunitinib (Sutent) is considered the first systemic agent to use for adjuvant treatment for all stages of RCC after primary treatment (surgical).
III. The FDA approval of pembrolizumab (Keytruda) in combination with axitinib (Inlyta) was based on the results of KEYNOTE-426, an open-label, phase 3 trial. In the KEYNOTE-426 trial, the primary end points were overall survival and progression-free survival in the intention-to-treat population. Statistical significance as achieved after a median follow-up of 12.8 months, the estimated percentage of untreated advanced RCC patients who were alive at 12 months was 89.9% in the pembrolizumab-axitinib group compared to 78.3% in the sunitinib group.
    - Note: Sunitinib (Sutent) is considered the first systemic agent to use for adjuvant treatment for all stages of RCC after primary treatment (surgical).
IV. The FDA approval of avelumab (Bavencio) in combination with axitinib (Inlyta) was based on positive results from the Phase III JAVELIN Renal 101 study, involving previously untreated advanced RCC patients. In the JAVELIN Renal 101 study, the median progression-free survival was 13.8 months with avelumab plus axitinib, as compared with 7.2 months with sunitinib.
    - Note: Sunitinib (Sutent) is considered the first systemic agent to use for adjuvant treatment for all stages of RCC after primary treatment (surgical).

Investigational or Not Medically Necessary Uses

I. Non-metastatic Stage I-III Renal Cell Carcinoma
    A. Axitinib (Inlyta) has not been studied in non-metastatic, non-advanced (stage I-III) renal cell carcinoma.

*The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

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Policy Implementation/Update:

Date Created	July 2012
Date Effective	April 2016
Last Updated	June 2019
Last Reviewed	03/2016, 06/2019

Action and Summary of Changes	Date
Transitioned criteria to policy. In this transition, the following updates were made: added new indication for advance renal cell carcinoma to use axitinib (Inlyta) in combination with pembrolizumab (Keytruda) or avelumab (Bavencion) as first-line therapy.	06/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP2018

Description

Azacitidine (Onureg) is an orally administered hypomethylating agent (HMA).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
azacitidine (Onureg)	Acute Myeloid Leukemia (AML), maintenance treatment after first complete remission	200 mg tablet	14 tablets/28 days
		300 mg tablet	

Initial Evaluation

I. **Azacitidine (Onureg)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. Medication will be used as monotherapy; **AND**
   D. A diagnosis of **acute myeloid leukemia (AML)** when the following are met:
      1. Provider attestation the member has intermediate or poor-risk disease; **AND**
      2. Member has achieved first complete remission (CR) after induction chemotherapy (e.g. cytarabine, idarubicin, daunorubicin, mitoxantrone); **AND**
      3. Member received at least one cycle of consolidation chemotherapy; **OR**
         i. Provider attests that the member is not able to receive any or all of the recommended consolidation therapy; **AND**
      4. Provider attests that the member is ineligible for allogenic hematopoietic stem cell transplant (HSCT); **AND**
   E. Treatment with IV or subcutaneous (SC) azacitidine (Vidaza) or IV decitabine (Dacogen) has been ineffective, contraindicated, or not tolerated

II. Azacitidine (Onureg) is considered Not Medically Necessary when used for:
   A. Treatment of Myelodysplastic syndrome (MDS)

III. Azacitidine (Onureg) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute myeloid leukemia- newly diagnosed (Induction chemotherapy)

B. Acute myeloid leukemia – maintenance following allogenic HSCT
C. Acute myeloid leukemia – relapsed after first remission
D. In combination with other oncolytic agents

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by stabilization or improvement of disease (e.g. maintenance of remission; lack of disease relapse or progression)

Supporting Evidence

I. Azacitidine (Onureg) is an orally administered HMA FDA-approved for the treatment of AML in patients aged 18 years and older. It is indicated for patients who have achieved first CR after induction chemotherapy and/or consolidation therapy.
II. Many treatment options exist for AML. Initial and further line therapies in this setting are contingent upon patient specific characteristics, disease-risk, and cytogenetic stratification. Given the complexities surrounding diagnosis and treatment choices, azacitidine (Onureg) must be prescribed by or in consultation with an oncologist or hematologist.
III. Currently, AML treatment is stratified by patient age, cytogenetic and molecular risk status, actionable mutations, AML disease characteristics and classification, and the patient's ability to tolerate intensive therapy based on comorbidities and performance status. Patients with AML are encouraged to enroll in clinical trials during any phase of treatment. Initial induction therapy for AML usually involves use of antimetabolite (e.g. cytarabine) in combination with anthracycline analogs (e.g. daunorubicin), also known as 7+3 regimen. Although majority of patients achieve CR, or complete remission with incomplete blood count recovery (CRi), post induction therapy, consolidation chemotherapy is recommended in order to prolong remission.
IV. Historically, induction therapy utilizing an intensive chemotherapy regimen (e.g., cytarabine and an anthracycline) has been the standard of care in AML patients with a good performance status who can tolerate aggressive initial treatment. Post-remission therapy, which includes consolidation, allogeneic HSCT, maintenance, and/or continued treatment, is tailored based on the patient's overall risk of AML relapse. Relapse rates for AML can be as high as 80% depending on patient age, cytogenetic and molecular abnormalities, and other factors. Intensive curative therapy (e.g., allogeneic HSCT) may not be a feasible option for many older patients due to comorbidities, poor performance status, and a high risk of transplant-related mortality. Additionally, some patients experience a deterioration in their condition between the start of induction and achievement of CR, others refuse HSCT, and disadvantaged populations with high levels of poverty and living in rural geographic counties have inferior access to HSCT, such that only a minority (8%) of treated patients with AML receive an allogeneic HSCT. In such cases, additional interventions to decrease the likelihood of relapse and improve survival are practical. Consolidation with successive cycles of AML-directed therapy may be recommended for patients

with relatively low risk of AML relapse, while allogeneic HSCT may be offered to eligible patients with intermediate and high risk of relapse. Azacitidine (Onureg) is indicated for continued treatment for adult patients, who had CR or CRi post induction chemotherapy, with or without consolidation, and who are unable to complete intensive curative therapy. NCCN guidelines for AML has included azacitidine (Onureg) as a maintenance therapy agent. However, consolidation chemotherapy is still a preferred option for patients with favorable risk cytogenetics and those who do not have comorbidities precluding use of intensive consolidation chemotherapy.

V. The use of azacitidine (Onureg) has not been studied in combination with other treatment regimens for AML, such as venetoclax (Venclexta) and midostaurin (Rydapt). Due to lack of safety and efficacy data with a combination regimen, these agents should not be used together. Additionally, there is no data to support efficacy of azacitidine (Onureg) in place of HSCT, which remains the curative therapeutic alternative for majority of patients.

VI. The efficacy and safety of azacitidine (Onureg) was evaluated in a Phase 3, double-blind, randomized, placebo-controlled trial (N= 472). Patient were randomized to receive an oral 300 mg dose of treatment or matching placebo for 14 days. Overall survival (OS) was the primary endpoint and relapse-free survival (RFS) was a key secondary outcome. Median treatment duration was 12 cycles. Patients included had intermediate or poor cytogenetic risk AML, who were not candidates for HSCT and had CR or CRi post induction and/or consolidation therapy. Patients with prior history of HMA were excluded. Overall survival for azacitidine (Onureg) treatment arm was 24.7 months (95% CI; 18.7, 30.5) as compared to that of 14.8 months (95% CI; 11.7, 17.6) for placebo the arm [hazard ratio 0.69 (95% CI; 0.55, 0.86; *p*= 0.0009]. Additionally, median RFS was 10.2 months vs 4.8 months for treatment vs placebo [HR 0.65 (95% CI; 0.52, 0.81; *p*= 0.0001)].

VII. During the clinical trial, dose escalation to a 21-day regimen of azacitidine (Onureg) was allowed for patients showing 5% to 15% bone marrow (BM) blasts during treatment phase. However, increased drug exposure did not lead to additional survival benefits. Currently, there is insufficient data to support a 21 day treatment cycle with azacitidine (Onureg).

VIII. The most common adverse events (AE) reported for azacitidine (Onureg) during clinical trial were nausea, vomiting, and diarrhea. Additionally, grade 3 to 4 hematological AEs such as neutropenia, thrombocytopenia, and febrile neutropenia were reported. Azacitidine (Onureg) treatment led to 13% treatment discontinuation, 43% dose interruption due to AEs, and 16% dose reduction rates.

IX. The NCCN guideline for the treatment of AML was updated in June 2022, which upgraded the recommendation to use oral azacitidine (Onureg) as a maintenance treatment for AML to a Category 1 recommendation. This recommendation is limited to patients, who are ≥ 55 years of age, have intermediate to poor cytogenetic risk, and have undergone a consolidation therapy, or are unable to receive any consolidation regimens. This criteria is consistent with the clinical trial design for azacitidine (Onureg) wherein majority of trial participants were ≥ 55 years of age. It is important to note that the efficacy and safety of azacitidine (Onureg) have not been compared with IV or subcutaneous azacitidine (Vidaza) via a head-to-head clinical trial and the current clinical data does not establish the superiority of oral azacitidine (Onureg) over IV or SC azacitidine (Vidaza). Additionally, IV and SC azacitidine formulations remain a guideline recommended alternative for patients ≥ 55 years (Category 2A recommendation). IV azacitidine is not contraindicated in patients ≥ 55 years, nor a dose adjustment is recommended based on age. Although not FDA approved, IV and SC formulations of azacitidine (Vidaza) have been

utilized as maintenance therapy of AML and are expected to remain mainstay treatment alternatives. For members < 55 years of age, who are medically fit, and are not candidates for HSCT, surveillance may be considered over maintenance therapy. Although NCCN guideline recommend use of oral azacitidine (Onureg) as a maintenance treatment in this population, the NCCN panel notes that the data surrounding the efficacy of azacitidine (Onureg) in this setting is limited to the older population (≥ 55 years of age). Additionally, as of June 2022, use of decitabine (Dacogen) as a maintenance therapy, has been updated to a Category 2B recommendation.

X. The majority of the safety and efficacy data for use of hypomethylating agents in the maintenance treatment of AML are rooted in the trials for the IV and SC therapies. Approval of azacitidine (Onureg) was based on the reported survival outcomes data of this oral formulation. However, there is no evidence to suggest superiority of oral azacitidine (Onureg) over IV/SC azacitidine (Vidaza) and/or IV decitabine (Dacogen). Weighing the safety, efficacy, cost, and clinical experience, IV/ SC therapies are considered standard and appropriate high-value treatment options in this space and are preferred over azacitidine (Onureg).

Investigational or Not Medically Necessary Uses

I. Efficacy and safety of azacitidine (Onureg) for treatment of MDS was studied in a Phase 3 trial wherein 300 mg of azacitidine (Onureg) or a matching placebo were administered once daily for 21 days per 28-day cycle in patients with RBC transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk MDS (AZA-MDS-003). Although azacitidine (Onureg) treatment showed higher percentage of patients reporting RBC transfusion independence versus placebo, the study was halted due to safety concerns related to an excess of early mortality due to hematological toxicities in the treatment arm.

II. Azacitidine (Onureg) is currently being studied in multiple clinical trials in the settings of MDS maintenance post HSCT, for maintenance therapy after HSCT in patients with AML, and for induction chemotherapy for newly diagnosed AML. However, there are no published results for these trials indicating efficacy and safety of azacitidine (Onureg) in these conditions.

References

1. Azacitidine (Onureg) prescribing information. Summit, NJ: Celgene Corporation; September 2020.
2. Estey, E H. Acute myeloid leukemia: 2019 update on risk-stratification and management. *Am J Hematol*. 2018;93(10):1267-1291.
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5. Garcia-Manero G, Savona MR, Gore SD, et al. CC-486 (oral azacitidine) in patients with hematological malignancies who had received prior treatment with injectable hypomethylating agents (HMAs): Results from phase 1/2 CC-486 studies. *Blood* (ASH Annual Meeting Abstracts) 2016b;128: Abstract 905.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
NCCN updated recommendation (Category 1) reviewed; PA policy unchanged; updated formatting and supporting evidence	11/2022
Policy created	02/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP008

Description

Aztreonam (Cayston) inhibits bacterial cell wall synthesis by binding to one or more penicillin-binding proteins (PBPs). Bacteria eventually lyse due to ongoing activity of cell wall autolytic enzymes while cell wall assembly is arrested.

Length of Authorization

- Initial: Six months
- Renewal: Twelve months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
aztreonam (Cayston)	75 mg/vial inhalation powder	Cystic Fibrosis (CF)	6,300 mg (84 vials)/28 days*

* total of 7 fills in one year

Initial Evaluation

I. Aztreonam (Cayston) may be considered medically necessary when the following criteria are met:
   A. Prescribed by, or in consultation with, a pulmonologist; **AND**
   B. Member is 7 years of age or older; **AND**
   C. A diagnosis of **cystic fibrosis with Pseudomonas aeruginosa** when the following are met:
      1. Member has FEV_1 of 25% to 75% predicted; **AND**
      2. Member is not colonized *with Burkholderia cepacia*

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., reduction of cough/wheezing, reduction in sputum production, improvement in FEV_1, decrease in pulmonary exacerbations)

Supporting Evidence

I. Aztreonam (Cayston) was studied in a randomized, double-blind, placebo-controlled, multicenter trial that enrolled 164 patients who were seven years of age or older with cystic fibrosis (CF) and pseudomonas aeruginosa (P. aeruginosa) colonization for a period of 28 days.

The treatment difference at Day 28 between the patients in the aztreonam (Cayston) arm and placebo arm were 10% (95% CI: 6%, 14%), the FEV_1 was statistically significant favoring the aztreonam (Cayston) arm.

II. Safety and effectiveness have not been established in a clinical trial in patients with FEV1 less than 25% or greater than 75% predicted, or patients colonized with Burkholderia cepacian.

References

1. Cayston [Prescribing Information]. Foster City, CA: Gilead Sciences, Inc. September 2012.

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria added: Member is not colonized with Burkholderia cepacia	06/2020
Criteria update: The FEV_1 requirements were added to initial criteria as that was part of the inclusion criteria. Additionally, renewal criteria and supporting evidence sections were added.	10/2019
Criteria update: quantity limit has been updated to reflect the clinical use of Cayston.	2/2019
Created and effective	07/2011

Policy Type: PA/SP Pharmacy Coverage Policy: UMP112

Description

Belimumab (Benlysta) is a subcutaneously administered human IgG1 lambda monoclonal antibody that inhibits the binding of soluble human B lymphocyte stimulator protein (BLyS) to its receptors on the B cells.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
belimumab (Benlysta)	Systemic Lupus Erythematosus (SLE); Lupus Nephritis (LN)	200 mg/mL syringe	*4 syringes/28 days

**Does not include loading dose required for LN*

Initial Evaluation

I. Belimumab (Benlysta) may be considered medically necessary when the following criteria below are met:
   A. Member is five years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a rheumatologist or nephrologist; **AND**
   C. **Not** used in combination with other biologic(s)[e.g., rituximab (Rituxan), abatacept (Orencia), voclosporin (Lupkynis)]; **AND**
   D. A confirmed positive autoantibody test [antinuclear (ANA) and/or anti-double-stranded DNA (anti-ds-DNA)]; **AND**
   E. A diagnosis of one of the following:
      1. **Systemic Lupus Erythematosus (SLE)**; **AND**
         i. A SLE Disease Activity Index (SELENA-SLEDAI) score of ≥ 8 supported by documentation in chart notes; **AND**
         ii. Documentation of baseline Physician's Global Assessment (PGA) score; **AND**
         iii. Treatment with **one** standard therapy agent from each category below, has been ineffective, contraindicated, or **ALL** are not tolerated:
            a. Antimalarials (e.g., chloroquine, hydroxychloroquine)
            b. NSAIDs (e.g., ibuprofen, naproxen)
            c. Immunosuppressive (e.g., azathioprine, mycophenolate mofetil, methotrexate); **OR**
      2. **Lupus Nephritis (LN); AND**
         i. Biopsy indicating class III (focal), IV (diffuse) or V (membranous) LN; **AND**
         ii. Biopsy shows active lesions or active AND chronic lesions; **AND**

iii. Provider attestation indicating medication will be given in combination with mycophenolate for induction and maintenance OR cyclophosphamide for induction followed by azathioprine for maintenance; **AND**

F. Provider attestation indicating member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated

II. Belimumab (Benlysta) is considered investigational when used for all other conditions, including but not limited to:
   A. Severe active central nervous system lupus

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of **Systemic Lupus Erythematosus (SLE**); **AND**
   A. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in SELENA-SLEDAI score or PGA score); **OR**
IV. A diagnosis of **Lupus Nephritis (LN)**; **AND**
   A. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in proteinuria, improved/stable serum creatinine, reduction in urinary sediment); **AND**
V. **Not** used in combination with other biologic(s); **AND**
VI. Member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated.

Supporting Evidence

I. The safety and efficacy of belimumab (Benlysta) in the pediatric SLE population was studied via the intravenous formulation in an international, randomized, double blind, placebo-controlled, 52-week, trial involving 93 pediatric patients as young as five years of age. The primary efficacy endpoint was the SLE Responder Index (SRI-4) at Week 52; of the 53 randomized participants to the belimumab (Benlysta) arm, the SRI-4 was 53% while the placebo arm was 44% with an odds ratio of 1.49 and 95% CI (0.64, 3.46).
II. FDA approval of belimumab (Benlysta) in pediatric patients with lupus nephritis was based on the extrapolation of efficacy from the intravenous (IV) study in adults with active lupus nephritis, and supported by pharmacokinetic data from IV studies in adults with active lupus nephritis and from pediatric patients with SLE. The estimated Benlysta exposures for pediatric patients were comparable to adults with active lupus nephritis.

III. Belimumab (Benlysta) was shown to be ineffective in seronegative patients, and is therefore only indicated in patients with active SLE who are autoantibody positive (seropositive). Clinical trials in the setting of LN also included patients who are autoantibody positive.

IV. Per label, the use of belimumab (Benlysta) in combination with other biologics has not been studied and is not recommended.

Systemic Lupus Erythematosus (SLE)

V. The safety and efficacy of belimumab (Benlysta) administered subcutaneously were evaluated in a randomized, double-blind, placebo-controlled trial involving 836 patients with SLE. Patients with severe active lupus nephritis and severe active CNS lupus were excluded. The primary efficacy endpoint was the SRI-4 at Week 52; in the belimumab (Benlysta) arm SRI-4 was 61% compared to placebo 48% with an odds ratio of 1.7 and 95% CI (1.3, 2.3).

A. As reported in the trial baseline concomitant medications included corticosteroids (86%), antimalarials (69%), and immunosuppressives (46%, including azathioprine, methotrexate, and mycophenolate). Most patients (approximately 80%) were receiving 2 or more classes of SLE medications.

Lupus Nephritis (LN)

VI. LN is a kidney disease that develops in about 40% of patients with SLE with approximately 10% of patients with LN developing end stage renal disease (ESRD). Kidney failure, dialysis, and kidney transplants are all common in this patient population. Patients with SLE with any sign of kidney involvement (glomerular hematuria and/or cellular casts, proteinuria >0.5 g/24 hours (or spot urine protein-to-creatine ratio (UPCR) >500 mg/g), unexplained decrease in glomerular filtration rate (GFR)) are candidates for kidney biopsy to confirm diagnosis/class of LN, which then guides treatment.

- Class I (minimal mesangial) and Class II (mesangial proliferative): Usually does not need specific immunosuppressive therapy but may be prone to histological transformation to more aggressive disease on repeat biopsy.
- Class III (focal) and Class IV (diffuse): active, chronic classifications at high risk of developing ESRD, thus are targeted populations for immunosuppressive therapies.
- Class V (membranous): presents similar to nephrotic syndrome with subendothelial deposits. Patients with Class III or IV disease may have these deposits and can be classified as Class III or IV in combination with Class V, can also present as pure Class V. Immunosuppressive therapy is indicated.
- Class VI (advanced sclerosing): patients with sclerosing lesions; generally do not respond to immunosuppressive therapy; treatment requires dialysis and/or kidney transplant.

VII. European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) 2019 and 2012 American College of Rheumatology guidelines on LN recommend immunosuppressive therapy for LN starting with an induction phase to achieve a renal response, which is recommended for the first six months of treatment, followed by maintenance therapy. Initial (induction) treatment is recommended with mycophenolate mofetil (MMF) or low-dose intravenous cyclophosphamide, both combined with glucocorticoids (pulses of IV methylprednisolone, then oral prednisone). Subsequent long-term maintenance treatment with MMF or azathioprine should follow, with no, or low-dose (<7.5 mg/day) glucocorticoids. If a patient fails to respond to the first six months of induction therapy, guidelines suggest switching the immunosuppressive agent in combination with glucocorticoid pulse.

VIII. The safety and efficacy of belimumab (Benlysta) in the setting of LN was evaluated in a randomized, double-blind, placebo-controlled trial involving 448 patients with Class III-V LN. Patients with severe active CNS lupus were excluded. The primary efficacy endpoint was renal response (complete or no response) at week 104. Renal response was defined as urinary protein to creatinine ratio of <0.7, eGFR no worse than 20% below the pre-flare value or ≥60 ml per minute per 1.73 m2, and no rescue therapy. In the belimumab (Benlysta) arm renal response was 43% compared to placebo 32.3% with an odds ratio of 1.6 and 95% CI (1.0, 2.3), P= 0.0311.

- All patients included in the trial were on background therapy with mycophenolate mofetil or cyclophosphamide–azathioprine. Patients were 18 years of age and older with antibody positive SLE, ratio of urinary protein to creatinine > 1 or more, biopsy proven LN class III (focal lupus nephritis) or IV (diffuse lupus nephritis) with, or without, coexisting class V (membranous lupus nephritis), or pure class V lupus nephritis within last 6 months. All patients also had biopsy specimens showing active lesions or active and chronic lesions.

Investigational or Not Medically Necessary Uses

I. Severe active central nervous system lupus
   A. Per label, the use of belimumab (Benlysta) in the setting of severe active central nervous system lupus has not been evaluated, and efficacy has not been established; therefore, use is not recommended by the manufacturer in this setting.

References

1. Benlysta [Prescribing Information]. Philadelphia, PA: GlaxoSmithKline. July 2022.
2. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64(6):797-808.
3. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 Update of the EULAR Recommendation for The Management of Systemic Lupus Erethmatosus. Annals of the Rheumatic Diseases 2019;78:736-745. Available at: https://ard.bmj.com/content/78/6/736
4. Lam NC, Ghetu MV, and Bieniek M. Systemic Lupus Erythematosus: Primary Care Approach to Diagnosis and Management. Am Fam Physician. 2016 Aug 15;94(4):284-294. Available at: https://www.aafp.org/afp/2016/0815/p284.html
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Policy Implementation/Update:

Action and Summary of Changes	Date
Expanded age requirement to five years and older.	10/2022
Added voclosporin (Lupkynis) in examples of biologics that cannot be used in combination with Benlysta	08/2021
Addition of new indication of lupus nephritis and further specified specialist to include nephrologist. Removal of criteria excluding concomitant use of cyclophosphamide	02/2021
Criteria transitioned into policy with the following updates made: addition of supporting evidence and investigational section, removal of active infection question, removal of vaccine question, updated renewal question relating to symptom improvement into one question, and removing specific symptom improvement parameters to be consistent with the market.	11/2019
Previous review	11/2017
Criteria created	09/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP239

Description

Belumosudil (Rezurock) is an orally administered Rho-associated kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
belumosudil (Rezurock)	200 mg tablets	Chronic graft-versus-host disease after failure of at least two prior lines of therapy	30 tablets/30 days*

*Quantity exceptions are not allowed.

Initial Evaluation

I. Belumosudil (Rezurock) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist, hematologist, dermatologist, or immunologist; **AND**
   B. A diagnosis of **chronic graft-versus-host disease (cGVHD)** when the following are met:
      1. Documentation of moderate-to-severe disease (e.g., Grade 2-4, or Grade B-D); **AND**
      2. Member is 12 years of age or older; **AND**
      3. The medication will not be used in combination with ibrutinib (Imbruvica) or ruxolitinib (Jakafi); **AND**
      4. Member has had in inadequate response to two prior lines of systemic therapy for the treatment of cGVHD (e.g., corticosteroids, calcineurin inhibitors [tacrolimus, cyclosporin], mycophenolate, mTOR inhibitors [sirolimus], ibrutininb [Imbruvica], ruxolitinib [Jakafi]); **AND**
      5. Proton pump inhibitor therapy (e.g., omeprazole, pantoprazole, lansoprazole, esomeprazole) will not be used in combination with belumosudil (Rezurock).

II. Belumosudil (Rezurock) is considered <u>not medically necessary</u> when criteria above are not met and/or when used:
   A. In combination with proton pump inhibitors
   B. At doses greater that 200 mg daily

III. Belumosudil (Rezurock) is considered investigational when used for all other conditions, including but not limited to:
   A. Systemic sclerosis
   B. Plaque psoriasis
   C. Acute graft-versus-host disease
   D. Graft-versus-host disease in combination with ibrutinib (Imbruvica) or ruxolitinib (Jakafi)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation of positive treatment response (e.g., stability or reduction in symptoms associated with GVHD: gastrointestinal, ophthalmic, cutaneous, pulmonary); **AND**
IV. Not used in combination with ibrutinib (Imbruvica) or ruxolitinib (Jakafi); **AND**
V. Proton pump inhibitor therapy (e.g., omeprazole, pantoprazole, lansoprazole, esomeprazole) will not be used in combination with belumosudil (Rezurock).

Supporting Evidence

I. Graft-versus-host disease is a complication of allogenic hematopoietic stem cell transplant. Treatment is dependent on severity and location of disease. The GVHD Grade depends on severity and location, and ranges from I-IV. Grade I is reflective of skin involvement, Grade IV is severe disease with severe skin involvement (e.g., blistering) and internal organ involvement, and Grade II-IV correlate with moderate-to-severe disease. The International Bone Marrow Transplant Registry Severity Index uses Grade A-D, which align with grading I-IV.
II. For Grade I or A, or mild disease, topical therapy is indicated. For Grade II or B or greater, or moderate-to-severe disease, systemic therapy is warranted. Chronic GVHD (cGVHD) is characterized by that in which symptoms arise more than 100 days after transplant. Glucocorticoids are the mainstay therapy; however, for those with glucocorticoid resistant disease, participation in clinical trials is recommended, or use of tacrolimus, cyclosporine, extracorporeal photopheresis, mycophenolate, rituximab, etanercept (Enbrel), everolimus, sirolimus and others may be considered as second-line therapy. There is lack of consensus on standard second-line therapy given limited or lack of sufficient safety and efficacy data from clinical trials to support use; however, given the poor data available to support any therapy for the treatment of cGVHD, and the established safety profiles of other therapies in this space – utilization of belumosudil (Rezurock) is limited to those that have tried and failed at least two other lines of systemic therapy. This follows the FDA-labeled diagnosis.
III. Other therapies used for the treatment of cGVHD include ibrutinib (Imbruvica) and ruxolitinib (Jakafi) which are indicated in the second-line setting or beyond; however, are often used as later line therapy given safety concerns, cost, and recent approval for this condition. As of

August 2021, guidelines did not specifically recommend any of these therapies over another in the second-line setting or beyond. Given lack of standard of care therapy, safety concerns with drug therapy, and specialized monitoring required for treatment, prescribing by, or in consultation with, a specialist is required.

IV. Use of belumosudil (Rezurock) in combination with other specialty therapies such as ibrutinib (Imbruvica) or ruxolitinib (Jakafi) has not been evaluated for safety and efficacy. Given the safety risks of ibrutinib (Imbruvica) and ruxolitinib (Jakafi), the largely unknown safety profile of belumosudil (Rezurock), as well as lack of data that combination use would provide additional benefit, use of belumosudil (Rezurock) is not allowed at this time. In clinical trials, belumosudil (Rezurock) was evaluated in combination with corticosteroids and calcineurin inhibitors (e.g., tacrolimus); thus, if adjunctive therapy is warranted, these therapies are recommended in combination given availability of safety data with combination use.

V. Belumosudil (Rezurock) was evaluated in two Phase 2 clinical trials, both uncontrolled and open-label. Patients were ≥ 12 years of age, with persistent cGVHD, at least moderate disease, receiving corticosteroids (CS) or CS + calcineurin inhibitor (CI). Patients failed multiple lines of therapy; thus, a standardized control was not available. Primary outcome: objective response rate (ORR). Secondary outcomes: duration of response (DoR), proportion achieving a clinically significant improvement in Lee Symptom Score (LSS), proportion with a reduction in CS doses, mean change in CS dose, proportion of patients discontinuing CS, failure-free survival (FFS).
    - Phase 2a: 54 patients, three treatment arms of various doses, a median of four organs involved, and median of two prior lines of therapy (up to three).
    - Phase 2b: 132 patients, two treatment arms, a median of four organs involved, median of three prior lines of therapy (up to five). Notable past therapies: 34% had ibrutinib (Imbruvica) therapy, 29% had ruxolitinib (Jakafi).

VI. The Phase 2b trial had two treatment arms: 200 mg once daily and 200 mg twice daily. Given similar safety and efficacy, the FDA evaluated data from the 200 mg once daily treatment arm to support approval; however, efficacy across treatment arms were similar. Additionally, the FDA utilized data out to cycle 7 (of 28-day cycles) as a reasonable timeframe to evaluate medication efficacy. The ORR was 75% in one trial and 50% in the other, and the median DoR was 1.9 months, 70% of patients experienced clinical improvement in LSS, the proportion of patients able to reduce the dose of CS was 65%, 20% of patients were able to discontinue CS, and FFS was 75% at six months and 56% at one year.

VII. Use of belumosudil (Rezurock) has not been evaluated in patients less than 12 years of age, and safety implications associated with treatment are largely unknown; thus, use in patients under 12 years of age should be used with extreme caution. Additionally, should be considered only in those that have exhausted all other appropriate therapies for this age group and where benefits of therapy are largely expected to outweigh the risks.

VIII. The NIH recommends ORR as the primary outcome in trials for GVHD: complete resolution of all disease manifestations or improvement in at least one organ site without other progression. The NIH has indicated a 30% ORR in the third-line setting is considered clinically meaningful, and recommends other patient centered outcomes be measured as well (e.g., QoL). These outcomes are expected to correlate with improvement in disease manifestations, reduction in mortality and patient perceived burden of disease.

IX. Results from two trials exceed NIH recommended thresholds, in a population with limited or no further treatment options; thus, the quality of the data is considered moderate, despite the observational nature of the trials. Consistently high ORR, clinically meaningful improvements in QoL parameters, and reduction in corticosteroids across various populations gives confidence that belumosudil (Rezurock) provides clinical value.

X. Common adverse events: fatigue (38%), diarrhea (33%), nausea (31%), cough (28%), URTI (27%), dyspnea (25%), headache (24%), peripheral edema (23%), vomiting (21%), muscle spasms (20%), LFT changes (24%), pneumonia (8%). There is a warning for embryo-fetal toxicity, and no contraindications to therapy. Determined to be unrelated to drug therapy, death occurred in 13 patients in both trials. Dose interruptions occurred in 11% of patients, and drug discontinuations in 18%. Cytopenias and serious infections are known risks of ibrutinib (Imbruvica) and ruxolitinib (Jakafi), leading to high rates of treatment discontinuation. Belumosudil (Rezurock) has not been associated with these safety concerns to date; however, given the observational nature of the data and small number of patients in the clinical trial, the true safety profile is unknown. Additionally, given lack of control, it is unknown what safety characteristics are due to drug or disease.

XI. Belumosudil (Rezurock) has a significant drug-drug interaction with proton pump inhibitors (PPIs). Examples of these include omeprazole, pantoprazole, lansoprazole, esomeprazole. When used concurrently, the belumosudil (Rezurock) dose needs to be doubled, to 200 mg twice daily compared to the standard 200 mg once daily dosing. This results in double the cost of therapy (up to $31,000) per 30-day supply. Additionally, puts members at risk of increased toxicity with therapy with belumosudil (Rezurock) therapy if PPI adherence is inconsistent or not achieved. Thus, the plan requires members be transitioned off of PPI therapy prior to initiating belumosudil (Rezurock). For members with severe symptoms of GERD or another condition requiring PPI therapy; members and providers may consider dietary and lifestyle modifications, or use of an H2 blocker (e.g., famotidine). Belumosudil (Rezurock) also has drug-drug interactions with strong CYP3A inducers (e.g., rifampicin, phenytoin, St. John's Wort). Quantity exceptions will not be allowed in the setting of drug-drug interactions where other management strategies may be employed (e.g., finishing courses of transient therapies, transitioning to other effective therapies). Additionally, belumosudil (Rezurock) was evaluated at doses greater than 200 mg daily in clinical trials; however, additional benefit/efficacy was not shown. Thus, quantity exceptions will not be allowed if the member is unable to achieve adequate efficacy at the 200 mg daily dose.

Investigational or Not Medically Necessary Uses

I. Belumosudil (Rezurock) used in combination with proton pump inhibitors is considered not medically necessary given that concomitant use doubles the cost of belumosudil (Rezurock) therapy. Given alternative management strategies for conditions warranting use of proton pump inhibitors, this drug-drug interaction should be mitigated in ways aside from doubling the dose of belumosudil (Rezurock). See supporting evidence for details. Additionally, clinical trials evaluated doses of belumosudil (Rezurock) therapy greater than 200 mg daily and there was lack of additional efficacy (with increased safety concerns). Thus, use of belumosudil (Rezurock) treatment at doses greater than 200 mg daily is not indicated.

II. Belumosudil (Rezurock) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Systemic sclerosis
    B. Plaque psoriasis
    C. Acute graft-versus-host disease
    D. Graft-versus-host disease in combination with ibrutinib (Imbruvica) or ruxolitinib (Jakafi)

References

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5. Jakafi [Prescribing Information]. Wilmington, DE; Incyte Corporation. May 2019.
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7. Imbruvica [Prescribing Information}. Horsham, PA; Janssen Biotech, Inc. April 2020.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP240

Split Fill Management*

Description

Belzutifan (Welireg) is an orally administered selective inhibitor of hypoxia inducible factor-2α (HIF-2α).

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
belzutifan (Welireg)	40 mg tablets	von Hippel-Lindau (VHL) disease associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastoma, or pancreatic neuroendocrine tumors (pNET)	90 tablets/30 days

Initial Evaluation

Belzutifan (Welireg) is considered investigational when used for all conditions, including but not limited to VHL-disease associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastoma, or pancreatic neuroendocrine tumors (pNET).

Renewal Evaluation

I. N/A

Supporting Evidence

I. Belzutifan (Welireg) is the first systemic therapy FDA-approved for the treatment of adult patients with von Hippel-Lindau (VHL) disease associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastoma, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery. It is also the only orally administered drug indicated in this setting.

II. Von Hippel-Lindau syndrome (VHL) is a hereditary condition associated with tumors arising in multiple organs. VHL-related tumors include hemangioblastomas, which are blood vessel tumors of the brain, spinal cord, and retina. Patients with VHL also have an increased risk of developing clear cell renal cell carcinoma (cc-RCC), pheochromocytoma, or pancreatic

neuroendocrine tumor (pNET). Initial features of VHL include kidney cysts, pancreatic cysts, epididymal cystadenomas, broad ligament cystadenomas, and endolymphatic sac tumors (ELST), which are tumors of the inner ear that may cause hearing loss.

III. Patients with VHL disease may present with cysts in any one or multiple organ systems. For example, it is possible for a patient to show radiographic presence of pNET or other neuroendocrine lesions without presence of kidney lesions. However, the prevalence data shows kidney lesions and cc-RCC as the most common progressive manifestation in VHL (up to 70% of cases). On the other hand, pNET, hemangioblastoma, pheochromocytoma may be prevalent between 5% and 30% of the VHL cases.

IV. Additionally, VHL disease associated tumors are slow growing in nature. Depending on the tumor type, natural evolution and progression for VHL tumors may be between four years to 10 years after onset. Onset of symptoms is mostly observed in adulthood with median age of onset 24 to 44 years of age.

V. VHL protein deactivation followed by HIF-2α buildup may be one of the key drivers to VHL-associated tumorigenesis. Unregulated levels of HIF-2α may stimulate several oncogenes associated with angiogenesis and tumor growth, leading to both benign and malignant tumors.

VI. The only way to diagnose VHL is with genetic testing. Nearly all patients with VHL will be found to have a genetic mutation in their *VHL* gene once tested. There are no universal guidelines regarding who should be screened for VHL. However, VHL should be suspected when a person has a family history of VHL.

VII. There are no FDA-approved systemic therapies for VHL associated tumors. Current standard of care (irrespective of tumor type at diagnosis) involves active surveillance, surgical resection when necessary (e.g., partial nephrectomy or ablation) and radiation (e.g., for spinal cord tumors). Active surveillance may involve radiographic imaging, biomarker screenings, and histological study. When tumors/cysts reach resectable mass (e.g., for RCC a 3 cm rule is followed), the patient may undergo resection. A patient may have to undergo multiple resections over lifetime. It is important to note that for initial manifestations, as well as lesions presenting later during life, surgical resection remains standard of care as long as the tumor/ lesions are determined to be benign.

VIII. For patients who progress to advanced carcinomas with metastatic potential, guideline recommended systemic therapies (e.g., tyrosine kinase inhibitors (TKI), vascular endothelial growth factor (VEGF) inhibitors) may be warranted as indicated for the tumor type and location. The National Comprehensive Cancer Network (NCCN) treatment guideline for kidney cancer (RCC) has included belzutifan (Welireg) as a Category 2A recommendation for systemic therapy for confirmed hereditary RCC associated with VHL disease. There are no treatment guidelines specific to the pharmacological management of the VHL disease.

IX. **Clinical Trial Data**:

- Belzutifan (Welireg) received FDA-approval based on an ongoing Phase 2, open-label, single-arm trial (Study004). Patients (N= 61) with VHL- associated cc-RCC (≥ 1 measurable localized tumor in the kidney and pancreas), received belzutifan (Welireg) 120 mg orally once a day for a median of 21.8 months. Primary efficacy outcome was Overall Response Rate (ORR) in RCC. Key secondary outcomes were ORR in non-RCC lesions, Progression-Free Survival (PFS), and Duration of Response (DoR). All participants were not candidates for immediate surgery and were naïve to chemotherapy. The study excluded patients with metastatic disease. Therapy with belzutifan (Welireg) for a median of 21.8 months showed 49.2% ORR (95% CI; 36.1, 62.3), all of which were partial responses (PR). DoR and PFS were not estimable

currently. Additionally, patients with pancreatic lesions (n=61), pancreatic neuroendocrine tumors (pNET; n= 12), and CNS hemangioblastoma (n= 24) exhibited 77%, 83%, and 62% ORR, respectively.

- Belzutifan (Welireg) showed significant safety concerns with common adverse reactions (AE): anemia (90.2%), fatigue (65%), headache (41%), nausea (34%), and dyspnea (23%). Serious AE (grade 3, 14.8% patients) included anemia, fatigue, dyspnea and hypertension, pneumonitis, and elevation of liver enzymes. Although no contraindications are listed, the drug information includes warnings of serious anemia and hypoxia. Treatment during clinical trial led to 39% therapy interruptions, 13% dose reductions, 3.3% discontinuations, and one death. The real-world safety profile of belzutifan (Welireg) remains undetermined at this time.
- Additionally, a Phase 1, open-label, single arm clinical trial for belzutifan (Welireg) studied safety and efficacy of belzutifan (Welireg) in advanced cc-RCC. Enrolled patients in this trial had advanced cc-RCC with ECOG PS 1 through ≥ 3. All patients were treatment experienced (62% had ≥3 systemic therapies) with majority (91%) exposed to vascular endothelial growth factor (VEGF) inhibitors, along with mTOR inhibitors and checkpoint inhibitors. At median 27.7 months of follow-up, belzutifan (Welireg) treatment led to a 25% ORR (95%CI; 15, 39) in the cc-RCC cohort.

X. FDA-approval for belzutifan (Welireg) followed an accelerated approval pathway. Continued approval may be contingent upon verification of clinical benefits in confirmatory trials. Currently, clinical trials are underway for advanced cc-RCC as monotherapy as well as in combination with other oncolytic agents.

XI. Therapies based on targeting molecular pathways in oncology have garnered interest in recent years and may be considered part of a paradigm shift in the pharmacological management of cancers. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Specifically, in the setting of VHL-associated tumors, this resistance may be associated with feedback activation of other downstream pathways such as vascular endothelial growth factor (VEGF), platelet derived growth factor receptor beta (PDGFRβ), and hypoxia inducible factor-1 (HIF-1) mediated oncogenesis. Thus, selective inhibition of HIF-2α (which is found mainly in renal cells) by belzutifan (Welireg) may not provide a clear path to complete suppression of VHL-associated tumors.

XII. Proposed place in therapy for belzutifan (Welireg) is as an initial (first-line) agent for the treatment of VHL associated tumors in patients, who do not require immediate surgery; and it may be considered an option to prolong progression to malignancy and/or surgery. However, available clinical data do not support clinically meaningful outcomes in mortality, quality of life, and morbidity (e.g., measurable reduction in the need for surgery, and/ or progression to malignancy). At this time, the quality of the available evidence is considered low. Although an acceptable surrogate marker in oncology, ORR does not establish true causal relation between the intervention and effect. Given the slow natural progression of VHL disease, lack of comparator, and open-label trial design, medication efficacy and true clinical value of belzutifan (Welireg) remains uncertain.

Investigational or Not Medically Necessary Uses

I. Belzutifan (Welireg) has not been sufficiently studied for safety and efficacy for any condition to date.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Belzutifan (Welireg) [Prescribing Information]. Merck Sharp & Dohme Corp., Whitehouse Station, NJ. August 2021.
2. Srinivasan R, Donskov F, Iliopoulos O, et al. Phase 2 Study of Belzutifan (MK-6482), an Oral Hypoxia inducible Factor 2α Inhibitor, for Von Hippel-Lindau Disease–associated Clear Cell Renal Cell Carcinoma. Abstract #4555. Presented at: American Society of Clinical Oncology (ASCO); June 4-8, 2021; Virtual Meeting.
3. Jonasch E, Donskov F, Iliopoulos O, et al. Phase 2 study of the oral HIF-2α inhibitor MK-6482 for Von Hippel-Lindau disease-associated renal cell carcinoma. Abstract #5003. Presented at: American Society of Clinical Oncology (ASCO); May 29-31, 2020; Virtual Meeting.
4. NCCN Clinical practice Guidelines in Oncology for kidney cancer; V2.2022; updated September 8th, 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2021

Policy Type: PA Pharmacy Coverage Policy: UMP182

Description

Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) is an orally administered adenosine triphosphate-citrate lyase inhibitor, and ezetimibe is an intestinal cholesterol absorption inhibitor.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
bempedoic acid (Nexletol)	180 mg tablets	As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C	30 tablets/30 days
bempedoic acid/ezetimibe (Nexlizet)	180 mg/10 mg tablets		30 tablets/30 days

Initial Evaluation

I. **Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Therapy is prescribed by, or in consultation with, a provider specializing in lipid management (e.g. cardiology, lipidology, endocrinology); **AND**
   C. Therapy with a maximally tolerated statin for at least an 8-week duration has been ineffective; **AND**
      1. The member continues to have an LDL-cholesterol level greater than, or equal to, 70 mg/dL while on maximally tolerated statin therapy; **AND**
      2. The member will continue maximally tolerated statin therapy in combination with bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet); **OR**
         i. The member has a history of statin intolerance defined as <u>failure</u> of TWO statin medications due to at least ONE of the following:
            a. CK exceeds 10 times the upper limit of normal
            b. LFTs exceed 3 times the upper limit of normal
            c. Severe rhabdomyolysis leading to hospitalization

d. Severe muscle weakness inhibiting activities of daily living, employment, or leading to temporary disability; **AND**

3. The member will **not** use bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) in combination with simvastatin (Zocor) >20 mg or pravastatin (Pravachol) >40 mg; **AND**

D. Treatment with ezetimibe (Zetia) has been ineffective, contraindicated, or not tolerated; **AND**

E. Treatment with a PCSK9 inhibitor (e.g. alirocumab [Praluent]), evolocumab [Repatha]) or icosapent ethyl (Vascepa) has been ineffective, contraindicated, or not tolerated; **AND**

F. The member has a history of **atherosclerotic cardiovascular disease (ASCVD)**; **AND**

1. Documentation of clinical atherosclerotic disease via invasive or non-invasive testing (e.g., stress test, imaging); **OR**
2. Diagnosis of atherosclerotic disease and primary prevention failure (e.g., member has had a stroke, myocardial infarction); **OR**

G. The member has a diagnosis of **heterozygous familial hypercholesterolemia (HeFH)** confirmed by one of the following:

1. Genotyping or clinical criteria using either the Simon Broome diagnostic criteria (Definite diagnosis classification) or Dutch Lipid Network criteria (score of at least 8)
2. Physical signs of familial hypocholesteremia (e.g., arcus cornealis, tendon xanthomas, xanthelasma)
3. Clinical documentation or a DNA mutation analysis supporting the diagnosis of heterozygous familial hypercholesterolemia

II. Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) are considered investigational when used for all other conditions, including but not limited to:

A. Primary prevention of ASCVD

B. Homozygous familial hypercholesterolemia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has experienced a decrease from baseline LDL while on therapy or LDL remains stable since previous renewal

Supporting Evidence

I. Bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) was primarily studied in patients over the age of 18 with a history of ASCVD or HeFH. Bempedoic acid (Nexletol) was also studied in two trials in patients that were intolerant to two different statins.

II. Bempedoic acid (Nexletol) has drug-drug interactions with doses of simvastatin >20 mg and pravastatin >40 mg due to the potential for increased risk of myopathy.
III. Bempedoic acid (Nexletol) was studied in four randomized, double-blind, placebo-controlled Phase 3 trials, and bempedoic acid/ezetimibe (Nexlizet) was studied in one randomized, double-blind, four-arm, Phase 3 trial, in a total of 4,005 patients.
IV. The primary efficacy outcome was change in LDL from baseline to 12 weeks compared to placebo. Bempedoic acid (Nexletol) demonstrated reductions of -18.1% (95% CI -20%, -16.1%), -17.4% (95% CI -21%, -13.9%), -21.4% (95% CI -25.1%, -17.7%), -28.5% (95% CI -34.4%, -22.5%), for the Wisdom, Harmony, Serenity, and Tranquility trials respectively.
V. Bempedoic acid/ezetimibe (Nexlizet) demonstrated a reduction in LDL of -38% (95% CI -46.5%, -29.6%) compared to placebo.
VI. The new active molecular entity bempedoic acid does not currently have any data to support its use in improving clinically meaningful endpoints (e.g. cardiovascular death, stroke, myocardial infarction). However, alternative agents for lowering LDL and other forms of cholesterol have established data to support their use in preventing cardiovascular endpoints.
VII. AHA/ACC, ESC/EAS, AACE, and NLA guidelines have not been updated to include bempedoic acid, bempedoic acid/ezetimibe (Nexletol, Nexlizet) in the treatment of dyslipidemia. Guidelines currently recommend the use of statins, ezetimibe (Zetia), evolocumab (Repatha), alirocumab (Praluent), and icosapent ethyl (Vascepa) due to their evidence for reducing cardiovascular events.
VIII. Ezetimibe (Zetia) is a common, widely utilized add-on therapy to statin therapy and has well-known safety and efficacy. Ezetimibe (Zetia) also has data on cardiovascular outcomes and has evidence for benefit in patients being treated for dyslipidemia.
IX. Insight from cardiology specialists indicate that diagnosis of clinical ASCVD in the absence of a cardiovascular event can be achieved by angiography, ischemia on stress test, or stenosis of 50% or more using other imaging techniques. While evidence of coronary calcification on CTA (calcium score >1) is indicative of high-risk of developing ASCVD, this number should be integrated into the member's clinical profile to determine individual patient risk and treatment, but should not necessarily be used alone for the purposes of clinical diagnosis.
X. **Heterozygous familial hypercholesterolemia**: The presence of tendon xanthoma is a genetically modulated clinical syndrome of familial hypercholesterolemia. In addition, DNA testing can be used to diagnose familial hypercholesterolemia functional mutations. In clinical trials, enrolled patients with heterozygous familial hypercholesterolemia were diagnosed either by genotyping or clinical criteria ("definite FH" using either the Simon Broome or Dutch Lipid Network).

Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia	
Criteria	**Description**
A	Total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in adults or a total cholesterol concentration above 6.7 mmol/liter (259 mg/dL) in children aged less than 16 years, or
	Low density lipoprotein cholesterol concentration above 4.9 mmol/liter (189 mg/dL) in adults or above 4.0 mmol/liter (155 mg/dL) in children
B	Tendinous xanthomata in the patient or a first-degree relative

C	DNA-based evidence of mutation in the *LDLR, PCSK9,* or *APOB* gene
D	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
E	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
A "definite" FH diagnosis requires either criteria a and b, or criterion c. A "probable" FH diagnosis requires either criteria a and d, or criteria a and e.	

Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolemia	
Criteria	**Points**
Family history	
• First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or • First-degree relative with known LDL-C above the 95th percentile	1
• First-degree relative with tendinous xanthomata and/or arcus cornealis, or • Children <18 years of age with LDL-C above the 95th percentile	2
Clinical History	
• Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
• Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
Physical examination	
• Tendinous xanthomata	6
• Arcus cornealis before age 45 years	4
LDL-C levels	
• LDL-C ≥8.5 mmol/L (325 mg/dL)	8
• LDL-C 6.5-8.4 mmol/L (251-325 mg/dL)	5
• LDL-C 5.0-6.4 mmol/L (191-250 mg/dL)	3
• LDL-C 4.0-4.9 mmol/L (155-190 mg/dL)	1
DNA analysis	
• Functional mutation in the LDLR, apoB, or PCSK9 gene	8
Choose only one score per group, the highest applicable diagnosis (diagnosis is based on the total number of points obtained) • A "definite" FH diagnosis requires >8 points • A "probable" FH diagnosis requires 6-8 points • A "possible" FH diagnosis requires 3-5 points	

- Using DNA testing, patients with familial hypercholesterolemia (FH) have been identified as generally having a functional mutation of one of three genes: *LDLR, PCSK9,* or *APOB* gene. Mutations in these three genes can be detected in about 80 percent of patients with definite FH clinical syndrome.

Investigational or Not Medically Necessary Uses

I. Primary prevention of ASCVD
   A. There is currently no safety or efficacy data to support the use of bempedoic acid in reducing/preventing ASCVD
II. Homozygous familial hypercholesterolemia
   A. There is currently no safety or efficacy data to support the use of bempedoic acid in patients with homozygous familial hypercholesterolemia

References

1. Nexletol [Prescribing Information]. Esperion Therapeutics: Ann Arbor, MI. February 2020.
2. Nexletol/Nexlizet [E-Dossier]. Esperion Therapeutics: Ann Arbor, MI. May 2019.
3. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial. JAMA. 2019;322(18):1780-1788.
4. Ray KK, Bays HE, Catapano AL, et al. Safety and Efficacy of Bempedoic Acid to Reduce LDL Cholesterol. N Engl J Med. 2019;380(11):1022-1032.
5. Ballantyne CM, Banach M, Mancini GBJ, et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study. Atherosclerosis. 2018;277:195-203.
6. Laufs U, Banach M, Mancini GBJ, et al. Efficacy and Safety of Bempedoic Acid in Patients With Hypercholesterolemia and Statin Intolerance. J Am Heart Assoc. 2019;8(7):e011662.
7. Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. Eur J Prev Cardiol. 2019;:2047487319864671.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated supporting evidence	12/2020
Policy created	05/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP174

Description

Benralizumab (Fasenra Pen) is a subcutaneously administered monoclonal antibody (IgG1 Kappa) that antagonizes interleukin-5 (IL-5).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
benralizumab (Fasenra)	30 mg/mL autoinjector	Asthma (severe)	Loading: 1 autoinjector/28 days for 3 doses Maintenance: 1 autoinjector/56 days

Initial Evaluation

I. Benralizumab (Fasenra Pen) may be considered medically necessary when the following criteria below are met:
   A. Member is 12 years of age or older**; AND**
   B. Medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); **AND**
   C. Must not be used in combination with another monoclonal antibody (e.g., dupilumab, mepolizumab, omalizumab, reslizumab, etc.); **AND**
   D. A diagnosis of **severe asthma** when the following are met:
      1. Member has **SEVERE** asthma as defined by one of the following:
         i. Symptoms throughout the day
         ii. Nighttime awakenings, often 7x/week
         iii. SABA (e.g., albuterol, levalbuterol) use for symptom control occurs several times per day
         iv. Extremely limited normal activities
         v. Lung function (percent predicted FEV1) < 60%
         vi. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**
      2. Member must have asthma with an eosinophilic phenotype defined as blood eosinophils ≥300 cells/µL within previous 12 months OR ≥150 cells/µL within 6 weeks of dosing; **AND**

3. Member must have two or more exacerbations in the previous year requiring daily oral corticosteroids for at least 3 days (in addition to the regular maintenance therapy defined below); **AND**
4. Member is currently being treated with:
    i. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
        a. One additional asthma controller medication (e.g., long-acting beta-2 agonist [LABA] {e.g., Serevent Diskus}, long-acting muscarinic antagonist [LAMA] {e.g., Spiriva Respimat }, leukotriene receptor antagonist [e.g., Singular], or theophylline); **OR**
    ii. A maximally tolerated ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **AND**
5. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of benralizumab (Fasenra), unless contraindicated; **AND**
6. Treatment with mepolizumab (Nucala) has been ineffective, contraindicated, or not tolerated

II. Benralizumab (Fasenra) is considered investigational when used for all other conditions, including but not limited to:
    A. Non-severe, non-eosinophilic phenotype asthma
    B. Atopic dermatitis
    C. Eosinophilic gastritis
    D. Exercise-induced asthma
    E. Chronic obstructive pulmonary disease (COPD)
    F. Hypereosinophilic syndrome

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Must not be used in combination with another monoclonal antibody (e.g., dupilumab, mepolizumab, omalizumab, reslizumab, etc.); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **AND**
V. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of benralizumab (Fasenra), unless contraindicated.

Supporting Evidence

I. Benralizumab (Fasenra Pen) is indicated as an add-on maintenance treatment for patients 12 years and older with a diagnosis of severe eosinophilic asthma (SEA). It is now available for self-administration via an autoinjector based off one phase III and one phase I trial that was conducted with the primary objective of usability and pharmacokinetic (PK) exposure. These trials demonstrated that the safety and tolerability of benralizumab (Fasenra Pen) was consistent with the established profile of the medication.

II. The provider administered benralizumab (Fasenra), was FDA approved in the setting of severe eosinophilic asthma and was evaluated in one 52-week dose ranging exacerbation trial, three confirmatory randomized, double-blind trials, and one 12-week lung function trial.
   A. The 52- week dose ranging exacerbation trial was a phase 2 randomized, double-blind, placebo-controlled trial. Benralizumab (Fasenra) was administered every 4 weeks for 3 doses followed by every 8 weeks thereafter. In the benralizumab (Fasenra) treatment arm, there was a decrease in annual exacerbation rate with 2, 20, and 100 mg (-12% [80% CI: -51, 18), -34% [80% CI: 6, 54], and -29% [80% CI: 10, 44], respectively).
   B. The two confirmatory trials were 48 and 52 weeks in duration. The primary outcome was rate of asthma exacerbations in patients with baseline eosinophil counts of ≥300 cells/µL taking both high-dose ICS and LABA. Rates of exacerbation per year in the benralizumab (Fasenra) arm of both trials was 0.74 and 0.73 compared to 1.52 and 1.01 with placebo (Rate Ratio [95% CI: 0.37, 0.64], [95% CI: 0.54, 0.95], respectively).
   C. The third confirmatory trial was 28 weeks in duration and evaluated the effects of benralizumab (Fasenra) on reducing the use of maintenance oral corticosteroids (OCS). The primary endpoint was percent reduction from baseline of OCS use during weeks 24 to 28. The median percent reduction from baseline in the benralizumab (Fasenra) arm was 75% compared to 25% in placebo (95% CI: 60, 88).
   D. The 12-week lung function trial measured lung function by the change from baseline FEV_1 at week 12. The benralizumab (Fasenra) arm showed an increase of 0.057 liters compared to -0.016 liters in placebo (p=0.040)

III. The Global Initiative for Asthma (GINA) 2020 update recommends the addition of respiratory biologics, with respect to their allergic biomarkers, after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 (medium dose ICS-LABA) or Step 5 (high dose ICS-LABA) therapy. Other controller options for Step 4 include high dose ICS-LABA, add-on tiotropium, or add-on LTRA. Other controller options for Step 5 include add-on anti-IL5 or add-on low dose OCS, though guidelines do note to consider side effects.

Investigational or Not Medically Necessary Uses

I. Benralizumab (Fasenra) has not been adequately studied for the following conditions and does not have established safety and efficacy in these populations:
   A. Non-severe, non-eosinophilic phenotype asthma
   B. Atopic dermatitis
   C. Eosinophilic gastritis
   D. Exercise-induced asthma
   E. Hypereosinophilic syndrome
   F. Chronic obstructive pulmonary disease (COPD)

i. A single phase IIa study compared benralizumab to placebo in patients with COPD and showed there was no difference in rates of exacerbations; therefore, there is insufficient evidence in the safety and efficacy of benralizumab (Fasenra) for use in patients with COPD.

References

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3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2020 Update. Available from: http://www.ginasthma.org. Accessed February 2021.
4. Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. J Asthma Allergy. 2014; 7: 53–65.
5. Goldman M, Hirsch I, Zangrilli JG, et al. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies. Curr Med Res Opin. 2017 Sep;33(9):1605-1613. doi: 10.1080/03007995.2017.1347091. Epub 2017 Jul 19.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated renewal length of authorization from six months to 12 months. Revised "severe eosinophilic asthma" verbiage "asthma (severe)" in attempts to align with other respiratory biologics policies. For initial criteria: added dupilumab as an example for another monoclonal antibody that must not be used in combination; added prescribed by or in consultation with a specialist requirement; added member must have asthma with an eosinophilic phenotype defined as blood eosinophils ≥300 cells/µL within previous 12 months as an "OR" option to existing required ≥150 cells/µL within 6 weeks of dosing; revised verbiage for add-on maintenance treatment requirements to medium- to high-dose, or maximally tolerated ICS and one additional asthma controller medication OR maximally tolerated ICS/LABA combination, added requirement of continued use with background controller medications. For renewal criteria: added "must not be used in combination with another monoclonal antibody"; consolidated list of clinical improvement examples; added continued background controller medications. For supporting evidence: added GINA 2020 guideline recommendations. For investigational or not medically necessary uses: updated verbiage to current policy format.	03/2021
Policy created	02/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP113

Description

Betaine anhydrous (Cystadane) is an orally administered endogenous metabolite of choline.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
betaine anhydrous (generic Cystadane)	Homocystinuria	1 g/1.7 mL powder	540 grams/30 days
betaine anhydrous (Cystadane)		1 g/1.7 mL powder	540 grams/30 days

Initial Evaluation

I. **Betaine anhydrous (Cystadane)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a metabolic or genetic disease specialist; **AND**
   B. A diagnosis of **homocystinuria** when the following are met:
      1. Diagnosis associated with one of the following (i, ii, or iii):
         i. Cystathionine beta-synthase (CBS) deficiency; **AND**
            a. Treatment with **ALL** of the following has been ineffective, contraindicated, or not tolerated:
               i. Vitamin B6 (pyridoxine)
               ii. Vitamin B12 (cyanocobalamin)
               iii. Folic Acid
               iv. Diet restrictions; **OR**
         ii. Homocystinuria associated 5,10-methylenetetrahydrofolate reductase (MTHFR) deficiency; **OR**
         iii. Cobalamin cofactor metabolism (cbl) defect; **AND**
      2. Treatment with generic betaine anhydrous (generic Cystadane) has been ineffective, contraindicated, or not tolerated

II. Betaine anhydrous (Cystadane) is considered investigational when used for all other conditions, including but not limited to:
   A. Non-alcoholic fatty liver

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms

Supporting Evidence

I. Betaine anhydrous (Cystadane) is indicated in pediatric and adult patients for the treatment of homocystinuria, and is used to decrease elevated homocysteine blood concentrations. Homocystinuria results from deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylenetetrahydrofolate reductase (MTHFR), and/or cobalamin cofactor metabolism (CBL).
II. Homocystinuria is a rare autosomal recessive disorder characterized by severe elevations in plasma and urine homocysteine concentrations. It may result from a deficiency of several enzymes involved in the conversion of methionine to cysteine or, less commonly, it is due to impaired conversion of the compound homocysteine to methionine. There are multiple forms of homocystinuria, which are distinguished by their signs, symptoms, and genetic cause. Clinical manifestations of homocystinuria includes developmental delay, Marfanoid appearance, osteoporosis, ocular abnormalities, thromboembolic disease, and severe premature atherosclerosis. The signs and symptoms of homocystinuria usually develop within the first year of life; although, the mildly-affected may not develop features until later in childhood or adulthood.
III. Guidelines for CBS deficiency state:
    - Betaine should be considered as adjunct treatment in patients who cannot achieve target levels of homocysteine by other means. Betaine treatment alone seldom achieves target homocysteine levels in those with a pyridoxine-unresponsive CBS deficiency. It is best used as adjunct treatment in patients who are partially responsive to pyridoxine, or, who are on dietary treatment but cannot achieve adequate control.
    - Patient response to betaine can vary, and, optimal doses require individualization. Standard initial dosing for children is 50 mg/kg twice daily; meanwhile, adults start at three grams two times a day. The dose and frequency are adjusted to the response of treatment with an added note that exceeding a dose of 150-200 mg/kg/day is unlikely to result in any additional benefit.
IV. Guidelines for MTHFR deficiency state:
    - Early identification and treatment with betaine for MTHFR deficiency is strongly recommended. Pre-symptomatic betaine treatment prevents severe neurological impairment with a high quality of evidence.

Investigational or Not Medically Necessary Uses

I. With limited evidence available, betaine anhydrous (Cystadane) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. Non-alcoholic fatty liver (NAFLD)
      i. Treatment betaine anhydrous (Cystadane) is not listed within the American Association for the Study of Liver Diseases (AASLD) NAFLD guidelines.

References

1. Cystadane [Prescribing Information]. Lebanon, NJ: Recordati Rare Diseases Inc. October 2018.
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8. Miglio F, Rovati LC, Santoro A, et al: Efficacy and safety of oral betaine glucuronate in non-alcoholic steatohepatitis. Arzneimmittelforschung Drug Res 2000; 50(8):722-727.
9. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-357.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added requirement to have tried and failed generic betaine anhydrous prior to use of branded Cystadane	04/2022
Policy created	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP115

Split Fill Management (Only Applies to bexarotene (Targretin) capsule)*

Description

Bexarotene (Targretin) is an orally and topically administered retinoid that binds to and activates retinoid X receptor subtypes to inhibit growth and induce the regression of tumor cells.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
bexarotene (generic Targretin)	Primary cutaneous T-cell lymphoma, refractory to one prior systemic therapy	75 mg capsule	Based on body surface area calculation, dose to be rounded to the nearest 75 mg
bexarotene (Targretin)		75 mg capsule	
bexarotene gel (generic Targretin)	Primary cutaneous T-cell lymphoma, refractory to one prior therapy	1% topical gel/jelly	60 grams/30 days
bexarotene gel (Targretin)		1% topical gel/jelly	60 grams/30 days

Initial Evaluation

I. **Bexarotene (Targretin)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Bexarotene (Targretin) will **not** be used in combination with mechlorethamine (Valchlor);; **AND**
   D. If the member is a woman of child-bearing potential, the prescriber attests the member has had a negative pregnancy test prior to starting therapy; **AND**
   E. A diagnosis of **primary cutaneous T-cell lymphoma** (e.g., mycosis fungosides, Sezary Syndrome) when the following are met:
      1. For the request of **bexarotene capsules or liquid capsules**;
         i. The member is relapsed and/or refractory to one prior systemic therapy (e.g., oral retinoids, interferon, methotrexate, cyclophosphamide, chemotherapy); **AND**

ii. The request is for generic bexarotene capsules or liquid capsules, unless generic bexarotene has been ineffective or contraindicated; **AND**
iii. A body surface area that has been documented utilizing weight recorded in the past three months ; **AND**
iv. The dose prescribed does not exceed 300 mg/m2/day for at least eight weeks before dose escalation to a maximum of 400 mg/m2/day; **OR**

2. For the request of **bexarotene (Targretin) topical gel/jelly**;
   i. The member has stage IA or IB disease (i.e., limited/localized skin involvement); **AND**
   ii. The member has had a relapse, refractory of, or intolerance to at least two other skin-directed therapies (e.g., mechlorethamine, corticosteroids, phototherapy, imiquimod, topical retinoids); **AND**
   iii. The request is for generic bexarotene gel, unless generic bexarotene gel has been ineffective or contraindicated

II. Bexarotene (Targretin) is considered investigational when used for all other conditions, including but not limited to:
   A. Breast cancer
   B. Lung cancer
   C. Gastroesophageal cancers
   D. Acute myeloid leukemia
   E. Non-Hodgkin Lymphoma
   F. Thyroid cancer
   G. Aids-related Kaposi's sarcoma
   H. Alzheimer's disease
   I. Schizophrenia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited response to therapy as evidenced by an improvement in CAILS score **or** a decrease in affected surface area, plaque/scale elevation, or severity; **AND**
IV. For **bexarotene capsules or liquid capsules**:
   A. A body surface area that has been documented utilizing weight recorded in the past three months; **AND**
   B. The dose will not exceed 400 mg/m2/day; **AND**
   C. The request is for generic bexarotene capsules or liquid capsules, unless generic bexarotene has been ineffective or contraindicated; **OR**
V. For **bexarotene (Targretin) gel/jelly**:

A. The request is for generic bexarotene gel, unless generic bexarotene gel has been ineffective or contraindicated

Supporting Evidence

I. Bexarotene (Targretin) gel was evaluated in an open-label, Phase I-II trial for the treatment of early stage (IA-IIA) cutaneous T-cell lymphoma in those that were refractory, intolerant to, or reached plateaued response to two prior therapies. Tumor response was assessed via the Composite Assessment of Index Lesion Disease Severity, and was based on a summation of the grades for index lesions, erythema, scaling, plaque elevation, hypo or hyperpigmentation, and area of involvement. Partial response was defined as improvement of at least 50% of the index lesions and did not require confirmation by biopsy. The primary outcome was overall response rate, which occurred in 26% (CI 15%, 40%) of subjects. There was no response seen in those that had stage II disease; thus, the FDA-approval was granted to stage IA/IB only. Additionally, due to the single-arm, open-label trial design, results should be interpreted with caution.

II. Bexarotene (Targretin) capsules were evaluated as systemic therapy in 152 subjects, with advanced and early stage cutaneous T-cell lymphoma in two, open-label trials. Those with advanced disease had been treated with at least one prior systemic therapy, but with a median of two, and up to six therapies. Early disease subjects were intolerant to, were refractory to, or reached plateaued response to two prior therapies. Therapy was initiated at a starting dose of 650 mg/m2/day, with a dose reduction to 500 mg/m2/day; however, neither was tolerated in the study population. The dose was further reduced to 300 mg/m2/day with a dose increase to 400 mg/m2/day if no response was see after eight weeks of therapy. Tumor response was assessed by observation using Composite Assessment of Index Lesion Disease Severity. The endpoint was based on a summation of the grades, erythema, scaling, plaque elevation, hypo or hyperpigmentation and area of involvement. Presence or absence of cutaneous tumors and extra cutaneous manifestations was considered in the response assessment. Tumor responses required confirmation over at least two assessments separated by at least four weeks and partial response was defined as improvement of at least 50% in the index lesions without worsening or development of new cutaneous tumors or non-cutaneous manifestations. At the initial dose of 300 mg/m2/day, one subject had complete clinical tumor response, and 30% (19/62) had partial response. Median duration of tumor response had not been reached by the end of the study. Reponses may be seen as early as four weeks. Due to the single-arm, open-label trial design, results should be interpreted with caution.

III. Commonly utilized skin-directed therapies for cutaneous T-cell lymphoma (e.g., mycosis fungosides, Sezary Syndrome) include the following: topical corticosteroids, topical mechlorethamine (nitrogen mustard), local radiation, topical retinoids (tazarotene, bexarotene), phototherapy, imiquimod, and topical carmustine.

IV. Commonly utilized systemic therapies for cutaneous T-cell lymphoma include the following: brentuximab vedotin, bexarotene, interferons, methotrexate, mogamulizumab, romidepsin, vorinostat, gemcitabine, doxorubicin, and pralatrexate.

V. The cost of one 60-gram tube of topical bexarotene (Targretin) is approximately $30,500; therefore, a quantity limit of one tube per 30-day supply is in place to ensure appropriate use without waste. Should a quantity exception be requested, clinical consideration will be taken to

the amount of body surface area the medication is being applied, rate of application, and amount utilized with administration.

Investigational or Not Medically Necessary Uses

I. Bexarotene (Targretin) has not been sufficiently evaluated and/or is currently in clinical trials for the following indications:
   A. Breast cancer
   B. Lung cancer
   C. Gastroesophageal cancer
   D. Acute myeloid leukemia
   E. Non-Hodgkin Lymphoma
   F. Thyroid cancer
   G. Aids-related Kaposi's sarcoma
   H. Alzheimer's disease
   I. Schizophrenia

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Brenaman D., Duvic M., Kuzel T., et al. Phase 1 and 2 trial of bexarotene gel for skin directed treatment of patients with cutaneous T cell lymphoma. Arch Dermatol 2002; 138:325-332.
2. Heald P., Mehlmauer M., Martin AG., et al. Topical bexarotene therapy for patients with refractory or persistent early stage cutaneous T cell lymphoma: results of the phase III clinical trial. J Am Acad Dermatol 2003; 49:801-815.
3. Duvic M., Martin AG., Kim Y., et al, Phase 2 and 3 clinical trial of oral bexarotene (Targretin capsules) for the treatment of refractory or persistent early-stage cutaneous T-cell lymphoma. Arch Dermatol. 2001; 137:581-593.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to include generic bexarotene gel (generic Targretin); added trial and failure of generic bexarotene gel (generic Targretin) prior to use of the branded product	06/2022
Prior authorization criteria transitioned to policy format, age edit added, updated specialist prescriber requirement to new format, removal of liver function test monitoring requirements. Addition of topical bexarotene (Targretin) to the policy. Initial approval criteria increased from six to 12 months.	11/2019
Previous Reviews	08/2008; 10/2008; 07/2012; 09/2012; 12/2012; 11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP116

Split Fill Management*

Description

Bosutinib (Bosulif) is a tyrosine kinase inhibitor that inhibits the Bcr-Abl kinase which promotes chronic myelogenous leukemia (CML). It is also known to inhibit Src-family kinases including Src, Lyn, and Hck.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
bosutinib (Bosulif)	100 mg tablets	CML, newly diagnosed chronic phase; CML, resistant or intolerant to prior therapy	90 tablets/30 days
	400 mg tablets		30 tablets/30 days
	500 mg tablets		30 tablets/30 days
	50 mg capsules		90 tablets/30 days
	100 mg capsules		30 tablets/30 days

Initial Evaluation

I. Bosutinib (Bosulif) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
   C. A diagnosis of **chronic myelogenous leukemia (CML)** when the following are met:
      1. Newly diagnosed chronic phase Philadelphia chromosome-positive (Ph+) CML; **OR**
      2. Chronic, accelerated, or blast phase Ph+ CML; **AND**
         i. Resistant or intolerant to prior treatment with a tyrosine kinase inhibitor [e.g. imatinib (Gleevec), dasatinib (Sprycel), nilotinib (Tasigna)]

II. Bosutinib (Bosulif) is considered investigational when used for all other conditions, including but not limited to:
   A. Glioblastoma
   B. Dementia
   C. Non-small cell lung cancer
   D. Mesothelioma
   E. Bladder cancer
   F. Ovarian, peritoneal, uterine cervical cancer
   G. Thymoma

H. Thymus cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication is prescribed by, or in consultation with, an oncologist; **AND**
IV. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
V. Documentation of response to treatment, defined by the stabilization of disease or a decrease in tumor size or tumor spread.

Supporting Evidence

I. Bosutinib (Bosulif) is indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy OR newly diagnosed chronic phase Ph+ CML.
II. Prior therapy may include, but is not limited to, one of the following: imatinib (Gleevec), dasatinib (Sprycel), and/or nilotinib (Tasigna).
III. All TKIs are all highly effective with no differences in overall survival between imatinib and the second generation TKI therapies bosutinib, dasatinib, or imatinib.
IV. Members with primary treatment resistance to imatinib can be treated with any second generation TKI therapy (bosutinib, dasatinib, or nilotinib), while giving consideration to BCR-ABL1 mutation status. The second-generation TKI therapies are active against many mutations resistant to imatinib.
V. Members with primary treatment resistance to bosutinib, dasatinib, or nilotinib may be treated with any alternate TKI other than imatinib and giving consideration for BCR-ABL Mutation status.
VI. Treatment recommendations from NCCN Guidelines - Version 02.2020 CML

THERAPY	CONTRAINDICATED MUTATIONS
Bosutinib	T315I, V299L, G250E, or F317L
Dasatinib	T315I/A, F317L/V/I/C or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I or G250E

VII. Intolerance is defined as progression while taking a TKI, and/or the inability to tolerate the current minimum recommended dose, or inability to dose-increase due to toxicity. Resistance and intolerance to both dasatinib (Sprycel) and nilotinib (Tasigna) are manifested similarly to that of imatinib (Gleevec).
VIII. Disease progression is defined as transformation to accelerated or blast phase, or loss of previously attained response. Treatment was continued until disease progression (transformation to accelerated or blast phase, or loss of previously attained response),

unacceptable toxicity, or withdrawal of consent. Patients were removed from the study if they were unable to tolerate a bosutinib (Bosulif) dose of ≥ 300 mg/d.

Investigational or Not Medically Necessary Uses

I. There is limited to no evidence to support the use of bosutinib (Bosulif) in any other condition.
II. Glioblastoma
    A. Bosutinib (Bosulif) was evaluated in small phase 2 study in adults with recurrent glioblastoma, however the study met pre-specified criteria for early closure due to progression. Bosutinib (Bosulif) monotherapy does not appear to be effective in recurrent glioblastoma.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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5. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia – v.2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 50mg and 100mg capsules to QL	2024
Prior authorization criteria transitioned to policy format. Updated requirement of prior therapy to state prior tyrosine kinase inhibitor rather than stating imatinib. Extended renewal duration from four months to 12 months. Required agent be used as monotherapy and not in combination with other oncologic medications.	12/2019
Previous Reviews	02/2013; 01/2018; 12/2018;

Policy Type: PA Pharmacy Coverage Policy: UMP067

Description

Testosterone is the primary endogenous androgen responsible for promoting growth and development of male sex organs and the maintenance of secondary sex characteristics.

Length of Authorization

- Initial:
  - i. **For delayed puberty in males (e.g. constitutional growth delay)**: six months
  - **ii. All other indications**: 12 months
- Renewal:
  - i. **For delayed puberty in males (e.g. constitutional growth delay)**: six months; NOT to exceed 18 months of treatment
  - ii. **All other indications**: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
testosterone (Androderm)	Primary hypogonadism; hypogonadotropic hypogonadism; metastatic breast cancer; delayed puberty (males) (e.g. constitutional growth delay)	2 mg/24 hour patch	60 patches/30 days
		4 mg/24 hour patch	30 patches/30 days
testosterone (Axiron)		30 mg actuation roll-on solution	110 ml/30 days
testosterone (Natesto)		5.5 mg/actuation nasal gel	22 g/30 days
testosterone (Striant)		30 mg buccal system	60 buccal systems/ 30 days
testosterone 1% (AndroGel, Testim, Vogelxo)		25 mg/2.5gm gel	300 g/30 days
		50 mg/5gm gel	300 g/30 days
		1.25 g/actuation gel pump	300 g/30 days
testosterone 1.62% (AndroGel, Vogelxo)		20.25 mg/ 1.25 gm gel packet	150 g/30 days
		40.5 mg/2.5gm gel packet	150 g/30 days
		20.25 mg/actuation gel pump	150 g/30 days
testosterone 2% (Fortesta)		10mg/ actuation gel	120 g /30 days
testosterone cypionate (Depo-testosterone)		100mg/ mL intramuscular injection	8 mL/28 days
		200mg/ mL intramuscular injection	4 mL/28 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Testosterone enanthate	Primary hypogonadism; hypogonadotropic hypogonadism; metastatic breast cancer; delayed puberty (males) (e.g. constitutional growth delay)	200 mg/mL intramuscular injection	4 mL/28 days
testosterone enanthate (Xyosted)	Primary hypogonadism; hypogonadotropic hypogonadism	50 mg/ 0.5 mL subcutaneous solution autoinjector	5 mL/28 days
		75 mg/0.5 mL subcutaneous solution autoinjector	5 mL/28 days
		100 mg/ 0.5 mL subcutaneous solution autoinjector	4 mL/28 days
testosterone undecanoate (Jatenzo, Tlando, Kyzatrex)	Primary hypogonadism; hypogonadotropic hypogonadism	100 mg capsule	60 capsules/30 days
		150 mg capsule	120 capsules/30 days
		158 mg capsule	120 capsules/30 days
		198 mg capsule	120 capsules/30 days
		200 mg capsule	120 capsules/30 days
		237 mg capsules	60 capsules/30 days
		112.5mg capsules	120 capsules/30 days
methyltestosterone (Methitest)	Primary hypogonadism; hypogonadotropic hypogonadism; metastatic breast cancer; delayed puberty (males) (e.g., constitutional growth delay)	10 mg tablets or capsules	Men: 150 tablets /30 days Women: 600 tablets/30 days

Initial Evaluation

Generic testosterone cypionate injection, generic testosterone enanthate injection, and generic topical testosterone (generic Androgel) are preferred agents.

- There is no prior authorization required on these preferred generic agents, unless requesting over the allowed quantity limits noted above.

I. **Methyltestosterone (Methitest), testosterone (Androderm, Axiron, Natesto, Striant), testosterone 1% (AndroGel, Testim, Vogelxo), testosterone 1.62% (AndroGel, Vogelxo), testosterone 2% (Fortesta), testosterone cypionate (Depo-testosterone), testosterone enanthate (Xyosted), testosterone undecanoate (Jatenzo, Tlando, Kyzatrex)** may be considered medically necessary when the following criteria are met:

A. A diagnosis of one of the following:

1. **Gender dysphoria; OR**
2. **Delayed puberty in males (e.g. constitutional growth delay); AND**
   i. Age is 14 years or older; **AND**

ii. Prescribed by, or in consultation with, an endocrinologist; **AND**
iii. Treatment with one of the following as been ineffective, contraindicated, or not tolerated:
a. generic testosterone enanthate; **OR**
b. generic testosterone cypionate; **OR**

3. **Metastatic breast cancer; AND**
i. Age is 18 years or older; **AND**
ii. Prescribed by, or in consultation with, an oncologist; **AND**
iii. Treatment with one of the following has been ineffective, contraindicated, or not tolerated:
a. Generic injectable testosterone cypionate; **OR**
b. Generic injectable testosterone enanthate; **OR**

4. **Primary or Secondary Hypogonadism; AND**
i. Diagnosis further defined as one of the following:
a. Primary hypogonadism (testicular failure) due to: Klinefelter syndrome (KS), cryptorchidism, orchiectomy, vanishing testes syndrome, chemotherapy affecting or radiation to the testes, testicular trauma, torsion, infectious orchitis, HIV infection, anorchia syndrome, or myotonic dystrophy; **OR**
b. Secondary hypogonadism (pituitary-hypothalamic hypogonadism) due to: hypothalamic or pituitary tumor, iron overload syndromes, idiopathic hypogonadotropic hypogonadism, hyperprolactinemia, head trauma, pituitary surgery, or radiation; **AND**
ii. (For adults only) Two sub-normal testosterone concentration levels taken on two separate mornings while fasting; **AND**
iii. Treatment with all of the following has been ineffective, contraindicated, or not tolerated**:**
a. Generic injectable testosterone; **AND**
b. Generic topical testosterone (generic AndroGel);

II. Testosterone is considered not medically necessary when used for all other conditions, including
A. Men with low testosterone concentration and without clinical symptoms and signs consistent with testosterone deficiency. The routine assessment of testosterone level in the absence of hypogonadal symptoms is not advised.
B. Men with a single, sub-normal testosterone concentration that is not repeatable per the U.S. Endocrine Society.
C. Men with symptoms of hypogonadism, however, present with testosterone level within normal range upon initial presentation.

III. Testosterone is considered investigational when used for all other conditions, including but not limited to:
A. Age-related hypogonadism in adults
B. Men with type 2 diabetes mellitus with low testosterone for the purpose of improving glycemic control

C. For the healing of fracture
D. Functional uterine bleed
E. Treatment of weight loss unrelated to HIV-wasting

Renewal Evaluation

I. Member has received a previous prior authorization approval for a brand testosterone or high cost generic agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member has exhibited improvement or stability of disease symptoms from baseline (e.g., improved mood, decreased fatigue, no or diminished signs of gynecomastia, endogenous testosterone levels increasing after stopping therapy, testes enlargement); **AND**
III. (For Adults Only) One testosterone level within mid-normal range taken within the last 12 months that indicates improvement from baseline levels (pre-treatment); **AND**
IV. If diagnosis of **Delayed puberty (e.g. constitutional growth delay):**
    a. Has NOT had more than 18 months of treatment.

Supporting Evidence

I. Per the 2018 AUA guidelines, diagnosis of hypogonadism should be confirmed prior to initiating testosterone replacement therapy. Testosterone levels should be drawn ideally between 8 and 10 AM while fasting due to the diurnal fluctuation of testosterone and its sensitivity to glucose ingestion. A separate, confirmatory measurement is recommended. Thirty percent of men with an initial testosterone concentration in the hypogonadal range can have a measurement within the normal range on repeat measurement.
II. The Endocrine Society strongly advises against “trial periods” of testosterone in men with a single sub-normal testosterone concentration and vague symptoms of deficiency.
III. The benefit of increasing testosterone concentration has only been shown in patients with organic hypogonadism due to disorders of the hypothalamus, pituitary or testes.
IV. In patients within normal range, or have low testosterone concentration due to age, obesity, or otherwise, the benefit of increased testosterone has not been shown. Rather, in this patient population with low testosterone and an intact gonadal system, increasing testosterone is associated with an increase of certain health risks, including cardiovascular disease. Due to this, the FDA has required manufacturers to label testosterone products warning of the increased risk for heart attack and stroke.
V. Lower limit of the normal total testosterone (TT) to the CDC standard in healthy, non-obese young men is 264 ng/dL (9.2 nmol/L).The lower limit of normal range is considered to be <150 ng/dL, with a noted normal range of 200 to 400 ng/dL. For adult patients, it is recommended to confirm low T concentrations as 30% of men will present with a normal T concentration value when measured again.
VI. Testosterone replacement therapy is subject to abuse at doses higher than recommended for approved indications and in combination with other anabolic androgenic steroids. Abuse-related adverse events include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, hepatotoxicity, and serious psychiatric complaints.

VII. Guidelines advise to monitor testosterone levels 3-6 months after initiation of therapy and then annually. Serum testosterone concentrations should be brought into the mid-normal range. Testosterone levels may vary depending on dosage form.

VIII. Boys undergo puberty development around the age of 14. Bone age is delayed by 2 years or more in bone maturation in patients with delayed puberty, though not a diagnostic approach but characteristic of disease. Delayed puberty can be treated with short term hormonal therapy by administering testosterone enanthate or cypionate (50 mg IM once monthly) for six months and then reassess endogenous gonadal function and size six months later. Pubertal development was indicated by testicular enlargement and increasing testosterone concentrations after the cessation of therapy. It is unusual for a boy with delayed puberty to require more than two three- to six-month courses of testosterone therapy before spontaneous puberty occurs.

IX. Pediatric testosterone levels are to be very low or not present as boys may not have functioning testes or without testes. Guidelines recommend testing for other blood tests including LH, FSH, TSH. It is not reasonable nor recommended to require pediatric patients to check multiple blood tests.

X. Generic injectable testosterone is primarily used in delayed puberty due to amount of reliable data available; other formulations or salts have not been studied in patients under the age of 18 and are otherwise not readily recommended.

XI. Use of bone age is indicated as characteristic of delayed puberty, but not an absolute indication. The potential adverse effect on bone maturation should be discussed with the patient and parents prior to androgen administration. X-ray of the hand and wrist to determine bone age should be obtained every six months to assess the effect of treatment on the epiphyseal centers.

XII. Androgens in metastatic breast cancer (women that are 1-5 years postmenopausal advanced inoperable metastatic breast cancer or in premenopausal women who have benefited from oophorectomy with hormone response tumors) is rare, including testosterone use. Androgens were found inferior to high-dose estrogens, even though response rates are high. Additionally, if androgen therapy is required, the preferred formulation is fluoxymesterone.

Investigational or Not Medically Necessary Uses

I. Testosterone products are considered not medically necessary when used for conditions or settings listed below:
   A. Men with low testosterone concentration and without clinical symptoms and signs consistent with testosterone deficiency. The routine assessment of testosterone level in the absence of hypogonadal symptoms is not advised.
   B. Men with a single, sub-normal testosterone concentration that is not repeatable per the U.S. Endocrine Society.
   C. Men with symptoms of hypogonadism, however, present with testosterone level within normal range upon initial presentation.

II. Testosterone products have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Age-related hypogonadism

i. The role of testosterone replacement to treat the natural decline in serum testosterone common in men over the age of 60, without identified pituitary or hypothalamic disease, is uncertain.

B. Men with type 2 diabetes mellitus with low testosterone for the purpose of improving glycemic control
C. For the healing of fracture
D. Functional uterine bleed
E. Treatment of weight loss unrelated to HIV-wasting

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Appendix:

I. Testosterone lab monitoring assessment based on dosage form

Dosage Form	Recommendation
Injectable enanthate/cypionate	Adjust dose or frequency if >600 or <350 ng/dL
Transdermal gels	Assess 2-8 hours following application
Transdermal patches	Assess 3-12 hours after application
Buccal bioadhesive tablet	Assess immediately before or after fresh application
Oral undecanoate	Assess 3-5 hours after ingestion with fat-containing meal

Injectable undecanoate	Assess at end of the dosing interval prior to next injection

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new medication Tlando capsules. Added methyltestosterone (Methitest) and accompanying indications. Removed Aveed® as it is HCP administered medication. Updated initial criteria to remove including removal of age requirement and pertinent negative cancer assessments in hypogonadism use. Added renewal criteria. Added criteria for delayed puberty in males and metastatic breast cancer. Updated policy name.	09/2022
Change to policy format; added supplementary evidence section; updated references	07/2018
Add methyltestosterone to policy, remove DDID column from QL section	12/2019
Policy created	06/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP258

Description

Budesonide (Tarpeyo) is an orally administered corticosteroid indicated to reduce the loss of kidney function in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression.

Length of Authorization

- Initial: Ten months
- Renewal: No renewal

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
budesonide (Tarpeyo)	Primary Immunoglobulin A Nephropathy (IgAN)	4 mg capsules	120 capsules/30 days

Initial Evaluation

I. **Budesonide (Tarpeyo)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a nephrologist; **AND**
   C. A diagnosis of **primary immunoglobulin A nephropathy (IgAN)** when the following are met:
      1. Diagnosis of Primary immunoglobulin A nephropathy (IgAN) has been confirmed by a kidney biopsy; **AND**
      2. Member has an eGFR ≥ 35mL/min/1.73 m^2; **AND**
      3. Documentation of elevated protein levels in urine as indicated by proteinuria ≥ 1 g/day or urine protein to creatinine ratio (UPCR) of ≥ 1.5 g/g; **AND**
      4. Member has been optimized on an ACE inhibitor (e.g., lisinopril, benazepril, etc.) or an ARB (e.g., losartan, olmesartan, valsartan, etc.) at a maximum tolerated dose for at least three months; **AND**
      5. Treatment will be used in combination with an ACE inhibitor or ARB; **OR**
         i. Treatment with an ACE inhibitor or ARB has been contraindicated or not tolerated; **AND**
      6. Member has documentation of intolerance or contraindication to generic systemic corticosteroid therapy (e.g., prednisone, prednisolone, methylprednisolone).

II. Budesonide (Tarpeyo) is considered investigational when used for all other conditions, including but not limited to:
   A. IgAN in members less than 18 years of age

B. Secondary IgA Nephropathy
C. Budesonide (Tarpeyo) used in combination with sparsentan (Filspari)
D. Focal segmental glomerulosclerosis (FSGS)
E. Chronic kidney disease (CKD) other than primary IgAN

Renewal Evaluation

I. N/A – Product not eligible for renewal

Supporting Evidence

I. Budesonide (Tarpeyo) is the first therapy FDA approved for the treatment of patients with primary immunoglobulin A (IgA) nephropathy. IgA nephropathy, also known as Berger's disease, is a rare kidney disease that occurs when IgA antibody deposits build up in the kidneys, causing inflammation that damages kidney tissues. The deposits can cause the kidneys to leak blood and protein into the urine. IgA nephropathy complications can include high blood pressure and chronic kidney disease, which can sometimes progress to kidney failure. As such, patients should be managed in consultation with a nephrologist.
II. Clinical studies NEFIGAN and NefIgArd were conducted in adult patient populations (18 years of age and older). The efficacy and safety of budesonide (Tarpeyo) in pediatric populations is unknown at this time. Additionally, guidelines indicate there is insufficient data currently available to recommend that pediatric IgAN populations be managed as adults.
III. Budesonide (Tarpeyo) was studied in a phase 3, multicenter, randomized, double-blind, placebo controlled trial (NefIgArd). The trial consisted of two parts. Part A which included a screening period, 9-month treatment period, with a 3-month follow-up (including a 2-week taper) and part B which consisted of a 15-month observational follow-up period where no treatment was given. The primary endpoint of part A was the ratio of urinary protein-creatinine ratio (UPCR) at 9 months following the first dose of study drug compared to baseline. In part B, the primary endpoint assessed the time-weighted average of change in eGFR from baseline.
    - The trial met the prespecified part A primary endpoint based on an interim analysis of 199 randomized patients who had completed the Month 9 visit. The interim analysis showed a 31% reduction in UPCR in patients treated with budesonide (Tarpeyo) 16 mg once daily compared to placebo (95% CI: 16% to 42% reduction; p=0.0001). In the final analysis of 364 patients, the percentage change in UPCR observed at 9 months was consistent with the results in the subset of 199 patients included in the interim analysis.
    - In the final analysis of 364 patients, the trial met the prespecified part B primary endpoint (p<0.0001). The favorable effect of budesonide (Tarpeyo) on eGFR was seen by Month 3 (the earliest assessment) and did not appear to increase in magnitude over two years. At Year 2, there was a 5.9 mL/min/1.73 m2 difference in the mean change from baseline in eGFR between budesonide (Tarpeyo) and placebo (95% CI: 3.3 to 8.5 mL/min/1.73 m2 ; p<0.0001).
    - The most commonly reported treatment-emergent adverse events during treatment with budesonide (Tarpeyo) were peripheral edema (31 [17%] of 182 patients vs placebo, 7 [4%] of 182 patients), hypertension (22 [12%] vs six [3%]), muscle spasms

(22 [12%] vs 7 [4%] patients), acne (20 [11%] vs 2 [1%]), and headache (19 [10%] vs 14 [8%]).

IV. In clinical studies participants underwent treatment for budesonide (Tarpeyo) for nine months followed by a two-week dose taper. Given treatment is a course of high dose steroid, dose tapering is recommended to avoid steroid withdrawal syndrome.

V. KDIGO guidelines indicate IgAN can only be diagnosed with a kidney biopsy. While there are several prognostic scoring tools that have been developed to assist in predicting kidney outcomes of IgAN patients (i.e., MEST-C, International IgAN Prediction Tool, etc.) there are currently are no validated diagnostic serum or urine biomarkers.

VI. Reduced glomerular filtration rates can be a marker of kidney disease; specifically, those under 35mL/min/1.73 m^2 which can indicate moderate-to-severe kidney disease (stage 3b). Guidelines recommend supportive care for these patients with moderate-to-severe kidney disease as opposed to therapy with corticosteroids.

VII. The primary focus of IgAN management is optimized supportive care (i.e., blood pressure management, maximally tolerated ACEi/ARBs, lifestyle modification, and reduction of cardiovascular risks). Proteinuria and eGFR are the only validated prognostic serum or urine biomarkers in IgAN. In all types of proteinuric glomerular diseases, including IgAN, higher levels of proteinuria are associated with worse kidney outcomes (acute kidney injury, chronic kidney disease, end stage renal disease, etc.). Reduction in proteinuria, independent of blood pressure control, is associated with improved kidney outcomes. KDIGO guidelines recommend that all patients with proteinuria >0.5 g/d, irrespective of whether they have hypertension, be treated with either an ACEi or ARB to further protect renal function.

VIII. Patients with IgAN who are at high risk of progressive chronic kidney disease (CKD) despite maximal supportive care are defined as those with proteinuria greater than 0.75 to 1 g/day despite treatment with a maximally tolerated or allowed daily dose of RAS blockade (ACEi/ARB) for ≥ 3 months. Guideline recommendations indicate proteinuria reduction to under 1 g/day as a surrogate marker of improved kidney outcomes in IgAN. Furthermore, a reduction to under 1 g/day is a reasonable treatment target.

IX. Incremental levels of sustained proteinuria above 1 g/d are associated with marked changes in the risk of loss of kidney function. Reduction of proteinuria, ideally to under 1 g/d, is associated with favorable outcomes. The urinary protein-creatinine ratio (UPCR) has relatively poor correlation with 24-hour urine protein excretion, particularly when proteinuria is over 1 g/d. This makes distinguishing smaller changes in proteinuria (e.g., 1.5 vs 2 g/d) challenging. UPCR cannot be directly compared with a 24-h proteinuria level; however, UPCR gives the ability to overcome possible collection errors and deviations from normal creatinine excretion (e.g., physically active and muscular men). Due to this reason both can be used to assess proteinuria.

X. Budesonide (Tarpeyo) has not been included in KDIGO guidelines. Currently guidelines recommend enrollment into clinical trials prior to use of corticosteroids or other immunosuppressants. If the benefit outweighs the risk, treatment with prednisone or methylprednisolone is recommended based on limited clinical trial experience. Budesonide (Tarpeyo) was able to show sustained benefit UPCR reduction eGFR maintenance at two years. Other glucocorticoid therapies (prednisone, methylprednisolone, and IV methylprednisolone) have demonstrated similar reductions in proteinuria and have comparable safety profiles to budesonide (Tarpeyo). It is unknown if budesonide (Tarpeyo) is superior to other glucocorticoid

therapies that could be utilized. Additionally, budesonide (Tarpeyo) is significantly more costly than other glucocorticoid therapies. Of the other alternative agents, mycophenolate Mofetil (MMF) is the preferred option. There is limited clinical data to support the use of other immunosuppressive agents.

XI. Endpoints from other corticosteroid studies followed patients for up to 10 years. Safety and efficacy of treatment with subsequent courses of budesonide (Tarpeyo) have not been established at this time. Data to support possible retreatment with budesonide (Tarpeyo) is under evaluation in the NefigArd-OLE trial program. Similarly designed trials with long-term safety data have limited total glucocorticoid exposure to six months due to increased risks of treatment-related adverse events (infection risk, impaired glucose tolerance, weight gain, etc.).

Investigational or Not Medically Necessary Uses

I. Budesonide (Tarpeyo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. IgAN in members less than 18 years of age
      i. The use of budesonide (Tarpeyo) has not been evaluated in children. Additionally, while guidelines acknowledge use of immunosuppressants, specifically corticosteroids, are more widespread in children there is a lack of randomized controlled trials and consensus-driven indications for use in pediatric populations. As in adults, children with rapidly progressive IgAN have a poor outcome, and despite limited evidence, this subgroup should be offered treatment with glucocorticoids (usually as methylprednisolone pulses) and cyclophosphamide.
   B. Secondary IgA Nephropathy
      i. Secondary IgAN can be attributed to a variety of other disorders including but not limited to cirrhosis and other severe forms of liver disease, celiac disease, HIV infection, monoclonal gammopathy of renal significance (MGRS), seronegative arthritis, etc. While there is no standard of care treatment for IgAN in these patients, therapy should be directed at the underlying primary disease.
   C. Budesonide (Tarpeyo) used in combination with Sparsentan (Filspari)
   D. Focal segmental glomerulosclerosis (FSGS)
   E. Chronic kidney disease (CKD) other than primary IgAN

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease State
sparsentan (Filspari)	Primary IgA nephropathy; at high risk of progression

Policy Implementation/Update:

Action and Summary of Changes	Date
Added related policies table. Updated to allow a pathway to coverage through standard criteria.	01/2023
Policy created.	04/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP009

Description

FEIBA is an anti-inhibitor complex indicated for use in hemophilia A and B patients with inhibitors. NovoSeven RT is a recombinant coagulation factor VIIa for patients with hemophilia A and B with inhibitors, acquired hemophilia, congenital factor VII deficiency, and Glanzmann's thrombasthenia refractory to platelet transfusions. Sevenfact is a recombinant coagulation factor VIIa for patients with hemophilia A and B with inhibitors.

Length of Authorization

- Initial: 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- Renewal: 12 months (for prophylaxis); 6 months (for on-demand)

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit
FEIBA, anti-inhibitor coagulant complex	500, 1000, 2500 units	**Control and prevention of bleeding – Hemophilia A or B with inhibitors:** Up to 100 units/kg every six to 12 hours until resolution of bleeding **Routine prophylaxis – Hemophilia A or B with inhibitors:** Up to 85 units/kg every other day **Perioperative management – Hemophilia A or B with inhibitors:** Up to 100 units/kg administered as a one-time dose immediately prior to surgery or up to 100 units/kg administered every six to 12 hours postoperatively until resolution of bleed and healing is achieved	**Control and prevention of bleeding – Hemophilia A or B with inhibitors:** Up to the number of doses requested every 28 days **Routine prophylaxis – Hemophilia A or B with inhibitors:** Up to 1,190 units/kg every 28 days **Perioperative management – Hemophilia A or B with inhibitors:** Up to the number of doses requested for 28 days
NovoSeven RT, coagulation factor VIIa (recombinant)	1 mg/vial (1000 mcg/vial) 2 mg/vial (2000 mcg/vial)	**Control and prevention of bleeding – Hemophilia A or B with inhibitors:** Up to 90 mcg/kg every three to six hours until hemostasis is achieved **Control and prevention of bleeding episodes – Acquired hemophilia:** Up to 90 mcg/kg every two to three hours until hemostasis is achieved	**Control and prevention of bleeding – Hemophilia A or B with inhibitors:** Up to the number of doses requested every 28 days **Control and prevention of bleeding episodes – Acquired hemophilia:** Up to the number of doses requested every 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit
	5 mg/vial (5000 mcg/vial) 8 mg/vial (8000 mcg/vial)	**Control and prevention of bleeding episodes – Factor VII deficiency:** Up to 30 mcg/kg every four to six hours until hemostasis is achieved	**Control and prevention of bleeding episodes – Factor VII deficiency:** Up to the number of doses requested every 28 days
		Control and prevention of bleeding episodes – Glanzmann's Thrombasthenia: Up to 90 mcg/kg every two to six hours until hemostasis is achieved	**Control and prevention of bleeding episodes – Glanzmann's Thrombasthenia:** Up to the number of doses requested every 28 days
		Routine prophylaxis – hemophilia A or B with inhibitors: 90 mcg/kg once daily	**Routine prophylaxis – Hemophilia A or B with inhibitors:** 2,520 mcg/kg per 28 days
		Perioperative management – hemophilia A or B with inhibitors: Up to 90 mcg/kg immediately before surgery, repeat every two hours during surgery, then up to 90 mcg/kg every two hours after surgery for five days, then every four hours or by continuous infusion, via pump, at 50 mcg/kg/hr until healing occurs	**Perioperative management – hemophilia A or B with inhibitors:** Up to the number of doses requested for 28 days
		Perioperative management – acquired hemophilia: Up to 90 mcg/kg immediately before surgery and every two to three hours for the duration of surgery and until hemostasis is achieved	**Perioperative management – acquired hemophilia:** Up to the number of doses requested for 28 days
		Perioperative management – factor VII deficiency: Up to 30 mcg/kg immediately before surgery and every four to six hours for the duration of surgery and until hemostasis is achieved	**Perioperative management – factor VII deficiency:** Up to the number of doses requested for 28 days
		Perioperative management – Glanzmann's Thrombasthenia: Up to 90 mcg/kg immediately before surgery and repeat every two hours for the duration of the procedure,	**Perioperative management – Glanzmann's Thrombasthenia:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit
		then up to 90 mcg/kg every two to six hours to prevent post-operative bleeding	
Sevenfact, coagulation factor VIIa (recombinant) [eptacog beta]	1 mg/vial (1000 mcg/vial) 5 mg/vial (5000 mcg/vial)	**Treatment and control of bleeding – Hemophilia A or B with inhibitors:** 75 mcg/kg repeated every 3 hours until hemostasis is achieved Or Initial dose of 225 mcg/kg. If hemostasis is not achieved within 9 hours, additional 75 mcg/kg doses may be administered every 3 hours as needed to achieve hemostasis	**Treatment and control of bleeding – Hemophilia A or B with inhibitors:** Up to the number of doses requested every 28 days

Initial Evaluation

Hemophilia A (congenital factor VIII deficiency)

I. **FEIBA or NovoSeven RT** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   B. A diagnosis of hemophilia A has been confirmed by blood coagulation testing; **AND**
   C. Clinical documentation confirming that the member has inhibitors to factor VIII [i.e. high anti-FVIII titer (≥ 5 Bethesda units)]; **AND**
   D. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding episodes; **OR**
      2. Perioperative management of bleeding; **OR**
      3. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
         i. Member has had more than one documented episode of spontaneous bleeding; **OR**
         ii. Member has had an inadequate response to Immune Tolerance Induction (ITI); **AND**
      4. Prior therapy with emiziumab-kxwh (Hemlibra) was ineffective, not tolerated, or contraindicated

II. **Sevenfact** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   B. A diagnosis of hemophilia A has been confirmed by blood coagulation testing; **AND**
   C. Clinical documentation confirming that the member has inhibitors to factor VIII [i.e. high anti-FVIII titer (≥ 5 Bethesda units)]; **AND**
   D. Use is planned for on-demand treatment and control of bleeding episodes ***only***

Hemophilia B (congenital factor IX deficiency)

I. **FEIBA** or **NovoSeven RT** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   B. A diagnosis of hemophilia B has been confirmed by blood coagulation testing; **AND**
   C. Clinical documentation confirming that the member has inhibitors to factor VIX [i.e. high anti-IX titer (≥ 5 Bethesda units)]; **AND**
   D. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding episodes; **OR**
      2. Perioperative management of bleeding; **OR**
      3. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
         i. Member has had more than one documented episode of spontaneous bleeding; **OR**
         ii. Member has had an inadequate response to Immune Tolerance Induction (ITI)

II. **Sevenfact** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   B. A diagnosis of hemophilia B has been confirmed by blood coagulation testing; **AND**
   C. Clinical documentation confirming that the member has inhibitors to factor VIX [i.e. high anti-IX titer (≥ 5 Bethesda units)]; **AND**
   D. Use is planned for on-demand treatment and control of bleeding episodes ***only***

<u>Acquired Hemophilia</u>

I. **NovoSeven RT** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   B. A diagnosis of acquired hemophilia has been confirmed by blood coagulation testing; **AND**
   C. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding episodes; **OR**
      2. Perioperative management of bleeding

<u>Congenital Factor VII Deficiency</u>

I. **NovoSeven RT** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   B. A diagnosis of congenital factor VII deficiency has been confirmed by blood coagulation testing; **AND**
   C. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding episodes; **OR**
      2. Perioperative management of bleeding

<u>Glanzmann's Thrombasthenia</u>

I. **NovoSeven RT** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   B. A diagnosis of Glanzmann Thrombasthenia has been confirmed by blood coagulation testing; **AND**
   C. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding episodes; **OR**
      2. Perioperative management of bleeding; **AND**
   D. The use of platelet transfusions is known or suspected to be ineffective or contraindicated

II. FEIBA, NovoSeven RT, Sevenfact are considered investigational when used for all other conditions.

Renewal Evaluation

I. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline

Supporting Evidence

I. People with hemophilia A can develop antibodies to the factor replacement product that can interfere with the ability to treat bleeding and achieve adequate homeostasis. These antibodies, called inhibitors, develop in about 23-30% of people with Hemophilia A. Inhibitors often develop during childhood, especially during the first 50 exposure days to factor, with the greatest risk occurring between the first ten to 20 treatments.
II. Patients with hemophilia A or B who develop inhibitors to factor VIII or IX may no longer respond to clotting factor VIII or IX products to prevent or control bleeding episodes.
III. Treatment options for people who develop inhibitors are limited. Immune tolerance induction (ITI) is the main method for inhibitor eradication. It involves the administration of repeated doses of factor to tolerize the individual's immune system to the factor and reduce antibody production.
IV. Other options to treat bleeding in patients with inhibitors include bypassing products [e.g. recombinant activated factor VII (NovoSeven RT), factor eight inhibitor bypassing agent (FEIBA)], plasmapheresis, recombinant coagulation factor VII activated (Sevenfact), and high-dose factor infusion. Emicizumab-kxwh (Hemlibra) is indicated for prophylaxis in patients with hemophilia A and inhibitors. Choice of therapy is individualized and dependent on many factors.
V. A bypassing agent is generally the first choice in a patient with hemophilia A or B who has a high titer inhibitor and requires treatment for bleeding or surgery. Bypassing agents can also be used prophylactically to prevent bleeds. Sevenfact is only indicated for the treatment and control of bleeding episodes at this time. Emicizumab-kxwh (Hemlibra) is only indicated in the setting of prophylaxis.
VI. The bypassing agents contain an activated form of a downstream clotting factor in the coagulation cascade. Activated factor VII (factor VIIa) can directly activate factor X, bypassing the need for factors VIII and IX.

VII. The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) recommends that bypassing agents be used in patients with hemophilia A or B with inhibitors to prevent or control bleeding in settings in which clotting factor VIII or IX would otherwise be used, including before and after surgery and physical therapy.

VIII. In addition, MASAC recommends that prophylaxis with bypassing agents should be considered in patients with inhibitors. Furthermore, any patient with hemophilia A with an inhibitor who is having frequent bleeding episodes and is on either episodic therapy for prophylaxis with bypassing agents will likely derive significant benefit from emicizumab-kxwh (Hemlibra).

IX. Both FEIBA and NovoSeven RT contain activated clotting factors and both are effective for hemostasis in hemophilia. A randomized trial comparing FEIBA and NovoSeven RT demonstrated similar efficacy between the agents for controlling joint bleeds.

X. The safety and efficacy of emicizumab-kxwh (Hemlibra) in adult and pediatric patients with inhibitors was established in two Phase 3 trials (HAVEN 1 and HAVEN 2). Patients treated with emicizumab-kxwh (Hemlibra) experienced significantly fewer bleeds compared to patients who received no prophylaxis.

XI. Emicizumab-kxwh (Hemlibra) prophylaxis has not been directly compared to any other prophylactic regimen (e.g. bypassing agent, factor VIII replacement); therefore, the comparative safety and efficacy is unknown.

XII. The safety and efficacy of NovoSeven RT for congenital factor VII deficiency, acquired hemophilia, and Glanzmann's Thrombasthenia was established based on small trials, including compassionate use trials and registries. NovoSeven RT was shown to be effective in controlling bleeding episodes.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of FEIBA, NovoSeven RT or Sevenfact in any other condition in the outpatient setting.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of Sevenfact	08/2020
New policy created for bypassing agents	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP010

Split Fill Management* [Applies to Cabometyx ONLY]

Description

Cabozantinib (Cabometyx, Cometriq) is an orally administered tyrosine kinase inhibitor of RET, MET, VEGFR1/2/3, KIT, TRKB, FLT3, and TIE2.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*
cabozantinib (Cabometyx®)	20 mg tablet	Advanced and metastatic renal cell carcinoma (aRCC) Progressive or metastatic Hepatocellular (Liver) carcinoma (HCC), in patients previously treated with sorafenib Advanced or metastatic differentiated thyroid carcinoma (DTC) in patients previously treated with vascular endothelial growth factor (VEGF) targeted therapy	30 tablets/30 days
	40 mg tablet		30 tablets/30 days
	60 mg tablet		30 tablets/30 days
cabozantinib (Cometriq®)	60 mg per day blister cards	Progressive or metastatic medullary thyroid carcinoma	84 capsules/28 days
	100 mg per day blister cards		56 capsules/28 days
	140 mg per day blister cards		112 capsules/28 days

**Quantity limits are based on recommended daily dose of cabozantinib for each indication; QL exceptions allowed only for dose reductions*

I. **Cabozantinib (Cabometyx)** may be considered medically necessary when the following criteria below are met:

A. Treatment is prescribed by, or in consultation with, an oncologist; **AND**
B. The member has a diagnosis of one of the following:
    1. **Differentiated Thyroid carcinoma (DTC); AND**
        i. Member is 12 years of age or older; **AND**
        ii. Disease is locally advanced or metastatic (stage III or IV); **AND**
        iii. Member has one of the following subtypes of DTC:
            a. Papillary thyroid carcinoma; **OR**
            b. Follicular thyroid carcinoma; **OR**
            c. Hürthle cell thyroid carcinoma; **AND**
        iv. The disease is refractory to radioactive iodine (RAI) treatment or the member is not eligible for radioactive iodine treatment; **AND**
        v. Member has been previously treated with at least <u>one</u> vascular endothelial growth factor (VEGF) targeted therapy (e.g., Lenvatinib [Lenvima], sorafenib [Nexavar], etc.); **AND**
        vi. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
    2. **Renal cell carcinoma (RCC); AND**
        i. Member is 18 years of age or older; **AND**
        ii. Disease is advanced or metastatic (stage III or IV); **AND**
        iii. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
            a. Prescribed in combination with nivolumab (Opdivo); **OR**
    3. **Hepatocellular (Liver) carcinoma (HCC); AND**
        i. Member is 18 years of age or older; **AND**
        ii. Disease is progressive or advanced stage or greater (stage III or IV); **AND**
        iii. Member has been previously treated with sorafenib (Nexavar); **AND**
        iv. Provider attests the member has Child-Pugh class A liver function; **AND**
        v. Cabozantinib (Cabometyx) is prescribed as monotherapy

II. **Cabozantinib (Cometriq)** may be considered medically necessary when the following criteria below are met:
A. Member is 18 years of age or older; **AND**
B. Treatment is prescribed by, or in consultation with, an oncologist; **AND**
C. Member has a diagnosis of **medullary thyroid carcinoma (MTC)**; **AND**
    1. Disease is locally recurrent progressive or metastatic (stage III or IV); **AND**
    2. Cabozantinib (Cometriq) is prescribed as monotherapy; [cabozantinib (Cabometyx) should not be used for medullary thyroid carcinoma (MTC)].

III. Cabozantinib (Cabometyx or Cometriq) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
A. Adrenocortical carcinoma
B. Anaplastic Thyroid Cancer
C. Breast cancer
D. Cervical Cancer
E. Cholangiocarcinoma
F. Colorectal cancer

G. Head and neck cancer
H. Merkel cell carcinoma and skin cancer
I. Multiple myeloma, acute myeloid leukemia
J. Neuroendocrine Tumors
K. Neurofibromas
L. Non-small cell lung cancer
M. Pheochromocytomas and paraganglioma
N. Prostate cancer
O. Salivary gland cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this Health Plan or has been established on therapy from a previous Health Plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this Health Plan; **AND**
III. There is clinical documentation of response to treatment, such as stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. A diagnosis of one the following:
    A. **Differentiated Thyroid Carcinoma (DTC)**; **AND**
        1. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
    B. **Renal Cell Carcinoma (RCC); AND**
        1. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
            ii. Cabozantinib (Cabometyx) is prescribed in combination with nivolumab (Opdivo); **OR**
    C. **Hepatocellular Carcinoma (HCC); AND**
        1. Cabozantinib (Cabometyx) is prescribed as monotherapy; **OR**
    D. **Medullary Thyroid Carcinoma (MTC)**; **AND**
            i. Cabozantinib (Cometriq) is prescribed as monotherapy

Supporting Evidence

I. Given the complexities surrounding diagnosis and treatment choices, targeted drug therapies such as multi-kinase inhibitors must be prescribed by, or in consultation with, an oncologist.
II. Cabozantinib (Cabometyx) carries three FDA approved indications and is used in the treatment of advanced renal cell carcinoma (RCC) with or without nivolumab (Opdivo), hepatocellular carcinoma (HCC) in patients previously treated with sorafenib, and advanced or metastatic differentiated thyroid carcinoma (DTC) patients previously treated with a vascular endothelial growth factor receptor (VEGFR) targeted therapy. Cabozantinib (Cabometyx) should only be used for these indications due to its specific formulation, dosing, and packaging differences compared to Cabozantinib (Cometriq).
III. Efficacy and safety of cabozantinib (Cometriq) and cabozantinib (Cabometyx) has not been established in patients less than 18 years of age diagnosed with medullary thyroid carcinoma

(MTC), RCC, and HCC. Only cabozantinib (Cabometyx) has been approved for ages 12 years and older in DTC.

IV. Multi-kinase inhibitors are considered medically necessary when used as monotherapy. Efficacy and safety has not been studied in combination with other oncology agents with the exception of cabozantinib (Cabometyx) in combination with nivolumab (Opdivo) in the advanced RCC.

V. **Differentiated thyroid carcinoma (DTC)**

a. DTC is categorized into papillary, follicular, or Hürthle cell cancer subtypes and is unrelated to MTC due to differing pathophysiology, evaluation, and treatment strategies than MTC. Additionally, cabozantinib (Cabometyx) has not been studied for the treatment of MTC.

b. Cabozantinib (Cabometyx) is FDA approved in patients twelve years of age or older with locally advanced or metastatic DTC that are RAI-refractory or ineligible and have progressed on a prior VEGFR-targeted therapy (lenvatinib and/or sorafenib). Cabozantinib (Cabometyx) was evaluated for efficacy and safety in the treatment of DTC via a double-blind, placebo-controlled trial (COSMIC-311). Although the COSMIC-311 trial did not meet one of its co-primary endpoint of statistically significant objective response rate in the first 100 randomized patients versus placebo, the other co-primary endpoint, progression-free survival (PFS) in all patients, was met. Cabozantinib (Cabometyx) significantly reduced the risk of disease progression or death in the primary PFS analysis compared to placebo (median 11 months vs. 1.9 months [HR 0.22; 95% CI 0.15-0.31; p<0.0001]).

c. NCCN v3.2021 guidelines for thyroid carcinoma recommend lenvatinib as the first line preferred regimen in advanced or metastatic DTC. Cabozantinib (Cabometyx) received a Category 1 recommendation for patients that had progression on lenvatinib and/or sorafenib for advanced or metastatic DTC.

d. The recommended dose for cabozantinib (Cabometyx) is 60mg once daily for adults with BSA greater than, or equal to, 1.2 m^2 and 40 mg once daily in pediatric patients 12 years of age and older, with BSA less than 1.2m^2.

VI. **Renal Cell Carcinoma (RCC)**

a. The NCCN guidelines have been updated to favor the use of multi-TKI in combination with immune checkpoint inhibitors. Cabozantinib (Cabometyx) in combination with nivolumab (Opdivo) joins lenvatinib in combination with pembrolizumab (Keytruda) as a first-line (category 1) treatment for clear-cell advanced RCC.

i. Cabozantinib (Cabometyx) in combination with nivolumab (Opdivo) was studied against sunitinib in a phase 3, randomized, open-label trial (CheckMate-9ER, N=651). PFS was doubled with cabozantinib (Cabometyx) plus nivolumab than with sunitinib (median, 16.6 months vs. 8.3 months; HR 0.51; 95% CI, 0.41 to 064; P<0.0001). Additionally, overall survival (OS) was longer with cabozantinib (Cabometyx) in combination with nivolumab than with sunitinib (HR 0.60; 99% CI, 0.40 to 0.89; P = 0.001).

b. The NCCN guidelines recommend cabozantinib (Cabometyx) monotherapy as second-line (category 1) treatment in clear-cell advanced RCC and in first-line (category 2A) intermediate or poor-risk clear-cell advanced RCC.

i. Cabozantinib (Cabometyx) was evaluated for the treatment of advanced RCC against everolimus in a phase 3 RCT (METEOR study). The open-label trial enrolled 658 patients with clear-cell advanced RCC that have trialed at least one prior anti-angiogenic therapy. Cabozantinib monotherapy showed a statistically significant improvement in progression-free survival, overall survival, and objective response rate compared to everolimus.
ii. Additionally, cabozantinib (Cabometyx) monotherapy was evaluated for first line treatment for patients with intermediate or poor risk clear-cell advanced RCC against sunitinib in a phase 2, randomized, open-label trial (CABOSUN, N=157). Cabozantinib significantly prolonged PFS compared to sunitinib (median, 8.6 months vs. 5.3 months; HR 0.48; 95% CI, 0.31 to 074; P=0.0008).

VII. **Hepatocellular Carcinoma (HCC)**

a. Cabozantinib (Cabometyx) was evaluated in Child-Pugh class A patients with advanced and progressing hepatocellular carcinoma against a placebo. All patients had been previously treated with sorafenib in this phase III trial and had received a maximum of two previous systemic therapies for advanced hepatocellular carcinoma. Overall survival was statistically significantly longer with cabozantinib compared to placebo. (10.2 months vs. 8 months [HR 0.76; CI 0.63-0.92; p=0.005]).
b. NCCN guideline for HCC was recently updated to include atezolizumab (Tecentriq) and bevacizumab (Avastin) as the preferred first-line therapy (category 1 recommendation). Sorafenib (Nexavar) and lenvatinib (Lenvima) are other recommended monotherapy options for first-line therapy (category 1) in patients with a Child-Pugh Class A score [or class A/ B7 for sorafenib], and those who are treatment naïve in the first-line setting. Incidence of hematological, respiratory, and hepatic adverse reactions is significant with atezolizumab and bevacizumab regimen and in many situations, patients discontinue the regimen due to adverse reactions and transition to multi-TKI agents without having progressed on the first-line therapy. Cabozantinib monotherapy received a NCCN Category 1 recommendation along with regorafenib as subsequent-line therapy for patients with Child-Pugh A liver function following disease progression on or after sorafenib. Additionally, lenvatinib and sorafenib are also recommended as subsequent-line agents with category 2A NCCN recommendations should there be progression on first-line therapy with atezolizumab and bevacizumab. Other than sorafenib or nivolumab, there is no data to define optimal treatment for those who progress after first-line systemic therapy; therefore, treatment with cabozantinib (Cabometyx) for progressive HCC is recommended based on the clinical benefit limited to patients who progressed on sorafenib.

VIII. **Medullary thyroid carcinoma (MTC)**

a. MTC accounts for 1-2% of thyroid cancers in the United States and is characterized as sporadic or hereditary as part of the multiple endocrine neoplasia type 2 (MEN2) syndrome with elevated calcitonin as a hallmark feature. MTC is not a type of DTC and cabozantinib (Cometriq) shall be used for MTC due to its specific formulary, dosing, and packaging differences compared to cabozantinib (Cabometyx). Systemic treatment may be warranted in advanced and metastatic MTC for high volume, symptomatic, or progressive disease.

b. Cabozantinib (Cometriq) is FDA-approved for the treatment of medullary thyroid carcinoma in adult patients with progressive, metastatic disease in the phase III EXAM trial against a placebo. Patients in the trial had either hereditary, sporadic, or metastatic disease. Fifty nine percent of patients had a RET positive mutation while 40% had unknown RET mutation. Cabozantinib (Cometriq) demonstrated statistically significant median PFS compared to placebo (11.2 months vs. 4 months [HR: 0.28; 95% CI 0.19-0.40; p<0.001]). The follow up analysis, published in 2017, indicated that cabozantinib did not show a statistically significant difference in overall survival compared to placebo for the overall group of 330 patients; however, in an exploratory assessment of overall survival, cabozantinib showed a statistically significant difference in overall survival for the RET M918T mutation population (44.3 months vs 18.9 months [HR 0.60; CI 0.38-.094; p=0.03]). Cabozantinib and vandetanib received a category 1 preferred recommendation for advanced and metastatic medullary thyroid carcinoma in the NCCN v3.2021 guidelines, regardless of RET-mutation status. Additionally, cabozantinib (Cometriq) remains a preferred (category 1) systemic therapy for recurrent, persistent-locoregional or asymptomatic MTC, wherein genomic testing is not a recommended common practice. Selpercatinib and pralsetinib are FDA-approved in RET-mutated MTC and carry a category 2A recommendation for treatment.

Investigational or Not Medically Necessary Uses

I. Cabozantinib (Cabometyx or Cometriq) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Adrenocortical carcinoma
   B. Anaplastic Thyroid Cancer
   C. Breast cancer
   D. Cervical Cancer
   E. Cholangiocarcinoma
   F. Colorectal cancer
   G. Head and neck cancer
   H. Merkel cell carcinoma and skin cancer
   I. Multiple myeloma, acute myeloid leukemia
   J. Neuroendocrine Tumors
   K. Neurofibromas
   L. Non-small cell lung cancer
   M. Pheochromocytomas and paraganglioma
   N. Prostate cancer
   O. Salivary gland cancer

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side*

effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy	Disease State
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Thyroid Carcinoma
	Hepatocellular Carcinoma (HCC)
	Renal Cell Carcinoma (RCC)
	Soft Tissue Sarcoma (STS)
	Endometrial Carcinoma (EC)
selpercatinib (Retevmo™), pralsetinib (Gavreto™)	RET Fusion-Positive Non-Small Cell Lung Cancer
	RET-Mutant Medullary Thyroid Cancer

	RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory
vandetanib (Caprelsa®)	Locally advanced or metastatic medullary thyroid cancer
everolimus (Afinitor®, Afinitor Disperz®)	Advanced Renal cell Carcinoma
	Angiomyolipoma of the kidney, tuberous sclerosis syndrome
	Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole
	Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic
	Subependymal giant cell astrocytom
	Partial seizure, adjunct, tuberous sclerosis syndrome
	Subependymal giant cell astrocytoma
axitinib (Inlyta®)	Advance renal cell carcinoma
sunitinib (Sutent®)	Advance renal cell carcinoma
	Gastrointestinal stromal tumor
	Renal cell carcinoma, adjuvant following nephrectomy
	Neuroendocrine pancreatic tumor

Policy Implementation/Update

Action and Summary of Changes	Date
Updated policy to separate criteria for Cabometyx and Cometriq. Added criteria for Cabometyx in members 13 years of age and older in DTC. Added criteria for use of Cabometyx in combination with nivolumab in advanced RCC. Added Child-Pugh A liver function status requirement for Cabometyx in HCC given guidelines recommendations. Removed criteria requiring RET-mutation status for MTC. Removal of oncologist requirements upon renewal. Updated supporting evidence and references accordingly. Added anaplastic thyroid cancer, NETS, cervical cancer, NSCLC to E/I. Added Related Policies section.	03/2022
Transitioned criteria to policy format, added hepatocellular carcinoma indication, added age criteria and monotherapy criteria to all indications.	02/2019
Removed step therapy in RCC; Updated renewal language to assess response to therapy	01/2018
Previous Reviews	12/2012

Policy Type: PA Pharmacy Coverage Policy: UMP088

Description

Calcifediol (Rayaldee) is an orally administered prohormone of vitamin D3, calcitriol (1,25-dihydroxyvitamin D3).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
calcifediol (Rayaldee)	30 mcg ER Capsule	Secondary hyperparathyroidism in Stage 3 or 4 CKD	60 capsules/30 days	195578

Initial Evaluation

I. Calcifediol (Rayaldee) may be considered medically necessary when the following criteria below are met:
   A. Member has a diagnosis of stage 3 (GFR 30-59 mL/min) or stage 4 (GFR 15-29 mL/min) chronic kidney disease (CKD); **AND**
   B. Member has a diagnosis of secondary hyperparathyroidism (enlarged parathyroid glands due to excessive secretion of parathyroid hormone) ; **AND**
   C. Member is **not** on dialysis; **AND**
   D. Member has a 25-hydroxyvitamin D serum level of < 30 ng/mL; **AND**
   E. Medication is prescribed by, or in consultation with a nephrologist or endocrinologist; **AND**
   F. Treatment with ALL the following has been ineffective, contraindicated, or not tolerated:
      i. calcitriol (Rocaltrol)
      ii. paricalcitol (Zemplar)

II. Calcifediol (Rayaldee) is considered investigational when used for all other conditions, including but not limited to:
   A. Chronic Kidney Disease (CKD) stages 1, 2 and 5 with hyperparathyroidism
   B. End Stage Renal Disease (ESRD) on dialysis with hyperparathyroidism
   C. Secondary hyperparathyroidism without CKD stage 3 or 4 diagnosis

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member has received a previous prior authorization approval for this agent; **AND**
III. Medication is prescribed by, or in consultation with a nephrologist or endocrinologist; **AND**
IV. Member has a diagnosis of stage 3 (GFR 30-59 mL/min) or stage 4 (GFR 15-29 mL/min) chronic kidney disease (CKD); **AND**
V. Member has a diagnosis of secondary hyperparathyroidism (enlarged parathyroid glands due to excessive secretion of parathyroid hormone); **AND**
VI. Member is **not** on dialysis; **AND**
VII. Member has exhibited improvement or stability of disease symptoms defined by the following:
   A. Intact parathyroid hormone (PTH) remains above the treatment goal; **AND**
   B. Total 25-hydroxyvitamin D serum level is between < 100 ng/mL; **AND**
   C. Serum calcium < 9.8 mg/dL; **AND**
   D. Serum phosphorous < 5.5 mg/dL

Supporting Evidence

I. Calcifediol (Rayaldee) was studied in two identical multicenter, randomized, placebo-controlled, double-blind trials in 429 patients with secondary hyperparathyroidism with stage 3 or 4 CKD and serum concentration of 25-hydroxyvitamin D levels between 10 and 30 ng/mL.
II. The primary efficacy outcome was the reduction in plasma PTH from baseline when comparing calcifediol (Rayaldee) to placebo which were 33% versus 8% in trial one and 34% versus 7% in trial two by 26 weeks.
III. There is currently insufficient evidence to suggest that there is a difference between calcifediol ER (Rayaldee) from other vitamin D analogs.
IV. The treatment goal for intact PTH is patient dependent, and will be defined by the provider. In clinical trials the patient's Rayaldee dose was increased to 60 mcg per day when the intact PTH level was greater than 70 pg/mL, the serum 25-hydroxyvitamin D level was less than 65 ng/mL, and the serum calcium level was less than 9.8 mg/dL.
V. Stages of CKD

Stage	GFR (mL/min/1.73 m^2	
1	≥ 90	Normal kidney or high
2	60-89	Mildly reduced kidney function
3 A	45-59	Mild to moderately reduced kidney function
3 B	30-44	Moderate to severely reduced kidney function
4	15-29	Severely reduced kidney function
5	<15 or on dialysis	End stage kidney failure (sometimes called established renal failure)
Stage 1 or Stage 2 are not considered CKD in the absence of kidney damage		

Investigational or Not Medically Necessary Uses

I. There is currently limited evidence to suggest safety and/or efficacy with calcifediol (Rayaldee), when used for the treatment of CKD stage 1, 2, and 5, ESRD on dialysis, and secondary hyperarathyoroidism without CKD stage 3 or 4.

References

1. Rayaldee [Prescribing Information]. OPKO Pharmaceuticals, LLC. Miami, FL. March 2016.

Policy Implementation/Update:

Date Created	January 2017
Date Effective	February 2017
Last Updated	October 2019
Last Reviewed	01/2017, 02/2017, 10/2019

Action and Summary of Changes	**Date**
Criteria was transitioned into policy format with the addition of renewal criteria, investigational section, and supporting evidence.	10/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP025

Description
Erenumab (Aimovig), galcanezumab (Emgality), and fremanezumab (Ajovy) are subcutaneous injections of monoclonal antibodies that bind to the calcitonin gene-related peptide (CGRP) receptor or ligand. Rimegepant (Nurtec ODT) and atogepant (Qulipta) are orally administered CGRP receptor antagonists.

Length of Authorization
- Initial:
  - **rimegepant (Nurtec ODT)**
    - at a quantity less than, or equal to, 8 tablets per 30 days (categorized as treatment of acute migraine): 12 months
    - at a quantity of 9-16 tablets per 30 days (categorized as migraine preventive treatment, or preventive treatment should be considered prior to use of this quantity): Six months
  - **All other agents**
    - Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
erenumab (Aimovig)	Migraine prophylaxis	70 mg/1 mL autoinjector	1 mL/30 days
		140 mg/1 mL autoinjector	
galcanezumab (Emgality)	Migraine prophylaxis	120 mg/1 mL autoinjector	**Initial:** 2 mL (240 mg)/30 days for one fill **Maintenance:** 1 mL (120mg)/30 days
		120 mg/1 mL prefilled syringe	
	Episodic cluster headache	100 mg/1 mL prefilled syringe	3 mL/30 days
fremanezumab (Ajovy)	Migraine prophylaxis	225 mg/1.5 mL prefilled syringe	1.5 mL/30 days **OR** 4.5 mL per 90-day supply
		225 mg/1.5 mL autoinjector	
rimegepant (Nurtec ODT)	Acute migraine treatment Migraine prophylaxis	75 mg orally disintegrating tablet	8 tablets/30 days
			16 tablets/30 days
atogepant (Qulipta)	Migraine prophylaxis	10 mg tablet	30 tablets/30 days
		30 mg tablet	
		60 mg tablet	

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Initial Evaluation

Migraine

I. **Erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), and atogepant (Qulipta)** may be considered medically necessary when the following criteria are met:
   A. A diagnosis of migraine; **AND**
   B. The member is 18 years of age or older; **AND**
   C. Medications in this policy will not be used in combination with each other (exception: rimegepant (Nurtec ODT) at a dose of less than or equal to 8 tablets per 30 days); **AND**
   D. Medication overuse headache has been ruled out as the cause of, or as an aggravating contributor to, the member's migraines or cluster headaches; **AND**
   E. The member has a history of four or more monthly migraine days; **AND**
   F. The member has experienced migraine for one year or longer; **AND**
   G. The member has tried and failed, or is intolerant to, prophylactic therapy with at least one specified agent listed in each of the following groups: (Note, if a class of agents is contraindicated, a trial and failure of at least three agents from the remaining groups is required.):
      1. Group 1: propranolol, metoprolol, atenolol, timolol, nadolol
      2. Group 2: amitriptyline, venlafaxine
      3. Group 3: topiramate, sodium valproate, divalproex sodium; **AND**
   H. The patient has tried each of the prophylactic therapies at therapeutic doses for at least three months **OR** the member is intolerant of the therapies; **AND**
   I. Fremanezumab (Ajovy) is being requested; **OR**
      1. Treatment with fremanezumab (Ajovy) has been ineffective, contraindicated, or not tolerated

II. **Rimegepant (Nurtec ODT)** may be considered medically necessary when the following criteria below are met:
   A. The request is for less than, or equal to, 8 tablets per 30 days (categorized as treatment of acute migraine); **AND**
      1. Member is 18 years of age or older; **AND**
      2. Two serotonin 5-HT1 receptor agonists (i.e., sumatriptan, naratriptan, rizatriptan) have been ineffective, contraindicated, or not tolerated; **AND**
      3. One nasal (i.e., sumatriptan nasal spray) serotonin 5-HT1 receptor agonist; **AND**
      4. One injectable (i.e., sumatriptan pen/vial/syringe) serotonin 5-HT1 receptor agonist; **OR**
   B. The request is for 9-16 tablets per 30 days (categorized as migraine preventive treatment, or preventive treatment should be considered prior to use of this quantity); **AND**
      1. Criteria I(A)-I(I) above are met

Cluster Headache Prophylaxis

III. Galcanezumab (Emgality) may be considered medically necessary when the following criteria are met:
   A. Diagnosis of cluster headache; **AND**

B. The provider attests the diagnosis is confirmed using the International Classification of Headache Disorders (ICHD) criteria for cluster headache; **AND**
C. The member has had an adequate prophylactic therapy trial and failure (considered to be one month or longer), contraindication, or intolerance to verapamil **and** lithium concurrently or consecutively. (Note, if one is contraindicated, a trial of the other is required.)

IV. Erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), rimegepant (Nurtec ODT), and atogepant (Qulipta) are considered investigational when used for all other conditions, including but not limited to:
A. Chronic cluster headache
B. Episodic cluster headache, with the exception of galcanezumab (Emgality)
C. Post-traumatic headache
D. Pediatric headache or migraine
E. Vasomotor symptoms or hot flashes
F. Fibromyalgia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
A. **Diagnosis of migraine**; **AND**
1. Request is for erenumab (Aimovig), galcanezumab (Emgality), fremanezumab (Ajovy), atogepant (Qulipta), or for 9-16 tablets per 30 days of rimegepant (Nurtec ODT); **AND**
i. The medications in this policy will not be used in combination with each other; **AND**
ii. The member has experienced a response to therapy, defined by a reduction of at least two migraine days per month compared to baseline upon first renewal; **OR**
a. Upon subsequent renewals the member has maintained the initial response or gained further response to therapy; **AND**
iii. Fremanezumab (Ajovy) is being requested; **OR**
a. Treatment with fremanezumab (Ajovy) has been ineffective, contraindicated, or not tolerated; **OR**
2. Request is for less than, or equal to, 8 tablets per 30 days of rimegepant (Nurtec ODT); **AND**
i. The member has experienced a response to therapy (e.g., reduction in symptoms, severity, or duration of migraine)
B. **Diagnosis of episodic cluster headache**; **AND**
1. The request is for galcanezumab (Emgality) only; **AND**

2. The member has experienced a response to therapy, defined by one of the following:
    i. A reduction in four weekly cluster headache attacks compared to baseline; **OR**
    ii. A complete reduction resolution of attacks (e.g., the member has a baseline of 3-4 attacks per week); **AND**
3. Provider attests the member continues to need therapy for cluster headache (i.e., the cluster period has not passed, or a trial of therapy taper has been attempted and was unsuccessful).

Supporting Evidence

I. There is a lack of safety and efficacy data in pediatrics; however, as of July 2019, clinical trials were underway for injectable CGRP agents in pediatrics.

II. There is lack of safety and efficacy data when CGRP agents are used concurrently. At acute dosing regimens, use of CGRP oral agents in combination with injectables for prophylaxis can be allowed given contraindications and tolerability challenges with triptans. Higher or frequent oral acute doses in combination with injectable CGRPs is not allowed. Combination use shall NOT be granted, nor should quantity exceptions. Historical studies of agents effecting CGRP have failed in clinical trials due to significant hepatotoxic safety concerns. The safety profile of increased CGRP inhibition is unknown with considerable safety risks at this time.

Acute Migraine Treatment:

III. After lifestyle modifications, non-pharmacologic therapies, and avoidance of triggers have been employed, pharmacologic therapy may be necessary. To which, triptans have an established safety and efficacy profile for the abortive treatment of migraine. Triptans are the mainstay of therapy and are recommended as first-line treatment by governing bodies and treatment guidelines such as American Academy of Neurology, American Family Physician, and American Headache Society. Triptans are not indicated for the continual prophylactic treatment of migraine.

Migraine Prophylaxis:

IV. In the pivotal trials for the agents listed in this policy, members had a history of four or more monthly migraine days for at least one year. Migraines may have numerous causes and triggers and may be transient in nature; thus, a strong history of migraine is warranted prior to consideration of coverage for CGRP agents.

V. Medication overuse headache (MOH) is a chronic daily headache or migraine secondary to acute medication in headache prone patients. In general, MOH presents in patients that use analgesics more than two to three days per week. Often, MOHs are refractory to both pharmacologic and non-pharmacologic therapies. The most effective way to treat MOH is to discontinue the overused medications, allow headaches to come back to baseline in number and severity, and then begin treatment with prophylactic therapy. Some of the agents in this policy have been shown to have efficacy in MOH, and others are under evaluation in clinical trials; however, the same considerations in III apply – the prescribing cascade should not continue with CGRP agents without first attempting to withdraw as many aggravating or unnecessary therapies if possible.

VI. Guidelines recommend select beta blockers, antidepressants, anticonvulsants, and onabotulinum toxin A as efficacious or probably efficacious (Level A and B, respectively) for the prophylactic treatment of migraine in adults. If onabotulinum toxin A has been listed as a

therapy that has been tried and failed this may be used as a qualifier of the three required agents to meet coverage consideration. Agents not listed specifically above in the policy have lower level, conflicting, or negative evidence. This includes, but is not limited to SSRIs, duloxetine, nortriptyline, cyproheptadine, clonidine, guanfacine, nebivolol, pindolol, carbamazepine, Lisinopril, candesartan, calcium channel blockers, gabapentin, pregabalin, lamotrigine, oxcarbazepine, clomipramine, telmisartan, and benzodiazepines. Specifically, nortriptyline does not have the same level of efficacy supporting use for migraine prophylaxis as amitriptyline and should not be considered for adequate trials of prophylactic therapy.

VII. A class review for migraine prophylactic therapies was completed in 2018, with conclusions that are consistent with guideline recommendations. The specific agents listed above, are shown to have the highest level of evidence for safety and efficacy.

VIII. Guidelines label a "treatment success" as a 50% reduction in migraine after three months of prophylactic therapy utilization. Additionally, some agents take one-to-three months to begin working. If the prophylactic therapies have not been trialed for three months, this does not constitute an adequate trial of that agent. Of note, adverse effects and contraindications may limit ability to utilize an agent, or class of agents, for three months and this should be taken into consideration when determining if criteria coverage has been met.

IX. In the absence of established differences in efficacy and/or safety amongst CGRP products, fremanezumab (Ajovy) has been chosen as the preferred product in this class. Treatment with, or contraindication to, this product is required prior to approval of others in the setting of chronic migraine.

Cluster Headache:

X. Cluster headaches are defined as severe, strictly unilateral pain, orbital, supraorbital, temporal or any combination of these, lasting 15-180 minutes and occurring from once every other day to eight times per day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness, or agitation. Cluster periods range from two weeks and three months

XI. Diagnostic criteria per ICHD3 include at least five attacks fulfilling the criteria in IX, either or both of the following: a sense of restlessness or agitation AND one of the following: conjunctival injections and/or lacrimation, nasal congestion and/or rhinorrhea, eyelid edema, forehead and facial sweating, miosis, and/or ptosis. Additionally, the diagnosis is not better accounted for by another IDHD3 diagnosis.

- Episodic is defined by the above occurring in periods lasting from seven days to one year, separated by pain free periods of at least three months.
- Chronic is defined as occurring for one year or longer without remission or with remission periods lasting less than three months

XII. Like migraine therapy, treatment for cluster headaches include acute/rescue therapy and prophylactic therapy; however, contrary to migraine, prophylactic therapy should be initiated without delay once a cluster headache bout begins.

- Acute therapies: Level A evidence includes: Supplemental oxygen, subcutaneous sumatriptan, and nasal zolmitriptan. Level B evidence includes: nasal sumatriptan, oral zolmitriptan, and sphenopalatine ganglion stimulation (not yet available in the U.S. outside of clinical trials). Therapies with convincing evidence for efficacy: octreotide, dihydroergotamine nasal spray, somatostatin, and corticosteroids.
- Prophylactic therapies: Level A evidence: suboccipital steroid injection as a transitional but not long term therapy. Several other therapies have been evaluated; however, available evidence coupled with expert opinion recommendations state verapamil and lithium should be first-line therapy; however, due to the 1-2 week

onset of efficacy, transitional therapy is recommended with oral or subcutaneous steroids.

XIII. Galcanezumab (Emgality) was evaluated for safety and efficacy in episodic cluster headache. One Phase 3, RCT of 106 adult patients was conducted over eight weeks. This included those with episoidic cluster headache in patients not on other therapies for headache prophylaxis. Patients were allowed to use acute/abortive headache treatment regimens (triptans, oxygen, APAP, NSAIDS). Patients with MOH were excluded. Outcomes included mean change from baseline in weekly cluster headache attach frequency from weeks one to three. Secondary endpoints included percentage of patients who achieved a response (50% or greater reduction from baseline in weekly cluster headache attack frequency) at week three, percentage of participants reporting a score of 1 or 2 on the PGI-I scale, and percentage of participants with suicidal behaviors assessed by C-SSRS.

XIV. Galcanezumab (Emgality) is indicated for the treatment of episodic cluster headache; however, a requirement of prophylactic therapy is required as prophylactic therapy should be administered without delay in all qualifying patients. Due to lack of long term safety and efficacy data, conventional therapy shall be tried prior to coverage consideration for galcanezumab (Emgality). Although the medication is not FDA approved for chronic cluster headache, there are very limited treatment options in this space beyond the conventional agents listed above. Additionally, there is an increased risk in suicidality in this population. If the medication is providing benefit to the member, as outlined in the criteria, and the clinical paradigm shifts from episodic to chronic cluster - benefits and risks of discontinuation or disapproved payment of the medication should be weighed.

Investigational or Not Medically Necessary Uses

I. The agents listed in this policy are being investigated for safety and efficacy in some the following indications. Safety and efficacy have not yet been established in all of the following:
   A. Chronic cluster headache
   B. Episodic cluster headache, with the exception of galcanezumab (Emgality)
   C. Post-traumatic headache
   D. Pediatric headache or migraine
   E. Vasomotor symptoms or hot flashes
   F. Fibromyalgia

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Policy Implementation/Update:

Action and Summary of Changes	Date
Removed restriction of combination use with onabotulinum toxin (Botox) based on real world evidence suggesting additive benefit for chronic migraines with no significant safety signals identified.	10/2023
Updated initial approval duration to 6 months for all products and to one year for acute treatment setting.	04/2022
Removed trial of triptan agents upon renewal of Nurtec. Restructured Nurtec requirements to improve clarity.	02/2022
Added migraine requirement in Nurtec; Restructured Nurtec requirements breaking down based on treatment setting (acute tx vs phx) in both initial and renewal; Removed age requirement upon renewal.	10/2021
Addition of new product atogepant (Qulipta) into policy, aligning non-preferred CGRP agents	09/2021
Addition of Nurtec ODT into policy (initial and renewal): reviewing coverage/setting of Nurtec via quantity requested; in migraine prophylaxis section aligned Nurtec ODT with non-preferred CGRP agents. Addition of standard language to renewal criteria addressing use of samples. Updates to supporting evidence.	04/2021
Update to require treatment of Ajovy prior to Aimovig or Emgality in the setting of migraines; effective 02/01/2021	01/2021
Added Ajovy autoinjector to policy	04/2020
Removed PFS and 2-pack of Aimovig from policy as it is no longer available one the market	02/2020
Criteria update: update to reflect preferred galcanezumab (Emgality)	11/2019
Criteria update: Transition from criteria to policy and compilation of all injectable CGRP therapies into one policy. Updated Aimovig quantity limit to 30 days vs 28 to align with other agents. Added comment that	07/2019

these therapies will not be used in combination with one another, clarified prophylactic requirement for migraine indication, reworded renewal criteria. Added Emgality new indication of cluster headache.	
No changes made	01/2019
Criteria update: Changed onabotulinum toxin requirement to three months versus previous four months of washout. Updated renewal questions to specify a reduction in monthly migraine days by two.	10/2018
Criteria created	10/2018

Policy Type: PA Pharmacy Coverage Policy: UMP011

Description

Cannabidiol (Epidiolex) is an orally administered cannabinoid.

Length of Authorization

- Initial: Twelve months
- Renewal: Twelve months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
cannabidiol (Epidiolex)	100 mg/mL oral solution/kit	Lennox-Gastaut Syndrome Dravet Syndrome	20 mg/kg/day (round up to nearest pack size)
		Tuberous Sclerosis Complex	25 mg/kg/day (round up to nearest pack size)
	60 mg/mL oral solution/kit	Lennox-Gastaut Syndrome Dravet Syndrome	20 mg/kg/day (round up to nearest pack size)
		Tuberous Sclerosis Complex	25 mg/kg/day (round up to nearest pack size)

Initial Evaluation

I. Cannabidiol (Epidiolex) may be considered medically necessary when the following criteria below are met:
   A. Member is one year of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. Documentation of the member's weight that has been measured in the past three months; **AND**
   D. Cannabidiol (Epidiolex) will be used in combination with one or more anticonvulsant medications; **AND**
   E. A diagnosis of one of the following:
      1. **Lennox-Gastaut Syndrome**; **OR**
      2. **Tuberous Sclerosis Complex**; **OR**
      3. **Dravet Syndrome**; **AND**
         i. Cannabidiol (Epidiolex) will **not** be used in combination with fenfluramine (Fintepla); **AND**
   F. Member's seizures are refractory to two or more anticonvulsant medications (e.g., clobazam [Onfi], valproate [Depakote], lamotrigine [Lamictal], levetiracetam [Keppra], rufinamide [Banzel], topiramate [Topamax], felbamate [Felbatol], stiripentol [Diacomit], zonisamide [Zonergan], vigabatrin [Sabril])

II. Cannabidiol (Epidiolex) is considered investigational when used for all other conditions, including but not limited to the diagnosis of:
   A. Infantile Spasms
   B. Other non-FDA approve seizure disorder
   C. Substance use disorder
   D. Prader-Willi Syndrome
   E. Gastrointestinal disorders
   F. Parkinson's Disease/Essential tremors

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
III. A diagnosis of one of the following:
   A. **Lennox-Gastaut Syndrome**; **OR**
   B. **Tuberous Sclerosis Complex**; **OR**
   C. **Dravet Syndrome**; **AND**
      1. Cannabidiol (Epidiolex) will not be used in combination with fenfluramine (Fintepla); **AND**
IV. Documentation of the member's weight that has been measured in the past three months; **AND**
V. Cannabidiol (Epidiolex) will continue to be used in combination with at least one other anti-epileptic medication (i.e. used as adjunct therapy) such as clobazam, valproate, levetiracetam, rufinamide, topiramate, felbamate, stiripentol, zonisamide, vigabatrin or lamotrigine; **AND**
VI. Documentation that the member has exhibited improvement or stability of disease symptoms [e.g., reduction in seizure frequency].

Supporting Evidence

I. Cannabidiol (Epidiolex) (CBD) is indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS), Dravet syndrome (DS), or Tuberous Sclerosis Complex (TSC) in patients one year of age and older. It received initial approval for treatment of seizures associated with LGS and DS for patients two years of age and older. This approval was expanded in 2020 to include new indication of seizures associated with TSC in patients one year and older. Additionally, CBD also received approval for expanded age range (one year and older) for patients with LGS and DS.
II. Differential diagnosis of LGS, DS, or TSC require detailed clinical examination in combination with advanced testing such as MRI, EEG, and genetic screening (SCN1A mutation for DS). Given the complexities of diagnosing and treating these conditions, supervision of treatment by a neurologist is required.

III. CBD was studied in four Phase 3, double blind, randomized placebo-controlled clinical trials in patients with baseline characteristics of history of use of two or more antiepileptic drugs (AED). Efficacy of CBD for LGS was studied in two randomized, double-blind, placebo-controlled trials in patients aged 2 to 55 years old. Study 1 (N=171) compared a dose of Epidiolex 20 mg/kg/day with placebo, while Study 2 (N=225) used 10 mg/kg/day and 20 mg/kg/day doses with a match with placebo. In both studies, patients had a diagnosis of LGS and were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. The primary efficacy measure in both studies was the percent change from baseline in the frequency (per 28 days) of drop seizures (atonic, tonic, or tonic-clonic seizures) over the 14-week treatment period. At 14 weeks, the median percent change from baseline (reduction) in the frequency of drop seizures was significantly greater for both dosage groups of CBD versus placebo with an observed reduction in drop seizures frequency within 4 weeks of initiating treatment.

IV. Study 3 (N= 120) assessed efficacy and safety of CBD for the treatment of convulsive seizures (tonic, clonic, atonic, and tonic-clonic) associated with DS in patients refractory to at least 2 AEDs. The median percent change from baseline (reduction) in the frequency of convulsive seizures was significantly greater for CBD 20 mg/kg/day treatment arm as compared to placebo (-39% versus -13%; *p*= 0.01).

V. Participants in study 4 (N=224) were aged 1 to 65 years. Cannabidiol (Epidiolex) was evaluated at 25 mg/kg/day (CBD25) and 50 mg/kg/day (CBD50) doses with a matching placebo, for efficacy in treatment of seizures (focal, tonic, clonic, atonic or tonic-clonic) associated with TSC. At 16 weeks cut-off, Percent reduction (per 28 days) in TSC-associated seizure frequency was significantly higher for CBD25 cohort (48.6%) and CBD50 cohort (47.5%) vs placebo (27%; p=0.0009 and p=0.0018, respectively). Ninety-nine percent (N=199) of the patients from the initial 16-week controlled trial elected to continue into a 48-week open-label extension phase, wherein safety of CBD was assessed. Although most common adverse reactions (diarrhea, anorexia and somnolence) were mild to moderate the CBD50 cohort reported higher incidence of AE including liver function impairment (ALT and/or AST elevation).

VI. CBD can cause dose-related elevations of liver transaminases (ALT and/or AST). In controlled studies for LGS and DS (10 and 20 mg/kg/day dosages) and TSC (25 mg/kg/day), the incidence of ALT elevations above 3 times the upper limit of normal (ULN) was 13% (10 and 20 mg/kg/day dosages) and 12% (25 mg/kg/day dosage) in CBD-treated patients compared with 1% in patients on placebo. Assessment of liver function (ALT, AST, total bilirubin) is recommended prior to initiating treatment with CBD, with dose changes, or with the addition of, or changes in, hepatotoxic medications.

VII. During clinical trials for all FDA-approved indications, participants received CBD as an adjunct therapy. Majority of participants in these trials were receiving a median of 2 concomitant antiepileptic drugs (AED). Inclusion in clinical trial also required documentation of seizures above the minimum threshold (≥ 8 drop seizures per 28 days for LGS, ≥ 4 convulsive seizures per 28 days for DS, and ≥ 8 seizures per 28 days for TSC). Efficacy and safety of CBD as monotherapy has not been studied and remains unknown.

Investigational or Not Medically Necessary Uses

I. There are ongoing trials for infantile spasms, substance use disorder, Prader-Willi Syndrome, gastrointestinal disorders, Parkinson's disease/essential tremors, and other seizure disorders, therefore these indications are considered investigational at this time.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added in Epidiolex 60mg/mL product	10/2020
Updated policy to include new indication for cannabidiol (Epidiolex) for treatment of seizures associated with Tuberous Sclerosis Complex (TSC); updated policy format for consistency of requirements for coverage for each approved indication; added weight-based dosing and quantity limit; renewal criteria and supporting evidence section were updated	10/2020
Policy created	01/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP012

Description

Caplacizumab-yhdp (Cablivi) is a von Willebrand factor (vWF) - directed antibody fragment (called a Nanobody) that inhibits the interaction between vWF and platelets, thereby reducing both vWF-mediated platelet adhesion and platelet consumption.

Length of Authorization

- Initial: 30 days
- Renewal: 28 days

Quantity limits

Dosage Form	Indication	Quantity Limit	DDID
Initial Request			
11mg vial	aTTP	30 vials/30 days	205773
Renewal Request			
11mg vial	aTTP	28 vials/28 days	205773

Initial Evaluation

I. Caplacizumab-yhdp (Cablivi) may be considered medically necessary when the following criteria below are met:
   A. Member is an adult age 18 and over; **AND**
   B. Prescribed in consultation with a hematologist; **AND**
   C. First administration will be done as an inpatient intravenous bolus infusion under the supervision of a healthcare professional; **AND**
   D. Caplacizumab (Cablivi) will be continued for 30 days beyond the last plasma exchange; **AND**
   E. A diagnosis of **acquired thrombotic thrombocytopenic purpura (aTTP)** when the following are met:
      1. Member has thrombocytopenia and microscopic evidence of red blood cell fragmentation (e.g. schistocytes); **AND**
      2. Taken in a regimen that includes both plasma exchange and an immunosuppressant (i.e. Rituximab, glucocorticoids); **AND**
      3. One of the following:
         i. A suppressed or deficient level of ADAMTS13*
         ii. A PLASMIC score to indicate an intermediate to high risk of ADAMTS13 deficiency, defined as a level less than or equal to 10% (5 to 7 points).
         iii. Presentation of severe features, including, but not limited to the following:
            a. Neurologic findings such as seizures, focal weakness, aphasia, dysarthria, confusion, coma
            b. Symptoms suggesting encephalopathy

c. High serum troponin levels

II. Caplacizumab (Cablivi) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Adjunct to treatments of thrombocytopenia other than plasma exchange and immunosuppressant.

III. Caplacizumab (Cablivi) is considered investigational when used for all other conditions, including but not limited to:
   A. Idiopathic thrombocytopenia
   B. Hereditary thrombotic thrombocytopenic purpura (TTP)
   C. Drug-induced thrombotic microangiopathy
   D. Hemolytic uremic syndrome
   E. Complement-mediated TMA
   F. Diarrheal hemolytic uremic syndrome
   G. Thrombocytopenia in pregnancy

Renewal Evaluation

I. Member has received caplacizumab (Cablivi) in combination with plasma exchange and immunosuppressive therapy for 30 days beyond the last plasma exchange; **AND**
II. Member has documented signs of persistent underlying disease with documentation of suppressed ADAMTS13 activity level; **AND**
III. Treatment will be extended one-time for a maximum of 28 days following the initially approved treatment course; **AND**
IV. Patient has not experienced more than 2 recurrences* while on caplacizumab (Cablivi).

Supporting Evidence

I. Caplacizumab (Cablivi) was studied and approved for the treatment of aTTP combination with plasma exchange and immunosuppressant in adult subjects age 18 years and older, under the supervision of a medical specialist.
II. Initial administration is performed as an inpatient, by intravenous bolus infusion, followed by subcutaneous injection. There is the potential for outpatient self-administration of subcutaneous injection, especially following the discontinuation of plasma exchange.
III. Diseases of thrombotic microangiopathy have varied etiologies and rule-out of differential diagnoses is important to determine effective and safe therapy. In practice, most hospitals do not have access to on-site testing for ADAMTS13 level. Results are typically delayed by use of off-site laboratories for confirmation as standard therapy is initiated.
   - An ADAMTS13 level is of less than ten percent would indicate a severe case;
   - Laboratory outcome may be pending at time of initial authorization request;
   - Laboratory outcome of ADAMTS13 is required upon renewal request.

IV. The PLASMIC scoring system is a validated diagnostic tool used to discriminate between the likelihood of ADAMSTS13 deficiency and other potential causes of microangiopathic hemolysis.
- Scoring
  i. Low risk category
    1. Score of 0-4
    2. Indicates a risk of severe ADAMTS13 deficiency (levels less than or equal to 10%) in 4.3%.
  ii. Intermediate risk category
    1. Score of 5-6
    2. Indicates a 56.8% likelihood of severe ADAMTS13 deficiency involvement.
  iii. High risk category
    1. Score of 7
    2. Indicates a 96.2% likelihood of severe ADAMTS13 deficiency
- Pre-existing liver or renal disease can falsely lower PLASMIC score.

V. Standard therapy of plasma exchange is initiated as soon as possible to mitigate the progressive course of neurologic deterioration, cardiac ischemia, irreversible renal failure and death.

VI. Treatment of initial acute episode with caplacizumab (Cablivi) is continued for at least 30 days following the last plasma exchange.

VII. *Terminology used in the setting of aTTP include the following:
- Response: normalization or stabilization of platelet count with plasma exchange.
- Remission: maintenance of normal platelet count for 30 days after stopping plasma exchange.
- Relapse: recurrence of TTP following remission.
- Exacerbation: recurrent thrombocytopenia within 30 days of stopping plasma exchange

VIII. The extension of treatment in the event of relapse may be considered when member experiences one of the following:
- A return of the clinical signs and symptoms of aTTP;
- Deficient ADAMTS13 level.

Investigational or Not Medically Necessary Uses

I. Include but are not limited to: Idiopathic thrombocytopenia, hereditary thrombotic thrombocytopenic purpura (TTP), drug-induced thrombotic microangiopathy, hemolytic uremic syndrome, complement-mediated TMA, thrombocytopenia in pregnancy
   A. Diseases of thrombotic microangiopathy have varied etiologies and effective therapies.
   B. Acquired thrombolic thrombocytopenia purpura is due to severely deficient levels of protease ADAMTS13, which manages thrombotic microangiopathy by limiting uncleaved vWF. Uncleaved vWF cause platelet consumption and thrombic microangiopathy by adhesion to platelets.
   C. Caplacizumab (Cablivi) prevents adhesion between vWF and platelets.

References

1. Cablivi [prescribing information]. Cambridge, MA: Genzyme Corporation; February 2019.

2. FDA approves first therapy for the treatment of adult patients with a rare blood clotting disorder. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630851.htm
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Policy Implementation/Update:

Date Created	March 2019
Date Effective	May 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	**Date**

Policy Type: PA/SP Pharmacy Coverage Policy: UMP189

Split Fill Management*

Description

Capmatinib (Tabrecta) is an orally administered tyrosine kinase inhibitor (TKI) that targets mesenchymal-epithelial transition (MET) receptor.

Length of Authorization

- N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
capmatinib (Tabrecta)	Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping	200 mg tablets	112 tablets/28 days
		150 mg tablets	

Initial Evaluation

I. Capmatinib (Tabrecta) is considered investigational when used for all conditions, including but not limited to Non-Small Cell Lung Cancer.

Renewal Evaluation

I. N/A

Supporting Evidence

I. Capmatinib (Tabrecta) is the first therapy FDA-approved for NSCLC with a mutation that leads to MET 14 exon 14 skipping. Other therapies that may be used in this setting include tepotinib (Tepmetko), crizotinib (Xalkori®), platinum-based doublet chemotherapy with or without bevacizumab, and/or immunotherapy (e.g., nivolumab, pembrolizumab); however, available data is limited and response in this population is generally poor.

II. Capmatinib (Tabrecta) is FDA-approved in the metastatic setting. It was evaluated in GEOMETRY mono-1, an open-label, Phase 2, multi-cohort, single-arm trial. Patients with METex14 skipping mutation or MET-amplified disease across various treatment settings (e.g., treatment naïve vs pretreated) were included. Initial FDA-approval under accelerated pathway, was based on those with METex14 skipping mutation only, Cohorts 4 and 5b. Cohort 4 patients were previously treated with one or two lines of therapy and Cohort 5b included treatment-naïve patients.

Patients had MET-dysregulated advanced NSCLC, with absence of EGFR or ALK mutations. Full FDA approval was granted based on additional data from Cohorts 6 and 7. Cohort 6 patients were previously treated, with majority receiving one prior line of therapy and Cohort 7 patients were treatment naïve. Cohorts 6 and 7 included patients with METex14 skipping mutation.

III. Primary efficacy outcomes were Overall Response Rate (ORR) and Duration of Response (DoR). Secondary outcomes were Progression-free Survival (PFS) and Overall Survival (OS); however, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as lack of clinically meaningful outcomes in morbidity, mortality, and quality of life. Capmatinib (Tabrecta) was FDA-approved under the accelerated approval pathway based on ORR and DoR. Conversion to regular FDA approval was based on additional ORR and DoR data for 63 patients as well as an additional 22 months of follow up. Despite receiving regular FDA approval, the medication efficacy continues to remain uncertain. There a several trials underway for NSCLC and other cancer types.

IV. The safety of capmatinib (Tabrecta) is based on patients from all cohorts (n=334). There were 37% of patients that were exposed to therapy for at least six months and 22% were exposed for at least one year. The most common adverse events include peripheral edema, nausea, fatigue, vomiting, dyspnea, and anorexia.

V. Serious adverse events occurred in 53% of patients and included dyspnea, pneumonia, pleural effusion, physical health deterioration, and peripheral edema. These events occurred in at least 2% of patients, and there was one case of fatal pneumonitis. There are no contraindications. Capmatinib (Tabrecta) showed a 54% dose interruption rate, a 23% dose reduction rate, and a 16% permanent discontinuation rate due to adverse events.

VI. As of January 2023, The National Comprehensive Cancer Network (NCCN) treatment guideline for NSCLC with a mutation that leads to MET exon 14 skipping give capmatinib (Tabrecta) a Category 2A, preferred recommendation. Tepotinib (Tepmetko) is also a preferred, Category 2A recommended treatment option. Crizotinib (Xalkori) has a Category 2A recommendation, useful in certain circumstances. These circumstances are not defined in the guideline.

VII. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Investigational or Not Medically Necessary Uses

I. Capmatinib (Tabrecta) has not been sufficiently studied for safety and efficacy for any condition to date.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side*

effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

References

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6. Drilon A, Clark J, Weiss J, et al. Updated antitumor activity of crizotinib in patients with MET exon 14-altered advanced non-small cell lung cancer. Abstract presented at: IASLC 19th World Conference on Lung Cancer. September 23-26, 2018.
7. Novartis. AMCP Formulary Dossier Version 4.1, Tabrecta (capmatinib). May 2020.
8. Novartis. Capmatinib (Tabrecta) METex14 Metastatic NSCLC Overview. January 2023.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
tepotinib (Tepmetko)	Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping

Policy Implementation/Update:

Action and Summary of Changes	Date
Added supporting evidence for regular FDA approval of capmatinib (Tabrecta) for the treatment of adults with metastatic NSCLC with METex14 skipping mutation, updated references, added related policies section.	02/2023
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy created	08/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP211

Description

Carglumic acid (Carbaglu) is an orally administered carbamoyl phosphate synthetase 1 (CPS 1) activator.

Length of Authorization

- Initial:
  - i. Acute hyperammonemia due to NAGS deficiency: 12 months
  - ii. Chronic hyperammonemia due to NAGS deficiency: 12 months
  - iii. Acute hyperammonemia due PA or MMA: 7 days
- Renewal:
  - i. Acute hyperammonemia due to NAGS deficiency: No renewal
  - ii. Chronic hyperammonemia due to NAGS deficiency: 12 months
  - iii. Acute hyperammonemia due to PA or MMA: No renewal

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
carglumic acid (generic Carbaglu)	Adjunctive therapy for acute hyperammonemia due to NAGS deficiency	200 mg tablet	250 mg/kg/day
	Maintenance therapy for chronic hyperammonemia due to NAGS deficiency		100 mg/kg/day
	Adjunctive therapy for acute hyperammonemia due to PA or MMA		≤15 kg: 150 mg/kg/day >15 kg: 3.3 g/m^2/day
carglumic acid (Carbaglu)	Adjunctive therapy for acute hyperammonemia due to NAGS deficiency	200 mg tablet	250 mg/kg/day
	Maintenance therapy for chronic hyperammonemia due to NAGS deficiency		100 mg/kg/day
	Adjunctive therapy for acute hyperammonemia due to PA or MMA		≤15 kg: 150 mg/kg/day >15 kg: 3.3 g/m^2/day

Initial Evaluation

I. **Carglumic acid (Carbaglu)** may be considered medically necessary when the following criteria are met:

A. Medication is prescribed by, or in consultation with, a metabolic disease specialist; **AND**

B. Documentation of member's weight within the past three months; **AND**
C. Documentation of baseline ammonia level indicating member has hyperammonemia (ammonia level is above the upper limit of normal based on member's age); **AND**
D. Treatment with generic carglumic acid (generic for Carbaglu) has been ineffective, contraindicated, or not tolerated; **AND**
E. A diagnosis of one of the following:
    1. **Hepatic enzyme N-acetylglutamate synthase (NAGS) deficiency**; **AND**
        i. Diagnosis is confirmed by mutation of the *NAGS* gene via molecular genetic testing; **AND**
        ii. The request is for acute treatment of hyperammonemia; **OR**
        iii. The request is for chronic treatment of hyperammonemia; **OR**
    2. **Propionic acidemia (PA) or methylmalonic acidemia (MMA); AND**
        i. The request is for acute management of hyperammonemia; **AND**
        ii. Diagnosis is confirmed by enzymatic, biochemical, or genetic testing; **AND**
        iii. Documentation of member's height or body surface area (BSA) within the past three months if member's weight is above 15 kg

II. Carglumic acid (Carbaglu) is considered investigational when used for all other conditions, including but not limited to:
A. Chronic treatment (use beyond 7 days) of hyperammonemia due to MMA/PA
B. Carbamoyl-Phosphate Synthase I Deficiency
C. Ornithine Carbamoyltransferase Deficiency
D. Other Urea Cycle disorders

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The request is for **chronic hyperammonemia due to NAGS deficiency**; **AND**
IV. Documentation of member's weight within the past three months; **AND**
V. Member has exhibited a reduction from baseline in plasma ammonia levels; **OR**
    A. Member has maintained a plasma ammonia level within normal range for member's age; **AND**
V. Treatment with generic carglumic acid (generic for Carbaglu) has been ineffective, contraindicated, or not tolerated.

Supporting Evidence

I. NAGS deficiency is a rare autosomal recessive genetic disorder caused by mutations of the NAGS gene leading to complete or partial deficiency in the enzyme N-acetylglutamate synthetase

(NAGS). The hepatic enzyme NAGS is necessary to break down nitrogen in the body. NAGS deficiency leads to accumulation of nitrogen in the form of ammonia in the blood (hyperammonemia). In most cases, onset of symptoms occurs at, or shortly following, birth (neonatal period); however, some individuals with NAGS deficiency may not exhibit symptoms until later during infancy, childhood, or even adulthood due to a partial deficiency of the NAGS enzyme. Symptoms of NAGS deficiency may include failure to thrive, poor growth, avoidance of protein from the diet, ataxia, lethargy, vomiting, and/or hypotonia. Severe manifestations include hyperammonemic coma and life-threatening complications.

II. Because NAGS deficiency is classified as an orphan disease and shares many symptoms with five other rare urea cycle disorders that result in hyperammonemia, diagnosis should be confirmed by genetic testing to verify the mutation in the *NAGS* gene. Furthermore, disease management should be by, or in consultation with, a physician who specializes in metabolic disorders.

III. Blood ammonia levels should be drawn to ensure the patient has hyperammonemia. Normal blood ammonia levels based on age are outline in the table below:

Age	Normal blood ammonia ranges
0 to 10 days (enzymatic)	170 - 341 mcg/dL
Infants and toddlers [10 days to 2 years] (enzymatic)	68 - 136 mcg/dL
Children [2 years and older]	19 - 60 mcg/dL
Adults	10 - 80 mcg/dL

IV. According to the FDA label, initial dosing for pediatric and adults with acute hyperammonemia is 100mg/kg/day to 250mg/kg/day. Maintenance for chronic hyperammonemia for pediatrics and adults is 10mg/kg/day to 100mg/kg/day. Dosage should be titrated and/or adjusted to target normal plasma ammonia level for age (referenced above).

V. The safety and efficacy of carglumic acid (Carbaglu) in the treatment of hyperammonemia due to NAGS deficiency was evaluated in a retrospective review of 23 NAGS deficiencient patients (including newborns, pediatrics, and adults) over a median period of 7.9 years (range 0.6 to 20.8 years). Due to the retrospective, unblinded, and uncontrolled nature of this review, formal statistical analyses of the data was not conducted; however, short term efficacy was evaluated using mean and median change in plasma ammonia levels from baseline to days one to three, while persistence of efficacy was evaluated using long-term mean and median change in plasma ammonia level. Thirteen out of 23 patients who received carglumic acid (Carbaglu), had documented ammonia levels prior to treatment initiation and after long-term treatment. All 13 patients had abnormally elevated ammonia levels at baseline with an overall mean baseline plasma ammonia level of 271 micromol/L. For acute treatment, normal ammonia levels were attained on day three of treatment. Long-term efficacy was measured using the last reported plasma ammonia level for each patient (median length of treatment was six years; range one to 16 years). The mean and median ammonia levels were 23 micromol/L and 24 micromol/L, respectively, after a mean treatment duration of eight years.

VI. For the treatment of acute hyperammonemia due to NAGS deficiency the length of authorization is limited to 12 months. In clinical studies, doses from acute to maintenance treatment of hyperammonemia due to NAGS deficiency were reduced over time. Dose reduction to achieve a maintenance dose was undertaken within days of initiation and took anywhere from one day to 15 days for a dose reduction to be performed in majority of patents (16 of 22 patients). In five patients, it took anywhere from one month to 10 months for the dose

reduction process. Thus, it is expected that 12 months initial authorization would be sufficient to allow for titration from acute to maintence dosing and renewal would not be necessary.

VII. Methylmalonic and propionic acidemia (MMA/PA) are autosomal recessive genetic disorders characterized by accumulation of propionic acid and/or methylmalonic acid due to deficiency of methylmalonyl-CoA mutase (MUT) or propionyl-CoA carboxylase (PCC). Patients may present in the first days to weeks of life with acute deterioration of their general clinical condition, metabolic acidosis and hyperammonemia, progressing to coma and death, if untreated. Late-onset cases of MMA and PA may present at any age with a more heterogeneous clinical symptoms. Prognosis is strongly influenced by the duration of coma and peak blood ammonia concentrations and immediate treatment in consultation with a metabolic disease specialist is required. For the treatment of acute hyperammonemia due to MMA or PA, carglumic acid (Carbaglu) is expected to be administered in an inpatient setting due to the severity of presenting symptoms, need for immediate treatment and frequent monitoring.

VIII. Length of authorization is limited to seven days of treatment which is consistent with how the drug was studied in clinical trials. Acute treatment with carglumic acid (Carbaglu) should be continued until ammonia level is less than 50 micromol/L or for a maximum duration of seven days to attain a normal blood ammonia, whichever is shorter. Efficacy and safety of treating a hyperammonemic episode beyond seven days has not been established. Patients requiring re-treatment with Carglumic acid (Carbaglu) for a second hyperammonemic episode and beyond must meet initial criteria.

IX. Determination of organic acids in urine and the acylcarnitine profile in blood are the most commonly used investigations to detect MMA and PA. Enzymatic studies and/or molecular genetic analyses should be performed to confirm diagnosis. This is ideally performed in specialized laboratories.

X. Carglumic acid (Carbaglu) was studied in one randomized, double-blind, placebo-controlled, multicenter clinical trial to determine efficacy and safety in patients with hyperammonemia due to PA and MMA. Patients were randomized 1:1 to receive carglumic acid (Carbaglu) or placebo for 7 days or until hospital discharge, which ever occurred earlier. A total of 24 patients were evaluated (PA=15, MMA=9) with median age of 8 years (range 4 days to 29 years), and all receiving standard of care, including combination of protein restriction, intravenous glucose, insulin, and/or L-carnitine. Carglumic acid (Carbaglu) was dosed at 150mg/kg/day for patients ≤15 kg or 3.3g/m^2/day for patients >15 kg administered by NG tube, G-tube, or oral syringe. Efficacy was determined based on 90 hyperammonemic episodes (42 treated with carglumic acid (Carbaglu) and 48 with placebo). Eligible hyperammonemic episodes were defined as admission to the hospital with a plasma ammonia level ≥70 µmol/L. The primary endpoint was the time from the first dose of drug to the earlier of plasma ammonia level ≤50 µmol/L (normal range) or hospital discharge. The median time to reach the primary endpoint was 1.5 days in the carglumic acid (Carbaglu) arm compared to 2 days in the placebo arm (0.5 day; 95% CI: -1.2,0.1). Throughout the first three days of treatment, a higher proportion of carglumic acid (Carbaglu) treated episodes reached the primary endpoint compared to placebo-treated episodes. At least one adverse reaction was reported during the course of hyperammonemic episodes in 42.2% of hyperammonemic episodes. The most common adverse reactions (≥5%) during hyperammonemic episodes were neutropenia, anemia, vomiting, electrolyte imbalance,

decreased appetite, hypoglycemia, lethargy/stupor, encephalopathy, and pancreatitis/increased lipase.

Investigational or Not Medically Necessary Uses

I. Carglumic acid (Carbaglu) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Chronic treatment (use beyond 7 days) of hyperammonemia due to MMA/PA
      i. Carglumic acid (Carbaglu) is not FDA approved or supported by current clinical guidelines for long-term management of PA or MMA. One low evidence grade, randomized, parallel-group, open-label clinical trial studied carglumic acid (Carbaglu) for long-term treatment of PA and MMA against standard of care. Long term effectiveness was evaluated as a reduction in the number of ER admissions due to hyperammonemia. There was a 51% reduction (p=0.0095) in the number of ER admissions during the two-year observation period. No serious safety concerns reported. Additional randomized clinical trials with clinically meaningful outcomes are required to confirm signals of efficacy.
   B. Carbamoyl-Phosphate Synthase I Deficiency
   C. Ornithine Carbamoyltransferase Deficiency
   D. Other Urea Cycle disorders

References

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2. Center for Drug Evaluation and Research. Application Number: 22-562. Summary Review. 30 July 2009. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022562s000sumr.pdf
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5. Ammonia. URMC Health Encyclopedia. Accessed 2 December 2020. Available at: https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=167&ContentID=ammonia
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Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication of acute treatment of hyperammonemia due to PA or MMA to initial criteria; changed initial authorization for acute hyperammonemia due to NAGS deficiency from 3 to 12 months; changed renewal authorization for acute hyperammonemia due to NAGS deficiency from 12 months to no renewal; updated supporting evidence section and experimental and not medically necessary sections.	05/2022

Added criteria of a trial and failure of generic Carbaglu prior to using branded product	12/2021
Transitioned criteria to policy format; Added requirement for weight documentation and supporting evidence section.	12/2020
Criteria created	12/2015

Policy Type: PA Pharmacy Coverage Policy: UMP013

Description

Cenegermin-bkbj (Oxervate) is a recombinant human eye growth factor ophthalmic solution indicated for the treatment of neurotrophic keratitis.

Length of Authorization

- Initial: Eight weeks
- Renewal: Cannot Be Renewed

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit*
cenegermin-bkbj (Oxervate)	Neurotrophic keratitis	0.002% (20 mcg/mL) vial	56mL per 56 days, per eye

**Quantity limit of 56 mL per 56 days (28 mL/28 days) is sufficient to treat one eye. If both eyes are affected/require treatment, allowance of 112 mL per 56 days (56 mL/28 days) can occur. Treatment is once per lifetime.*

Initial Evaluation

I. **Cenegermin-bkbj (Oxervate)** may be considered medically necessary when the following criteria are met:
   A. Prescribed by, or in consultation with, an ophthalmologist; **AND**
   B. A diagnosis of Neurotropic Keratitis; **AND**
   C. Antibiotic drops in combination with preservative-free artificial tears has been ineffective, contraindicated, or not tolerated; **AND**
   D. Member has Stage 2 (persistent epithelial defect) or Stage 3 (corneal ulceration, corneal perforation, or corneal stromal melting) disease; **AND**
      1. For Stage 2 disease: Therapeutic contact lens (scleral lens) have been ineffective, contraindicated, or are not tolerated; **AND**
   E. Member has NOT received prior therapy with cenegermin-bkbj (Oxervate) in the requested eye in their lifetime.

II. Cenegermin-bkbj (Oxervate) is considered investigational when used for all other conditions, including but not limited to:
   A. Treatment duration longer than 8 weeks

Renewal Evaluation

I. Product not eligible for renewal

Supporting Evidence

I. Neurotrophic keratitis (NK) is a rare, degenerative disease of the cornea caused by damage to the trigeminal nerve, which results in reduction/loss of corneal sensitivity, epithelium breakdown, decreased corneal healing, ulceration, melting, and perforation. NK severity is divided into three stages.
   - Stage 1: characterized by epithelial irregularity most commonly in the form of punctate keratopathy without epithelial defect.
   - Stage 2: defined by recurrent or persistent epithelial defects (PED) usually oval in shape and its margins are characteristically smooth and rolled due to impaired epithelial healing. Descemet's membrane folds and stromal edema may be observed.
   - Stage 3: characterized by stromal involvement that appears as a stromal corneal ulcer and stromal edema and infiltrates; this may result in perforation and/or corneal thinning due to stromal melting.

II. The goal of therapy is to prevent progression of corneal damage and promote healing of the corneal epithelium. Treatment of NK is based on disease severity; however, use of preservative-free artificial tears may help improve the corneal surface at all stages of disease severity. Topical antibiotic eye drops are recommended in eyes with NK at stages 2 and 3 to prevent infection. Nonpharmacological treatments for NK include therapeutic corneal or scleral contact lenses in the event of PED to promote corneal epithelial healing. Surgical treatments are reserved for refractory cases.

III. Cenegermin-bkbj (Oxervate) was studied in two 8-week, phase II multi-center, randomized, double blind, placebo controlled clinical trials (Study NGF0212 (REPARO) and Study NGF0214) in adult patients with Stage 2 or Stage 3 NK who were refractory to 1 or more conventional nonsurgical treatments. In NGF0212 72% of patients treated with cenegermin-bkbj (Oxervate) achieved complete corneal healing at week 8, as well as 65.2% of patients in Study NGF0214. In patients who were healed after 8 weeks of treatment, recurrences occurred in approximately 20% of patients in Study NGF0212 and 14% of patients in Study NGF0214. Retreatment following recurrence was not assessed in either study.

IV. Efficacy of cenegermin-bkbj (Oxervate) beyond a single 8-week course of treatment or repeat treatment has not been evaluated.

V. Cenegermin-bkbj (Oxervate) is packaged in a box of #7 x 1 mL vials and is dosed to a maximum of 1 vial (1 mL) per day for 8 weeks (56 days) per treated eye. If both eyes are being treated, the patient will require two vials (2 mL) each day.

Investigational or Not Medically Necessary Uses

I. Neurotrophic Keratitis
   A. Treatment beyond the initial 8 week duration is considered experimental and investigational due to lack of studies to demonstrate efficacy beyond a single eight week course of treatment.

References

1. Oxervate [Prescribing Information]. Boston, MA: Dompé US, Inc. October 2019.
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3. Shaheen B, Bakir M, Jain S. Corneal nerves in health and disease. *Surv Opthalmol.* 2014;59(3):263-285.
4. Mantelli F, Nardella C, Tiberi E, et al. Congenital corneal anesthesia and neurotrophic keratitis: diagnosis and management. *Biomed Res Int.* 2015;2015:805876. Epub Sept. 16, 2015.
5. Semeraro F, Forbice E, Romano V, et al. Neurotrophic keratitis. *Opthalmologica*. 2014;231(4):191-197.
6. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Opthalmol.* 2014;8:571-579.
7. An Evidence based Approach to the Diagnosis and Treatment of Neurotrophic Keratopathy. CME monograph. Johns Hopkins School of Medicine. March 2020. Available at: https://hopkinscme.cloud-cme.com/assets/hopkinscme/Presentations/28879/28879.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Clarified renewal language to confirm that this medication cannot be renewed	01/2024
Clarification of QL differences when treating one versus both eyes.	11/2022
Removal of requirement "lack of active ocular infection (bacterial, viral, fungal, or protozoal) and lack of current severe blepharitis and/or severe meibomian gland disease". Removal of "documentation of cause not due to infective or autoimmune keratitis". Removal of required history of use of a topical collagenase inhibitor as this is specific to the management of stromal melting. Broke down requirement of therapeutic contact lens to be specific to Stage 2 NK. Additional requirement assuring member has not received treatment with Oxervate in their lifetime. Updates to supporting evidence.	04/2021
Policy created	01/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP200

Description

Chenodiol (Chenodal®) suppresses hepatics synthesis of cholesterol and cholic acid, which leads to biliary cholesterol desaturation and gradual dissolution.

Length of Authorization

- Initial: Six months
- Renewal: up to 24 months (Maximum of **24** fills total)
    - Renewals are approved at six-month intervals

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
chenodiol (Chenodal)	250mg tablet	radiolucent gallstones	16 mg/kg/day

Initial Evaluation

I. Chenodiol (Chenodal) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
   C. Treatment with ursodiol (for at least six months) has been ineffective, contraindicated, or not tolerated; **AND**
   D. Member will not have received treatment with chenodiol (Chenodal) for more than two years during their lifetime; **AND**
   E. Medication will **NOT** be used for prophylaxis; **AND**
   F. A diagnosis of **radiolucent gallstones** when the following are met:
      1. Provider attests that member's symptoms effect quality of life (e.g. biliary colic, pain); **AND**
      2. Provider attests that the member is not a candidate for surgery (e.g. laparoscopic cholecystectomy).

II. Chenodiol (Chenodal) is considered investigational when used for all other conditions, including but not limited to:
   A. Cerebrotendinous xanthomatosis (CTX)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has not received treatment with chenodiol (Chenodal) for more than a total of **two** years (i.e., the maximum treatment duration is two years during a lifetime); **AND**
IV. Member has exhibited improvement or stability of disease symptoms [e.g., member doesn't exhibit biliary colic, has a loss of discomfort and pain].

Supporting Evidence

I. The safety and efficacy of chenodiol (Chenodal) was studied in a double blind, placebo controlled National Cooperative Gallstone Study (NCGS) involving 916 adult patients with radiolucent gallstones who were randomly assigned to the three treatment groups (placebo and chenodiol dosages of 375 mg and 750 mg) and followed for 24 months.
    - The placebo and chenodiol 375mg and 750mg per day treatment groups were associated with a 0.8%, 5.2%, and 13.5% complete stone dissolution, respectively. Chenodiol treatment (750 mg/day) compared to placebo was associated with a significant reduction in both biliary pain and the cholecystectomy rates in the group with floatable stones (27% versus 47% and 1.5% versus 19%, respectively). For patients with small (less than 15 mm in diameter) radiolucent stones, the observed rate of complete dissolution was approximately 20% on 750 mg/day.
II. The recommended dose range for chenodiol (Chenodal) is 13 to 16 mg/kg/day in two divided doses, or seven tablets a day. A maximum tolerated dose has not been well established.
III. The use of chenodiol (Chenodal) in pediatric patients has not been established in randomized controlled trials. There is no safety and efficacy data to support the use.
IV. In the absence of direct comparative trials there is no evidence to conclude that one product is safer or more effective than another. Ursodiol has been the standard of care in this space.
V. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy of chenodiol (Chenodal) beyond two years in a lifetime. Chenodiol should be discontinued if there is no response by 18 months.
VI. Chenodiol (Chenodal) is indicated for patients with radiolucent stones in well-opacifying gallbladders in whom selective surgery would be undertaken except for the presence of increased surgical risk due to systemic disease or age. Surgery (laparoscopic cholecystectomy) is the standard of care for gallstones and offers immediate and permanent stone removal.
VII. Per the American Association of Family Physician (AAFP) guidelines, no medical therapy aside from pain control is recommended for asymptomatic pigmented or calcified gallstones.
VIII. When a symptomatic patient is not a candidate for surgery, extracorporeal shock wave lithotripsy is a noninvasive therapeutic alternative, per the AAFP guidelines. Recent studies demonstrated efficacy of extracorporeal shock wave lithotripsy for large common bile duct (CBD) stones followed by ERCP, with results comparable to those of surgery with regard to pain

relief and duct clearance. Complete clearance of the CBD was achieved in 84.4% of and partial clearance in 12.3% of 283 patients.

IX. At therapeutic doses, chenodiol suppresses hepatic synthesis of both cholesterol and cholic acid and contributes to biliary cholesterol desaturation and gradual dissolution of radiolucent cholesterol gallstones. Chenodiol has no effect on radiopaque (calcified) gallstones or on radiolucent bile pigment stones.

X. Ultrasound remains the first line and best imaging modality to diagnose gallstones. A systematic review estimated that the sensitivity was 84% and specificity was 99% better than other modalities. If an ultrasound study is not equivocal for ruling out acute cholecystitis, then a nuclear medicine cholescintigraphy scan, also known as a HIDA scan, can be performed.

Investigational or Not Medically Necessary Uses

I. Chenodiol (Chenodal) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Cerebrotendinous xanthomatosis (CTX)
      i. Two-cohort studies, one for adult patients with a double-blind placebo withdrawal (with CDCA rescue) crossover in patients 16 years of age or older and second will dose titrate pediatric patients (one month of age to less than 16 years of age) into a stable, open-label treatment. The study is still recruiting as of November 2020 and there is a lack of safety and efficacy data to support the use.

References

1. Chenodal [Prescribing Information]. Retrophin, Inc. San Diego, CA. June 2015.
2. S M Grundy, et al. The effects of chenodiol on biliary lipids and their association with gallstone dissolution in the National Cooperative Gallstone Study (NCGS). J Clin Invest. 1984 Apr;73(4):1156-66. doi: 10.1172/JCI111301.
3. Jasmin Tanaja, et al. Cholelithiasis. StatPearls Publishing; 2020
4. Diehl AK, Sugarek NJ, Todd KH. Clinical evaluation for gallstone disease: usefulness of symptoms and signs in diagnosis. *Am J Med*. 1990;89(1):29-33. doi:10.1016/0002-9343(90)90094-t
5. Sherly Abraham, MD, et al. Surgical and Nonsurgical Management of Gallstones. Am Fam Physician. 2014 May 15;89(10):795-802.
6. Tandan M, Reddy DN. Extracorporeal shock wave lithotripsy for pancreatic and large common bile duct stones. *World J Gastroenterol*. 2011;17(39):4365–437
7. Retrophin, Inc. Study to Evaluate Patients With Cerebrotendinous Xanthomatosis. ClinicalTrials.gov Identifier: NCT04270682

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria updated to policy format. Removal of assessments on pregnancy or liver disease history. Addition of the following: limited treatment with chenodiol (Chenodal) for more than two years during member lifetime; required confirmation that medication will NOT be used for prophylaxis; provider attestation that member's symptoms effect quality of life	11/2020
Criteria created	02/2014

Policy Type: PA/SP Pharmacy Coverage Policy: UMP089

Description

Cholic acid (Cholbam) is an orally administered bile acid to help maintain bile acid homeostasis.

Length of Authorization

- Initial: three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
cholic acid (Cholbam)	50 mg capsules	Single Enzyme Defects (SEDs)	240 capsules/30 days	187995
	250 mg capsules	Peroxisomal disorders	240 capsules/30 days	187996

Initial Evaluation

I. Cholic acid (Cholbam) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a hepatologist or gastroenerologist; **AND**
   B. Member has **ALL** the following baseline lab values completed before initiation of therapy and continued monitoring when clinically appropriate:
      1. Aspartate aminotransferase test (AST)
      2. Alanine transaminase (ALT)
      3. Gamma-glutamyl transferase (GGT)
      4. Alkaline phosphate
      5. Bilirubin
      6. International normalized ratio (INR); **AND**
   C. A diagnosis of one of the following:
      1. **Single Enzyme Defects (SEDs); AND**
         i. Member has ONE of the following SEDs:
            a. 3-beta-hydroxy-delta-5-C27-steroid oxidoreductase (3β-HSD) deficiency
            b. Delta4-3 oxosteroid 5-beta-reductase, also known as aldoketoreductase (AKR1D1) deficiency
            c. Cerebrotendinous xanthomatosis (CTX)
            d. Alpha-methylacyl-CoA racemase (AMACR) deficiency

e. Sterol 27-hydroxylase (CYP27A1) deficiency
f. Smith-Lemli-Opitz; **AND**

ii. The request is for bile acid synthesis disorder due to one of the SEDs diagnosis above; **OR**

2. **Peroxisomal Disorders (PD); AND**

i. Member has ONE of the following peroxisomal disorders:
a. Neonatal Adrenoleukodystropyhy
b. Generalized Peroxisomal Disorder
c. Refsum Disease
d. Zellweger Syndrome
e. Peroxisomal Disorder, Type Unknown; **AND**

ii. Member exhibits manifestation of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption; **AND**

iii. Member will be using cholic acid (Cholbam) as adjunctive treatment

II. Cholic acid (Cholbam) is considered investigational when used for all other conditions, including but not limited to:
A. Extrahepatic manifestation of bile acid synthesis disorders due to SEDs or PDs
B. Familial hypertriglyceridemia without the diagnosis of SEDs or PDs

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent; **AND**
II. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

I. For the indication of single enzyme defects (SEDs), cholic acid (Cholbam) was studied in two clinical trials. Trial 1 was a non-randomized, open-label, single-arm trial in 50 patients over an 18 year period; trial 2 was an extension trial with 33 patients enrolled. Response to cholic acid (Cholbam) treatment was assessed with the following end points: ALT or AST values reduced to less than 50 U/L or baseline levels reduced by 80%, total bilirubin values reduced to less than or equal to 1 mg/dL, no evidence of cholestasis on liver biopsy, body weight increased by 10% or stable at greater than the 50th percentile, and survival for greater than 3 years on treatment or alive at the end of Trial 2. Regarding the 44 patients that were able to be measured at the end of the study, 28 patients (64%) were responders. Attrition information was limited.

II. For the indication of preoxisomal disorders (PDs) cholic acid (Cholbam) was studied in two clinical trials. Trial 1 was an open-label, single-arm trial in 29 patients followed over an 18 year period; while trial 2 was an extension trial with 12 patients enrolled. Response to cholic acid (Cholbam) treatment was assessed with the following end points: ALT or AST values reduced to less than 50 U/L or baseline levels reduced by 80%, total bilirubin values reduced to less than or equal to 1 mg/dL, no evidence of cholestasis on liver biopsy, body weight increased by 10% or

stable at greater than the 50th percentile, and survival for greater than 3 years on treatment or alive at the end of Trial 2. Of the 24 patients that were able to be measured at the end of the study, 11 patients (46%) were responders. Attrition information was limited.

III. Initial approval duration of three months allows for appropriate follow up with the prescriber per FDA label for cholic acid (Cholbam). It is then recommended to monitor AST, ALT, GGT, alkaline phosphatase, bilirubin and INR every month for the first 3 months, every 3 months for the next 9 months, every 6 months for the next three years, and annually for the remainder of the treatment.

Investigational or Not Medically Necessary Uses

I. Extrahepatic manifestation of bile acid synthesis disorders due to SEDs or PDs
   A. Cholic acid (Cholbam) has not been evaluated for safety and efficacy in the setting of extrahepatic manifestations.

II. Familial hypertriglyceridemia without the diagnosis of SEDs or PDs
   A. Although cholic acid (Cholbam) has an approved dosing regimen for concomitant familial hypertriglyceridemia, the safety and efficacy for patients diagnosed with familial hypertriglyceridemia without SEDs or PDs hasnot yet been evaluated.

References

1. Cholbam [Prescribing Information]. San Diego, CA: Manchester Pharmaceuticals, Inc. January 2016.

Policy Implementation/Update:

Date Created	April 2015
Date Effective	April 2015
Last Updated	
Last Reviewed	10/2019

Action and Summary of Changes	**Date**
Criteria was transitioned into policy. In this transition process, the following updates were made: addition of quantity limit, initial approval duration was changed from one year to three months following label recommendation for appropriate monitoring, renewal criteria and duration was added, supporting evidence was added, and investigational indications were added.	10/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP014

Description

The following biologics and biologic response modifiers are utilized in multiple chronic inflammatory disease states. Most of these agents target cytokines or other inflammatory mediators that are elevated in patients with such disease states. The purpose of this policy is to ensure the appropriate use of these agents.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Medications Included in this Policy

Medication	Indications
abatacept (Orencia®)	• Polyarticular Juvenile Idiopathic Arthritis • Psoriatic Arthritis • Rheumatoid Arthritis
adalimumab (Humira®)	• Ankylosing Spondylitis • Crohn's Disease • Hidradenitis Suppurativa • Polyarticular Juvenile Idiopathic Arthritis • Pediatric Crohn's Disease • Plaque Psoriasis • Psoriatic Arthritis • Ulcerative Colitis • Pediatric Ulcerative Colitis • Rheumatoid Arthritis • Uveitis/Panuveitis
anakinra (Kineret®)	• Cryopyrin-Associated Periodic Syndromes (CAPS) (including Chronic Infantile Neurological, Cutaneous and Articular Syndrome (CINCA) or Neonatal-Onset Multisystem Inflammatory Disease (NOMID)) • Rheumatoid Arthritis • Systemic Juvenile Idiopathic Arthritis (off-label) • Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) (off-label) • Familial Mediterranean Fever (off-label) • Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) (off-label)
apremilast (Otezla®)	• Plaque Psoriasis • Psoriatic Arthritis • Behcet Syndrome – ulcer of the mouth

brodalumab (Siliq®)	• Plaque Psoriasis
bimekizumab (Bimzelx®)	• Plaque Psoriasis
certolizumab (Cimzia®)	• Ankylosing Spondylitis • Crohn's Disease • Non-radiographic Axial Spondyloarthritis • Plaque Psoriasis • Psoriatic Arthritis • Rheumatoid Arthritis
etanercept (Enbrel®)	• Ankylosing Spondylitis • Plaque Psoriasis • Polyarticular Juvenile Idiopathic Arthritis • Psoriatic Arthritis • Rheumatoid Arthritis
golimumab (Simponi®/Simponi Aria®)	• Ankylosing Spondylitis • Psoriatic Arthritis • Rheumatoid Arthritis • Ulcerative Colitis
guselkumab (Tremfya®)	• Plaque Psoriasis • Psoriatic Arthritis
ixekizumab (Taltz®)	• Ankylosing Spondylitis • Non-radiographic Axial Spondyloarthritis • Adolescent Plaque Psoriasis • Plaque Psoriasis • Psoriatic Arthritis
rilonacept (Arcalyst®)	• Cryopyrin-Associated Periodic Syndromes (CAPS) (including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS)) • Recurrent Pericarditis
risankizumab (Skyrizi®)	• Plaque Psoriasis • Psoriatic Arthritis • Crohn's Disease
sarilumab (Kevzara®)	• Rheumatoid Arthritis • Polymyalgia Rheumatica
secukinumab (Cosentyx®)	• Ankylosing Spondylitis • Non-radiographic Axial Spondyloarthritis • Plaque Psoriasis • Psoriatic Arthritis • Enthesitis-related arthritis • Hidradenitis Suppurativa
ustekinumab (Stelara®)	• Crohn's Disease • Adolescent Plaque Psoriasis • Plaque Psoriasis • Adolescent Psoriatic Arthritis • Psoriatic Arthritis • Ulcerative Colitis

tocilizumab (Actemra®)	• Giant Cell Arteritis • Polyarticular Juvenile Idiopathic Arthritis • Rheumatoid Arthritis • Systemic Juvenile Idiopathic Arthritis • Systemic Sclerosis-Associated Interstitial Lung Disease
ozanimod (Zeposia®)	• Ulcerative Colitis
vedolizumab SC (Entyvio®)	• Ulcerative Colitis
mirikizumab (Omvoh®)	• Ulcerative Colitis
etrasimod (Velsipity™)	• Ulcerative Colitis
infliximab-dyyb (Zymfentra®)	• Ulcerative Colitis • Crohn's Disease
Adalimumab Biosimilars	
Preferred biosimilars: adalimumab-adaz (Adalimumab-ADAZ), adalimumab-bwwd (Hadlima™) **Non-preferred biosimilars**: adalimumab-aacf (Idacio®), adalimumab-aaty (Yuflyma®), adalimumab-adaz (Hyrimoz®), adalimumab-adbm (Cyltezo®), adalimumab-afzb (Abrilada™), adalimumab-aqvh (Yusimry™), adalimumab-atto (Amjevita™), adalimumab-fkjp (Hulio™), adalimumab-fkjp (Adalimumab-FKJP)	• Ankylosing Spondylitis • Crohn's Disease • Hidradenitis Suppurativa • Polyarticular Juvenile Idiopathic Arthritis • Pediatric Crohn's Disease • Plaque Psoriasis • Psoriatic Arthritis • Ulcerative Colitis • Pediatric Ulcerative Colitis • Rheumatoid Arthritis • Uveitis/Panuveitis

Applicable to All Disease States and Treatment Options Listed Below

I. Contraindication to one preferred treatment option listed in the policies below does not exempt the requirement to try another required agent prior to biologic approval. For instance, in the rheumatoid arthritis policy to follow, a contraindication to methotrexate but not to other available treatment options (sulfasalazine, hydroxychloroquine, leflunomide, etc.) would not satisfy criteria I(C)(1). In other words, a member would still need to try at least one of these other agents as clinically appropriate.

II. Approved treatments are not to be used in combination with other biologics or other non-biologic specialty medications used to treat autoimmune conditions. Use of TNF-alpha blockers such as adalimumab in combination with other biologics, such as anakinra or abatacept, has demonstrated and increased risk of serious infection with insufficient evidence for added benefit. Per product labeling, use of concomitant biologics is not recommended as there is insufficient data to support this. Similarly, non-biologic small molecules such as tofacitinib and baricitinib have not been studied sufficiently with other biologic disease-modifying antirheumatic drugs (DMARDs) to safely recommend their use as dual therapy. Likewise, sufficient data is not

currently available to support the safety and efficacy of apremilast use in combination with other agents listed in these criteria.

Rheumatoid Arthritis

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), or etanercept (Enbrel)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **rheumatoid arthritis** when the following are met:
      1. Treatment with an oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective or not tolerated, or all are contraindicated (e.g., guidelines direct to methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.).

II. **Abatacept (Orencia), anakinra (Kineret), certolizumab (Cimzia), golimumab (Simponi), sarilumab (Kevzara), tocilizumab (Actemra), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), upadacitinib (Rinvoq), and tofacitinib (Xeljanz/Xeljanz XR) have been ineffective, contraindicated, or not tolerated.

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product ; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The prescriber must document one or more of the following, indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **OR**
      2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
      3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
         i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: etanercept (Enbrel), upadacitinib (Rinvoq), and tofacitinib (Xeljanz/Xeljanz XR)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat rheumatoid arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.); **AND**
    A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
        1. The prescriber must document one or more of the following, indicating that the reaction:
            i. Was life-threatening; **OR**
            ii. Required hospitalization; **OR**
            iii. Required intervention to prevent impairment or damage; **OR**
        2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
        3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
            i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)].

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and

patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The agents listed above are approved for adult patients with rheumatoid arthritis (RA) based on safety and efficacy data from randomized-controlled trials.

III. The 2021 American College of Rheumatology (ACR) guidelines for rheumatoid arthritis address the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted-synthetic DMARDS (tsDMARDs) such as JAK inhibitors, and biologic DMARDS (bDMARDs) as TNF inhibitors and non-TNF inhibitors. A majority of recommendations are based on low or very low certainty of evidence.

- The 2021 ACR guidelines strongly recommend the use of csDMARD monotherapy (methotrexate preferred) in patients who are DMARD-naïve with moderate-to-severe RA. Recommended csDMARDs include methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. Despite moderate evidence in the SELECT-EARLY study noting higher efficacy of upadacitinib over methotrexate in DMARD-naïve patients with moderate-to-severe RA, there is limited long-term safety data to strongly recommend the use of tsDMARDs (e.g., JAK inhibitors) as first line therapy. Therefore, methotrexate monotherapy remains the preferred first-line therapy over tsDMARDs in DMARD-naïve patients based on established safety and efficacy. Additionally, JAK inhibitors are not FDA approved for use in csDMARD-naïve patients.
- For patients who are DMARD-naïve with low disease activity, initial trial of hydroxychloroquine over other csDMARDs, and sulfasalazine over methotrexate is conditionally recommended.
- For DMARD-naive patients with moderate-to-severe disease activity, methotrexate monotherapy is conditionally recommended over methotrexate in combination with a TNF inhibitor due to low-certainty evidence with combination use. The recommendation is conditional because patients with poor prognostic factors may benefit from a faster onset of action and greater change of improvement with dual therapy.
- In DMARD-naive patients with moderate-to-severe disease activity, methotrexate monotherapy is strongly recommended over the addition of a non-TNF inhibitor or tsDMARD based additional risks of adding a biologic or tsDMARD and low-quality data evaluating superiority over methotrexate monotherapy.
- For patients with moderate-to-severe disease activity despite adequate trial of csDMARD monotherapy, a treat-to-target approach is strongly recommended and the addition of a bDMARD or tsDMARD is conditionally recommended as combination therapy may provide a more rapid treatment response. The recommendation was based on very low certainty of evidence.
- The guidelines conditionally recommend switching to a bDMARD or tsDMARD of a different class over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target, however the recommendation is based on very low-quality evidence supporting greater improvement in disease activity among patients switching therapy classes. There are

no current recommendations for using a bDMARD over a tsDMARD, however patients and providers should engage in a shared decision-making approach based on the available safety data of JAK inhibitors.

- The 2021 ACR guidelines have additional recommendations for patient specific populations, including patients with co-morbid heart failure, lymphoproliferative disorder, Hepatitis B infection, nonalcoholic fatty liver disease (NAFLD), persistent hypogammaglobulinemia without infection, and populations with history of serious infection(s).

IV. The 2019 European League Against Rheumatism (EULAR) guidelines follow similar recommendations to the 2021 ACR guidelines, and state that patients who have failed one bDMARD or tsDMARD may switch to an agent from the same class. Studies have demonstrated primary TNF non-responders have responded to other agents of the same mechanism of action.

References:

1. Fraenkel L, Bathon JM, England BR, et al. 2021 American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res*. 2021;73(7):924-939.
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Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), or etanercept (Enbrel)** may be considered medically necessary when the following criteria below are met:
   A. Member is 2 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **Polyarticular Juvenile Idiopathic Arthritis (PJIA)** when the following is met:
      1. Treatment with at least one oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective, contraindicated, or not tolerated. Guidelines direct to use of methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.

II. **Abatacept (Orencia), tocilizumab (Actemra), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), and tofacitinib (Xeljanz) have been ineffective, contraindicated, or not tolerated.

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The prescriber must document one or more of the following, indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **OR**
      2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
      3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
         i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**
   D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: etanercept (Enbrel) and tofacitinib (Xeljanz)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat polyarticular juvenile idiopathic arthritis or another auto-immune condition (e.g., Humira, Xeljanz, Infliximab, etc.); **AND**
   A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the multi-source brand drug is to be considered medically necessary when the prescriber is requesting the multi-source brand drug due to a documented adverse reaction to the biosimilar; **AND**
   B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; AND
      1. The prescriber must document one or more of the following, indicating that the reaction:

i. Was life-threatening; **OR**
ii. Required hospitalization; **OR**
iii. Required intervention to prevent impairment or damage; **OR**

2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)].

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Juvenile idiopathic arthritis (JIA) is a grouping of inflammatory disorders that affect children. Polyarticular juvenile idiopathic arthritis (PJIA) is a subset of JIA, which is defined by the presence arthritis in five or more joints during the first six months of illness. Other subsets of JIA include ERA, oligoarthritis (less than five joints affected), systemic juvenile idiopathic arthritis (SJIA; fever, rash, hepatic/splenic/lymphatic involvement) and psoriatic arthritis (psoriasis and dactylitis). While these are distinct disease states, their pathogenesis and presentation are similar so there is significant overlap in effective treatments.

III. Adalimumab (Humira), etanercept (Enbrel), abatacept (Orencia) and tocilizumab (Actemra) are approved for pediatric patients greater than two years of age with PJIA based on safety and efficacy data from randomized-controlled trials.

IV. The 2019 ACR JIA guidelines for non-systemic polyarthritis (PJIA) strongly recommend initial therapy with a DMARD for all patients with JIA and active polyarthritis; methotrexate has the strongest evidence, but sulfasalazine and leflunomide can also be used. Adjunctive therapy with NSAIDs and oral or intra-articular glucocorticoids is common. Regardless of disease activity, initial therapy with a DMARD is recommended over a biologic, though there may be certain situations where a biologic as initial therapy is preferred (i.e., high risk joints such as cervical spine, wrist, or hip involved). ACR notes that while initial treatment with biologics was studied in

the TREAT-JIA and ACUTE-JIA studies, results were not deemed conclusive enough to make recommendations for biologics as initial therapy at this time. For patients with continued moderate to high disease activity, the guidelines recommend adding a TNF inhibitor, abatacept, or tocilizumab as second-line. The ACR guidelines make a conditional recommendation for switching to non-TNF inhibitor biologics (tocilizumab and abatacept) in patients receiving a TNF inhibitor with continued moderate or high disease activity. It is noted that a second TNF inhibitor may be appropriate for patients who had a good initial response to the first TNF inhibitor but had secondary failure due to suspected drug antibodies developing, and that this conditional recommendation stems from data in adult rheumatoid arthritis patients. Juvenile psoriatic arthritis follows the same treatment paradigm.

V. A phase 3 double-blind, randomized, placebo-controlled withdrawal study (PROPEL) evaluated the efficacy and safety of tofacitinib (Xeljanz) in patients aged 2-17 years old with active PJIA and who had inadequate response to at least one DMARD or biologic DMARD. The primary endpoint evaluated the occurrence of disease flare at week 44 and was found to be statistically significantly lower in tofacitinib (Xeljanz) group vs the placebo group (29.2 % vs 59.2%, p-value=0.0031). The secondary endpoint found improvements from baseline in questionnaires JIA ACR 30/50/70 and Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) in tofacitinib vs placebo. Some limitations to the study include potential bias in the open label arm of the study, and the study is unpublished with limited information such as the population of patients currently on DMARD or oral glucocorticoid.

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1. UpToDate, Inc. Spondyloarthritis in children. UpToDate [database online]. Waltham, MA. Last updated December 4, 2020. Available at uptodate.com. Accessed February 4, 2022.
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Enthesitis-Related Arthritis (ERA)

Initial Evaluation

I. **Secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is 4 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **Enthesitis-Related Arthritis (ERA)** when the following is met:
      1. Treatment with at least one oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective, contraindicated, or not tolerated. Guidelines direct to use of methotrexate, sulfasalazine,

hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat enthesitis-related arthritis (ERA) or another auto-immune condition (e.g., Humira, Xeljanz, Infliximab, etc.).

Supporting Evidence

I. Enthesitis-related arthritis (ERA) is a subset of juvenile idiopathic arthritis (JIA) and is characterized primarily by inflammation of the entheses, or connective tissue between tendon/ligament and bone, and commonly affects sacroiliac or lumbosacral joints. Other subsets of JIA include PJIA, oligoarthritis (less than five joints affected), systemic juvenile idiopathic arthritis (SJIA; fever, rash, hepatic/splenic/lymphatic involvement) and psoriatic arthritis (psoriasis and dactylitis). While these are distinct disease states, their pathogenesis and presentation are similar so there is significant overlap in effective treatments.
II. Secukinumab (Cosentyx) was approved for pediatric patients aged four years or older with ERA based on safety and efficacy from a phase 3 study (JUNIPERA) of children aged 2-17 years with a diagnosis of active ERA or juvenile psoriatic arthritis with an inadequate response or intolerance to at least 1 NSAID and at least 1 DMARD. The majority (67.6% of juvenile psoriatic arthritis, 63.5% of ERA) of patients were taking concomitant methotrexate throughout the study. The primary endpoint was time to flare over a 92-week period, which was met with a statistically significant longer time to flare in the secukinumab group compared to placebo group for both indications; risk of flare was reduced by 53% in ERA (HR 0.47, 95% CI 0.17-1.32) and 85% in juvenile psoriatic arthritis (HR 0.15, 95% CI 0.04-0.56). Improvements in secondary endpoint JIA ACR 30/50/70/90 were also seen in the intervention group relative to placebo. No new safety signals were discovered, and adverse effects were consistent with the established safety profile of secukinumab.
III. The 2019 ACR JIA guidelines provide recommendations for enthesitis, which include ERA, psoriatic arthritis, and undifferentiated arthritis, all of which fall under the JIA umbrella. For patients with ERA, initial therapy with an NSAID is recommended. In the second-line setting, ACR provides a conditional recommendation for TNF inhibitors over DMARD, though this is based on low-quality evidence; this recommendation is rooted in retrospective cohort and phase 3 studies of etanercept and adalimumab for several different subtypes of JIA, including ERA, which provided mixed signals that biologics are more effective than placebo or no comparator, but the majority of included patients had previously been treated with at least one NSAID and DMARD. It has also been suggested that methotrexate is not as

effective at managing axial manifestations of ERA. However, DMARDs remain a viable first-line option for ERA patients given their well-established efficacy and safety profile, especially in those with mild disease or concomitant active polyarthritis. Age-appropriate biologics approved for ERA, PJIA or juvenile psoriatic arthritis should be reserved for subsequent therapy.

IV. While other biologics have been evaluated for use in ERA or other JIA subtypes, only secukinumab (Cosentyx) is FDA-approved for ERA. Notably, etanercept and adalimumab have undergone one phase 3 study each in ERA patients but neither have pursued FDA approval. In a 12-week randomized, double-blind study of ERA patients age 6-18 years (n=46) followed by a 180-week open label single-arm extension, adalimumab was found to provide a statistically significant greater reduction in the number of active joints with arthritis at week 12 compared to placebo, but the majority of secondary endpoints, including ACR 30/50/70/90, were not met. In a 12-week single-arm open-label study of JIA patients, including ERA, extended oligoarticular JIA and PsA patients age 12-17 years (n=127) with an 86-week single-arm extension, a greater proportion of patients treated with etanercept achieved JIA ACR30 compared to historical placebo data. No new safety concerns arose during studies. At this time, quality of these data are considered low due to small sample size, single-arm open-label study design, and lack of clinically meaningful endpoints being met.

References

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Systemic Juvenile Idiopathic Arthritis (SJIA)

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is 2 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **active SJIA** when the following are met:
      1. Treatment with at least one NSAID (e.g., ibuprofen, naproxen, indomethacin, meloxicam, celecoxib, etc.) or glucocorticoid (i.e., prednisone, hydrocortisone,

methylprednisolone, etc.) has been ineffective, contraindicated, or not tolerated; **OR**

2. Patient has severe active disease as indicated by one of the following:
    i. Suspected early macrophage activating syndrome (MAS)
    ii. Disabling polyarthritis
    iii. Serositis

II. **Tocilizumab (Actemra)** may be considered medically necessary when the following criteria below are met:
    A. Criteria I(A)-I(C) above are met; **AND**
    B. Treatment with anakinra (Kineret) has been ineffective, contraindicated, or not tolerated.

III. **Abatacept (Orencia)** may be considered medically necessary when the following criteria below are met:
    A. Criteria I(A)-I(C) above are met; **AND**
    B. Treatment with anakinra (Kineret) AND tocilizumab (Actemra) has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat juvenile idiopathic arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Infliximab, etc.)

Supporting Evidence

I. Anakinra (Kineret) does not have FDA approval for SJIA but did gain approval recently by the European Medicines Agency for this indication in 2018. A prospective trial examined 42 children with new-onset disease after no response to a seven-day trial of NSAIDs. Rapid improvement was seen, with inactive disease noted in 55% and 71% of patients at one and three months, respectively. A similar rate of response was seen in a small RCT (ANAJIS) to that seen in the tocilizumab trial and is described below in terms of ACR30.
II. Tocilizumab is approved for treatment of active SJIA in patients two years and older. In a RCT of 112 children with SJIA for greater than six months, who had an inadequate response to NSAIDs and glucocorticoids, tocilizumab patients were more likely to achieve JIA ACR30 response by week 12 compared to placebo (85% vs 24%, $p<0.001$).
III. The SJIA guidelines updated in 2013 by the ACR note that NSAIDs are recommended as an initial treatment approach. However, based off expert opinion, monotherapy is inappropriate for patients with an MD global assessment score of 5 or greater (0-10 scale), indicating severe disease. Likewise, it is noted that macrophage activation syndrome (MAS) which occurs in approximately 10% of SJIA patients, is a severe, life-threatening condition and delay in IL-1 or IL-6 inhibitor therapy should not occur in this scenario. Anakinra (Kineret) is recommended as an

initial treatment option in patients with severely active disease, as well as for patients with continued disease activity after treatment with glucocorticoid or NSAID monotherapy. For those patients who have tried both anakinra (Kineret) and tocilizumab (Actemra) sequentially, abatacept (Orencia) is recommended based off expert opinion. A subset of 37 children with systemic JIA was examined in comparison to placebo in a RCT. After four months of treatment in the initial lead-in period, 24 of 37 patients (65%) treated with abatacept had a ACR30 response, which was similar to response rates seen in patients included with other JIA subtypes.

IV. TNF inhibitors demonstrate greater efficacy in patients with nonsystemic JIA compared to SJIA. For instance, a study of 45 children who had systemic symptoms at the start of TNF inhibitor therapy noted lower rates of remission and a high frequency of disease flare (24% and 45%, respectively).

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Psoriatic Arthritis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel), apremilast (Otezla), secukinumab (Cosentyx), ustekinumab (Stelara), risankizumab (Skyrizi), or guselkumab (Tremfya)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **OR**
      1. Member is 2 years of age or older and is prescribed secukinumab (Cosentyx) or etanercept (Enbrel); **OR**
      2. Member is 6 years of age or older and is prescribed ustekinumab (Stelara); **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist or dermatologist; **AND**
   C. A diagnosis of active **psoriatic arthritis** when the following are met:

1. Treatment with non-biologic, non-specialty oral small molecules (OSMs) such as methotrexate, leflunomide, sulfasalazine, or cyclosporine has been ineffective, contraindicated, or not tolerated; **OR**
2. Presence of active, severe disease as indicated by provider assessment and the presence of at least one of the following:
    i. Erosive disease
    ii. Elevated CRP or ESR
    iii. Long-term damage interfering with function (e.g., joint deformities, vision loss)
    iv. Major impairment of quality of life due to high disease activity at many sites (including dactylitis, enthesitis) or functionally limiting arthritis at a few sites

II. **Abatacept (Orencia), certolizumab (Cimzia), golimumab (Simponi), ixekizumab (Taltz), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
A. Criteria I(B)-I(C) above are met; **AND**
B. Member is 18 years of age or older; **OR**
    1. Member is two years of age or older if prescribed abatacept (Orencia); **AND**
C. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), apremilast (Otezla), secukinumab (Cosentyx), ustekinumab (Stelara), risankizumab (Skyrizi), guselkumab (Tremfya), tofacitinib (Xeljanz/Xeljanz XR), and upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(C) above are met; **AND**
B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product ; **AND**
C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
    1. The prescriber must document one or more of the following, indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage; **OR**
    2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
    3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**

i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: etanercept (Enbrel), apremilast (Otezla), secukinumab (Cosentyx), ustekinumab (Stelara), guselkumab (Tremfya), tofacitinib (Xeljanz/Xeljanz XR), risankizumab (Skyrizi), and upadacitinib (Rinvoq)

**Clinical note: If a patient has a diagnosis of both plaque psoriasis and psoriatic arthritis, approval of the requested medication can be made as long as the patient fulfills the criteria for at least one of the disease states and associated medication criteria.*

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms; **AND**

IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat psoriatic arthritis or another auto-immune condition (e.g., Humira, Otezla, Olumiant, etc.); **AND**

A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**

B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The prescriber must document one or more of the following, indicating that the reaction:
   i. Was life-threatening; **OR**
   ii. Required hospitalization; **OR**
   iii. Required intervention to prevent impairment or damage; **OR**
2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
   i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)].

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are approved for adult patients in the treatment of psoriatic arthritis based on safety and efficacy data from randomized-controlled trials. Additionally, secukinumab (Cosentyx) was approved for pediatric patients aged two years or older with psoriatic arthritis based on safety and efficacy from a phase 3 study (JUNIPERA) of children aged 2-17 years with a diagnosis of active enthesitis-related arthritis or juvenile psoriatic arthritis with an inadequate response or intolerance to at least 1 NSAID and at least 1 DMARD. See PJIA section for additional study details.

III. The 2018 ACR guidelines for psoriatic arthritis make a conditional recommendation for starting a TNF inhibitor over an OSM as a first-line option for patients who are treatment-naïve with active psoriatic arthritis. This recommendation is based on low- to very-low quality of evidence. Many of the studies in which greater benefit was seen in terms of disease severity or radiographic progression compared methotrexate to TNF inhibitors, however, most patients included in these groups were not truly treatment naïve to OSM medications. Guidelines note that OSM can be used first-line in naïve patients who do not have severe PsA, severe PsO, prefers oral therapy, or has contraindications to TNF inhibitors. In patients who continue to have active disease despite OSM treatment, it is recommended to switch to a TNF inhibitor rather than trying a different OSM.

IV. According to the 2019 ACR guidelines for juvenile idiopathic arthritis (JIA), which have been described in the PJIA section, treatment of pediatric PsA is similar to adult PsA: oral DMARD as first line, TNF inhibitors or other biologics as second line. Regardless of level of disease activity, initial therapy with a DMARD is recommended over a biologic. However, initial therapy with a biologic may be preferred for patients with risk factors for/involvement of high-risk joints (cervical spine, wrist, hip), high disease activity, and/or those judged by their physician to be at risk of disabling joint disease.

V. A systematic review of RCTs published in 2015 examined differences in terms of ACR20 response with biologic versus synthetic DMARDs. A statistically significant benefit was not demonstrated with methotrexate, cyclosporine, or sulfasalazine. Leflunomide did demonstrate a statistically significant benefit, though the magnitude of benefit was lower than all of the biologic DMARDs analyzed. There are many limitations to this review, such as a large proportion of trials/data that only included a small number of patients (less than 100). A recent study compared the TNF

inhibitor etanercept to methotrexate monotherapy in patients naïve to both biologics and methotrexate. Patients treated with etanercept were statistically more likely to achieve ACR20 response at week 24 compared to the methotrexate monotherapy group (difference 9.2%, 95% CI 1.0 to 17.3, p = 0.029).

VI. The 2018 ACR guidelines for psoriatic arthritis also conditionally recommend for use of a TNF inhibitor biologics over IL-17 inhibitors (ixekizumab, secukinumab) or IL-12/23 inhibitors (ustekinumab). In January 2022, the latest agent, risankizumab, an IL-23 inhibitor, was approved; however, the guidelines have not been updated with regard to place in therapy for risankizumab or other IL-23 inhibitors, such as guselkumab.

VII. Expanded approval of ustekinumab for active psoriatic arthritis for children and adolescents was based on data extrapolation from multiple phase 3 studies for adults and pediatric patients with moderate to severe plaque psoriasis (PSTELLAR, CADMUS, and CADMUS Jr) and multiple phase 3 studies for adults with active psoriatic arthritis (PSUMMIT I and II). Pharmacokinetic and safety data analysis in pediatric patients with active psoriasis and psoriatic arthritis are comparable to adult data in regard to pharmacokinetic concentrations and disease-medication response, with no additional safety issues present in the pediatric population (similar with no new safety signals when compared pediatric AE to adult AE rates).

VIII. Expanded approval of abatacept (Orencia) and etanercept (Enbrel) in pediatric patients ages two and up for psoriatic arthritis was based on data extrapolation from studies in adult populations (PsA and RA) and pediatric patients with PJIA (and PsO for Enbrel). Observed trough concentrations were found to be generally comparable between adults and pediatric patients. Pharmacokinetic exposure is expected to be comparable between adult and pediatric patients with PsA.

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Ankylosing Spondylitis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel) or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **ankylosing spondylitis** when the following are met:
      1. High disease activity as indicated by BASDAI score of at least 4 or ASDAS score of at least 2.1; **AND**
      2. Treatment with at least two different NSAIDs (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated; **AND**
      3. Disease manifested as axial disease; **OR**
      4. Disease manifested as peripheral arthritis

II. **Certolizumab (Cimzia), golimumab (Simponi), ixekizumab (Taltz), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), secukinumab (Cosentyx), tofacitinib (Xeljanz), and upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated.

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product ; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The prescriber must document one or more of the following, indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **OR**
      2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**

3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: etanercept (Enbrel) secukinumab (Cosentyx), tofacitinib (Xeljanz), and upadacitinib (Rinvoq)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat ankylosing spondylitis or another auto-immune condition (e.g., Rinvoq, Otezla, Olumiant, Infliximab, etc.); **AND**
    A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
        1. The prescriber must document one or more of the following, indicating that the reaction:
            i. Was life-threatening; **OR**
            ii. Required hospitalization; **OR**
            iii. Required intervention to prevent impairment or damage; **OR**
        2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
        3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
            i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)].

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in

promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are approved for adult patients in the treatment of ankylosing spondylitis based on safety and efficacy data from randomized-controlled trials.

III. The 2019 ACR/SAA/SPARTAN guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% responding). For those patients with inadequate response despite continuous NSAID treatment, the panel strongly recommends use of TNF inhibitors. For those patients with continued active disease, the panel conditionally recommends trial of a different TNF inhibitor over treatment with a non-TNF inhibitor biologic. Observational studies have demonstrated clinical improvement in patients who have switched TNF inhibitors compared to switching to a DMARD or non-TNF biologic.

IV. The ACR/SAA/SPARTAN guideline conditionally recommends against the use of DMARDs in patients with ankylosing spondylitis that remains active despite NSAID treatment. This is based off controlled trials demonstrating minimal to no benefit with agents such as sulfasalazine, methotrexate, and leflunomide. Some benefit has been seen in patients with peripheral arthritis, and thus these agents may be considered for patients with ankylosing spondylitis with predominantly peripheral arthritis symptoms.

V. The 2022 ASAS/EULAR guidelines for the treatment of axial spondyloarthritis (axSpA) reference the use of JAK inhibitors in the treatment algorithm. The term axial spondyloarthritis (axSpA), encompasses both active ankylosing spondylitis (or radiographic AS) and nr-axSpA as one entity part of the same chronic inflammatory musculoskeletal spectrum with similar clinical presentations, comorbidities, disease burden, and treatment response. ASAS/EULAR recommends patients try and fail at least 2 NSAIDs over 4 weeks as first line therapy and treat local musculoskeletal inflammation with glucocorticoid injection; sulfasalazine may be considered in patients with peripheral symptoms, however use of conventional non-biologic DMARDS (e.g. sulfasalazine, leflunomide, methotrexate, etc.) is not recommended in axial disease. In contrast to ACR/SAA/SPARTAN, ASAS/EULAR guidelines highly recommend treatment with a TNF inhibitor, IL-17 inhibitor, or JAK inhibitor for patients with high disease activity, defined by a BASDAI of at least 4 or an ASDAS of at least 2.1, despite conventional treatment with NSAIDS. Starting with a TNF inhibitor or IL-17 inhibitor is preferred clinically, given long term data for use of JAK inhibitors in axSpA is still missing. There is no specific treatment algorithm after primary non-response to biologic (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor therapy. In absence of data showing superiority in the treatment sequence, switching to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or a JAK inhibitor may be considered.

VI. Although specific JAK inhibitors were not referenced in the ASAS/EULAR guideline, precautions for cardiovascular risk, malignancy, and thromboembolic events should be considered in patients starting JAK inhibitors. It is unclear whether the increased risk of cardiovascular events and malignancies is specific to a diagnosis of RA, reflective of a JAK inhibitor class effect, or specific to tofacitinib. Until more data become available, ASAS/EULAR advises against starting JAK inhibitors in specific populations: patients above 50 years of age with one or more cardiovascular risk factor and patients older than 65 years of age.

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Non-radiographic Axial Spondyloarthritis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel), or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **non-radiographic axial spondyloarthritis** when the following are met:
      1. High disease activity as indicated by BASDAI score of at least 4 or ASDAS score of at least 2.1; **AND**
      2. Treatment with at least two different NSAIDs (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated; **AND**
      3. Disease manifested as axial disease; **OR**
      4. Disease manifested as peripheral arthritis

II. **Certolizumab (Cimzia), ixekizumab (Taltz), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), secukinumab (Cosentyx), and upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated.

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product ; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The prescriber must document one or more of the following, indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **OR**
      2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
      3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
         i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**
   D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: etanercept (Enbrel), secukinumab (Cosentyx), and upadacitinib (Rinvoq)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat non-radiographic axial spondyloarthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Infliximab, etc.); **AND**
   A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
   B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The prescriber must document one or more of the following, indicating that the reaction:

i. Was life-threatening; **OR**
ii. Required hospitalization; **OR**
iii. Required intervention to prevent impairment or damage; **OR**

2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)].

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Currently, certolizumab pegol, ixekizumab, secukinumab, and upadacitinib are the only FDA approved agent for adults with non-radiographic axial spondyloarthritis. Other TNF inhibitors are approved in Europe for this indication, have demonstrated efficacy in RCTs, and are utilized frequently in clinical practice. For instance, a study of 192 patients taking adalimumab demonstrated significant improvement compared to placebo in ASAS40 response by week 12 in patients with non-radiographic disease (36% vs 15%, $p < 0.001$). Likewise, etanercept and golimumab have also been approved by the European Medicines Agency, and the 2022 ASAS/EULAR guidelines note that efficacy in regard to musculoskeletal signs and symptoms appears comparable based off indirect comparison.

III. A phase 3 double-blind, randomized, placebo-controlled trial (C-AXSPAND) examined the use of certolizumab pegol in patients with non-radiographic axial spondyloarthritis who had an inadequate response to at least two prior NSAIDs. In terms of the primary endpoint of patients achieving a response in the Ankylosing Spondylitis Disease Activity Score-Major Improvement (ASDAS-MI) at week 52, a significantly more patients in the certolizumab pegol group achieved this clinical response compared to placebo (47% vs 7%, OR 15.2, 95% CI 7.3 to 31.6). Improvement was also seen in secondary outcomes such as quality of life questionnaires.

IV. A phase 3, double-blind, randomized, parallel-group, placebo-controlled trial (COAST-X) assessed the use of ixekizumab in patients with non-radiographic axial spondyloarthritis who had an inadequate response to at least two prior NSAIDs. Primary endpoint of Assessment of Spondyloarthritis International Society 40 (ASAS40) response at weeks 16 and 52 on ixekizumab 80 mg every four weeks compared to placebo was achieved (week 16: 35% vs 19%, OR 2.36, 95% Cl 1.23-4.51, p=0.0094, and week 52: 30% vs 13%, OR 2.82, 95% Cl 1.38-5.77, p=0.0045). Improvement was also seen in secondary outcomes such as Ankylosing Spondylitis Disease Activity Score (ASDAS) and quality of life.

V. A phase 3, double-blind, randomized, placebo-controlled trial (PREVENT) assessed the use of secukinumab in patients with non-radiographic axial spondyloarthritis who had active disease (BASDAI greater or equal to four, visual analogue scale (VAS) for total back pain greater or equal to 40) despite NSAID therapy. Primary endpoints of Assessment of Spondyloarthritis International Society 40 (ASAS40) response at week 16 in TNFi-naïve patients on secukinumab 150 mg with loading dose compared to placebo and ASAS40 response at week 52 in TNFi-naïve patients on secukinumab 150 mg without loading dose compared to placebo were achieved (week 16: 41.5% vs 29.2%, p=0.0197, and week 52: 39.8% vs 19.9%, p<0.0021). Improvement was seen in secondary outcomes at week 16 for Ankylosing Spondylitis Disease Activity Score (ASDAS) and quality of life.

VI. Per 2019 ACR/SAA/SPARTAN non-radiographic axial spondyloarthritis treatment guidelines, the panel strongly recommends treatment with TNF inhibitors over no treatment with TNF inhibitors. Moreover, the panel conditionally recommends treatment with TNF inhibitors over treatment with secukinumab or ixekizumab, and conditionally recommends treatment with secukinumab or ixekizumab over tofacitinib. In patients with primary nonresponse to the first TNF inhibitor, the panel conditionally recommends switching to secukinumab or ixekizumab over switching to a different TNF inhibitor. A systematic review by Corbett et al published in 2016 demonstrated significant improvement in disease state measures such as the ASAS20 and BASDAI50 in patients with non-radiographic axial spondyloarthritis taking TNF inhibitors such as adalimumab, certolizumab pegol, etanercept, and infliximab.

VII. The 2022 ASAS/EULAR guidelines for the treatment of axial spondyloarthritis (axSpA) reference the use of JAK inhibitors in the treatment algorithm. The term axial spondyloarthritis (axSpA), encompasses both active ankylosing spondylitis (or radiographic AS) and nr-axSpA as one entity part of the same chronic inflammatory musculoskeletal spectrum with similar clinical presentations, comorbidities, disease burden, and treatment response. ASAS/EULAR recommends patients try and fail at least 2 NSAIDs over 4 weeks as first line therapy and treat local musculoskeletal inflammation with glucocorticoid injection; sulfasalazine may be considered in patients with peripheral symptoms, however use of conventional non-biologic DMARDS (e.g. sulfasalazine, leflunomide, methotrexate, etc.) is not recommended in axial disease. In contrast to ACR/SAA/SPARTAN, ASAS/EULAR guidelines highly recommend treatment with a TNF inhibitor, IL-17 inhibitor, or JAK inhibitor for patients with high disease activity, defined by a BASDAI of at least 4 or an ASDAS of at least 2.1, despite conventional treatment with NSAIDS. Starting with a TNF inhibitor or IL-17 inhibitor is preferred clinically, given long term data for use of JAK inhibitors in axSpA is still missing. There is no specific treatment algorithm after primary non-response to biologic (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor therapy. In absence of data showing superiority in the treatment sequence, switching

to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or a JAK inhibitor can be considered.

VIII. Although specific JAK inhibitors were not referenced in the ASAS/EULAR guideline, precautions for cardiovascular risk, malignancy, and thromboembolic events should be considered in patients starting JAK inhibitors. It is unclear whether the increased risk of cardiovascular events and malignancies is specific to a diagnosis of RA, reflective of a JAK inhibitor class effect, or specific to tofacitinib. Until more data become available, ASAS/EULAR advises against starting JAK inhibitors in specific populations: patients above 50 years of age with one or more cardiovascular risk factor and patients older than 65 years of age.

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Plaque Psoriasis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel), secukinumab (Cosentyx), apremilast (Otezla), ustekinumab (Stelara), risankizumab (Skyrizi), or guselkumab (Tremfya)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older if prescribed adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], apremilast (Otezla), risankizumab (Skyrizi), or guselkumab (Tremfya); **OR**
      1. Member is 4 years of age or older if prescribed etanercept (Enbrel); **OR**
      1. Member is 6 years of age or older if prescribed ustekinumab (Stelara); **OR**
      2. Member is 6 years of age or older if prescribed secukinumab (Cosentyx); **AND**
   B. Member is being managed by, or in consultation with, a dermatologist; **AND**
   C. A diagnosis of one of the following:

1. **Mild to moderate plaque psoriasis** when the following are met:
    i. The request is for apremilast (Otezla); **AND**
    ii. Member has chronic disease (greater than 6 months), and a body surface area under 10% unless areas of the face, ears, hands, feet, genitalia are involved (moves to moderate-severe disease); **AND**
    iii. Treatment with the following has been ineffective or not tolerated, or all are contraindicated:
        a. Phototherapy (UVB or PUVA) unless is contraindicated: **OR**
        b. Treatment with at least <u>one</u> of the following groups has been ineffective or not tolerated, unless ALL are contraindicated:
            i. Group 1: Topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
            ii. Group 2: Topical calcineurin inhibitors (e.g., pimecrolimus cream, tacrolimus ointment)
            iii. Group 3: Topical vitamin D analogue (e.g., calcipotriene)
            iv. Group 4: Topical retinoid (i.e., tazarotene); **OR**
2. **Moderate to severe plaque psoriasis** when the following are met:
    i. Chronic disease (greater than 6 months), and at least 10% of body surface area is involved or involves areas of the face, ears, hands, feet or genitalia; **AND**
    ii. Treatment with the following has been ineffective or not tolerated, or all are contraindicated:
        a. Phototherapy (UVB or PUVA); **OR**
        b. At least one non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.)

II. **Brodalumab (Siliq), certolizumab (Cimzia), ixekizumab (Taltz), bimekizumab (Bimzelx), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(C) above are met; **AND**
B. The member is 18 years of age or older if prescribed brodalumab (Siliq), certolizumab (Cimzia), bimekizumab (Bimzelx), or non-preferred adalimumab biosimilars; **OR**
    1. The request is for ixekizumab (Taltz); **AND**
        i. Member is 6 years of age or older; **AND**
        ii. Member has a body weight > 50 kg (110 lb); **AND**
C. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), secukinumab (Cosentyx), apremilast (Otezla), ustekinumab (Stelara), guselkumab (Tremfya), and risankizumab (Skyrizi) have been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(C) above are met; **AND**

B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product ; **AND**
C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
    1. The prescriber must document one or more of the following, indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage; **OR**
    2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
    3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
        i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**
D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: etanercept (Enbrel), secukinumab (Cosentyx), apremilast (Otezla), ustekinumab (Stelara), guselkumab (Tremfya), and risankizumab (Skyrizi)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat plaque psoriasis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Rinvoq, etc.); **AND**
    A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
        1. The prescriber must document one or more of the following, indicating that the reaction:
            i. Was life-threatening; **OR**
            ii. Required hospitalization; **OR**

iii. Required intervention to prevent impairment or damage; **OR**

2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)].

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are approved in the treatment of moderate to severe plaque psoriasis in adult patients. Otezla, a small-molecule therapy, is the only specialty agent approved for mild psoriasis, making it approved for psoriasis at any severity. As of April 2024, only etanercept (Enbrel), ixekizumab (Taltz), ustekinumab (Stelara), and secukinumab (Cosentyx) have been studied and approved for use in pediatric patients. Etanercept (Enbrel) is indicated in patients at least four years of age; ixekizumab (Taltz), ustekinumab (Stelara), and secukinumab (Cosentyx) are indicated in patients at least six years of age.

III. Adalimumab (Humira), apremilast (Otezla), brodalumab (Siliq), certolizumab (Cimzia), etanercept (Enbrel), ixekizumab (Taltz), guselkumab (Tremfya), risankizumab (Skyrizi), secukinumab (Cosentyx), and ustekinumab (Stelara) statistically significantly improves PASI by at least 90% in patients with moderate to severe plaque psoriasis compared to placebo.

IV. As of March 2021, there are four head-to-head trials that studied both induction and maintenance treatment, 14 head-to-head induction trials, and seven head-to-head maintenance trials published. Although head-to-head comparisons have shown statistical advantages for one product over another, the clinical meaningfulness of these differences remain unknown, and all products offer improvements in relevant outcomes with comparable safety profile.

- Induction and maintenance:
    i. The following agents statistically and significantly improve PASI by at least 90% compared to ustekinumab (Stelara): brodalumab (Siliq) with low certainty evidence;

bimekizumab (Bimzelx), risankizumab (Skyrizi), and secukinumab (Cosentyx) with moderate certainty.

- Induction:
  i. The following agents statistically significantly improve PASI by at least 90% compared to adalimumab (Humira) with moderate certainty: guselkumab (Tremfya) and risankizumab (Skyrizi).
  ii. The following agents statistically and significantly improve PASI by at least 90% compared to etanercept (Enbrel) with moderate certainty: certolizumab (Cimzia), ixekizumab (Taltz), and ustekinumab (Stelara).
  iii. Ixekizumab (Taltz) statistically significantly improves PASI by at least 90% compared to ustekinumab (Stelara) with moderate certainty.
  iv. There is insufficient evidence to suggest that etanercept (Enbrel) is statistically inferior to apremilast (Otezla).
- Maintenance:
  i. Guselkumab (Tremfya) statistically significantly improves PASI by at least 90% compared to adalimumab (Humira) and secukinumab (Cosentyx) with moderate certainty.
  ii. Secukinumab (Cosentyx) statistically significantly improves PASI by at least 90% compared to etanercept (Enbrel) with low certainty.

V. **2019 American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) guidelines of care for the management and treatment of psoriasis with biologics:**

- "Majority of patients with mild to moderate disease (<10% BSA) are capable of adequately controlling disease solely with topical mediations or phototherapy."
- Guidelines define moderate psoriasis by 3 – 10% of the total body surface area involved and severe psoriasis is defined as ≥10% BSA involvement; however, psoriasis can be considered severe irrespective of BSA when it occurs in select locations (e.g., hands, feet, scalp, face, or genital area) or when it causes intractable pruritus.
- Biologics may be considered as monotherapy or in combination with other topical or systemic agents in patients with moderate to severe plaque psoriasis.
- Guidelines provide a Grade A recommendation for use of adalimumab (Humira), apremilast (Otezla), brodalumab (Siliq), etanercept (Enbrel), guselkumab (Tremfya), ixekizumab (Taltz), secukinumab (Cosentyx), and ustekinumab (Stelara) and a Grade B recommendation for risankizumab (Skyrizi) as a monotherapy treatment option in adult patients with moderate to severe plaque psoriasis. Guidelines were published in 2019 and precede the FDA-approval of risankizumab; however, phase II and phase III risankizumab (Skyrizi) trials were available and included during guideline development.
- Guidelines have not provided recommendations for certolizumab (Cimzia) and bimekizumab (Bimzelx).
- Guidelines do not point to a specific agent or class when initiating treatment with a biologic. Primary failure is defined as those who are nonresponsive to initial biologic treatment whereas secondary failure represents those who initially respond but lose efficacy over time. Guidelines suggest primary failure to one agent does not preclude successful response to another agent under the same class; however, this may foretell reduced efficacy.
- Guidelines do not provide recommendations for switching therapies.

- Guidelines provide a Grade C recommendation indicating use for adalimumab (Humira), etanercept (Enbrel), or ustekinumab (Stelara) may be combined with apremilast (Otezla) to augment efficacy for the treatment of moderate to severe plaque psoriasis in adults when clinically indicated. This recommendation comes from consensus guidelines, opinion, case studies, or disease-oriented evidence. There is lack of patient-oriented evidence to support combination use with other biologics or other non-biologic specialty medications used to treat plaque psoriasis. Therefore, coverage for combination use with other biologics or other non-biologic specialty medications remains experimental and investigational.
- Mild to moderate psoriasis: Guidelines state that because psoriasis generally recurs after discontinuation of topical corticosteroid treatment, it is important to consider using steroid sparing agents that have been developed to supplement and reduce over-reliance on topical corticosteroids as monotherapy, decreasing the risk of corticosteroid adverse effects. Agents such as vitamin D analogues (Grade A recommendation), topical retinoids (Grade B recommendation), and calcineurin inhibitors (Grade B recommendation) can be used as a maintenance treatment.
- As of January 2022, the guidelines have not been updated to place apremilast (Otezla) into a routine place of care in the treatment of mild to moderate psoriasis over the current guidelines of phototherapy, topical treatments, or a systemic DMARD.

VI. Coverage for the above agents in the setting of palmoplantar psoriasis (defined as psoriasis of the palms or soles presenting with hyperkeratotic, erythematous, plaques and fissures) may be appropriate when criteria for moderate-severe plaque psoriasis are met. Medical necessity for the treatment of guttate psoriasis and/or palmoplantar ***pustulosis*** are reviewed in the experimental and investigational section of this policy.

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Crohn's Disease

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), or ustekinumab (Stelara) , or risankizumab (Skyrizi)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **OR**
      1. Member is 6 to 17 years of age and the request is for adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)]; **AND**
         i. Member's current weight is provided; **AND**
   B. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   C. Diagnosis of **moderate to severe Crohn's disease**; **AND**
   D. Provider attestation or clinical documentation of at least one of the following:
      1. Treatment with systemic corticosteroids (e.g., prednisone, budesonide) has been ineffective, contraindicated, or not tolerated; **OR**
      2. Treatment with an immunomodulator (e.g., methotrexate, azathioprine, 6-mercaptopurine) has been ineffective, contraindicated, or not tolerated; **OR**
      3. Provider attestation or clinical documentation of high-risk disease (e.g., symptoms despite conventional therapy, obstruction, abscess, stricture, phlegmon, fistulas, resection, extensive bowel involvement, early age of onset, growth retardation)

II. **Certolizumab pegol (Cimzia) or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(B)-I(D) above are met; **AND**
   B. Member is 18 years of age or older; **OR**
      1. Member is 6 to 17 years of age and the request is for non-preferred adalimumab biosimilar; **AND**
      2. Member's current weight is provided; **AND**
   C. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], ustekinumab (Stelara), risankizumab (Skyrizi), and upadacitinib (Rinvoq) have been ineffective, contraindicated, or not tolerated.

III. **Infliximab-dyyb (Zymfentra)** is considered not medically necessary when used for all conditions, including but not limited to, maintenance of remission in Crohn's disease in place of intravenous (IV) formulation.
   A. Infliximab-dyyb (Zymfentra) is considered not medically necessary when used for all indications, including but not limited to maintenance of remission in Crohn's disease. Intravenous (IV) formulation is clinically comparable in efficacy and safety to the

subcutaneous (SC) formulation and is the preferred product which can be accessed via the medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

IV. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(D) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The prescriber must document one or more of the following, indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **OR**
      2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications, and angioedema] that required medical intervention to prevent impairment or damage; **OR**
      3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
         i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**
   D. Members 18 years of age or older: documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: ustekinumab (Stelara), risankizumab (Skyrizi), and upadacitinib (Rinvoq)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat Crohn's disease or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Infliximab, etc.); **AND**
   A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**

B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
    1. The prescriber must document one or more of the following, indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage; **OR**
    2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications, and angioedema] that required medical intervention to prevent impairment or damage; **OR**
    3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
        i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)].

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are FDA approved for the treatment of moderate to severe Crohn's Disease (CD) based on safety and efficacy data from randomized-controlled trials. Certolizumab pegol (Cimzia), ustekinumab (Stelara), risankizumab (Skyrizi), and infliximab-dyyb (Zymfentra) are FDA-approved in adults only, while adalimumab (Humira) is approved in patients six years of age and older.

III. Diagnosis of CD is based on a combination of clinical presentation, endoscopic, radiologic, histologic, and pathologic findings that demonstrate inflammation of the luminal GI tract. As such, it is recommended that diagnosis is made by a provider specialized in detecting and treating inflammatory bowel diseases, such as a gastroenterologist.

IV. Therapeutic recommendations for patients with CD are established based upon disease location, disease severity, disease associated complications, and future disease prognosis. The goals of

therapy are to induce remission, prevent relapse, and prevent occurrence of disease complications, such as stricture and fistula.

Moderate to severe CD

V. According to the 2018 American College of Gastroenterology (ACG) guidelines patients with moderate to severe CD are considered to have failed to respond to treatment for mild to moderate disease, or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia. They have moderate to severely active endoscopic mucosal disease and disease activity corresponding to Crohn's Disease Activity Index (CDAI) score of 220-450.

VI. Symptoms of CD do not correlate well with presence of active inflammation, and therefore should not be the sole guide for therapy. Objective evaluation by endoscopic imaging should be undertaken to avoid errors of under or overtreatment.

VII. Patients with CD are at risk of developing intestinal complications such as strictures, abscess, fistula, or phlegmon formation. According to the 2018 ACG guidelines features associated with high risk for progressive disease include age at diagnosis, initial extensive bowel involvement, ileal/ileocolonic or proximal gastrointestinal (GI) involvement, perianal/severe rectal disease, and patients presenting with a penetrating or stenosis disease phenotype.

VIII. For patients with moderate to severe disease and those with moderate to high-risk disease, the 2018 ACG guidelines recommend treatment with oral corticosteroids used short term to induce remission (strong recommendation, moderate level of evidence). However, it is noted that one in five patients will become steroid refractory which is thought to be the result of unreliable efficacy in healing of the mucosa associated with steroids (weak recommendation, low level of evidence). Corticosteroids are also implicated in the development of perforating complications (abscess and fistula) and are relatively contraindicated in those patients. The 2021 American Gastroenterological Association (AGA) clinical guidelines make similar recommendations and suggest the use of corticosteroids in adult outpatients with moderate to severe CD over no treatment for induction of remission (conditional recommendation, moderate level of evidence).

IX. In patients with moderate to severe CD who remain symptomatic despite current or prior corticosteroid therapy, 2018 ACG guidelines recommend immunomodulators such as azathioprine, 6-mercaptopurine (strong recommendation, moderate level of evidence), and methotrexate (conditional recommendation, low level of evidence) to be effective for maintenance of remission. Due to slow time to clinical response that may not be evident for as long as 12 weeks, these agents are not recommended for short-term induction. The 2021 AGA guidelines make similar suggestions and recommend use of thiopurines over no treatment for the maintenance of remission (conditional recommendation, low level of evidence).

X. ACG guidelines recommend anti-TNF-alpha agents (infliximab [e.g., Remicade, Inflectra], adalimumab [Humira], certolizumab pegol [Cimzia]) in patients resistant to treatment with corticosteroids and refractory to thiopurines or methotrexate (strong recommendation, moderate level of evidence). Additionally, combination therapy of infliximab (e.g., Remicade, Inflectra) with immunomodulators (thiopurines) is more effective than treatment with either immunomodulators alone or infliximab (e.g., Remicade, Inflectra) alone in patients who are naïve to those agents (strong recommendation, high level of evidence). Recommendations are also made regarding the use of vedolizumab (Entyvio), natalizumab (Tysabri), and ustekinumab (Stelara) without preference for one biologic over the other. The AGA guidelines recommend

early introduction of biologics with or without immunomodulators rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids; however, this recommendation is conditional with low certainty of evidence.

XI. Adalimumab (Humira), ustekinumab (Stelara), certolizumab (Cimzia), infliximab (e.g., Remicade, Inflectra), vedolizumab (Entyvio), natalizumab (Tysabri), risankizumab (Skyrizi), and infliximab-dyyb (Zymfentra) have not been studied in head-to-head trials to compare the efficacy and safety between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by all biologic agents FDA approved for the treatment of moderate to severe CD in adults is incremental or better when evaluated against placebo.

XII. The timing of introduction of biologic agents is a matter of debate and more studies are needed to assess stepwise approach versus earlier administration of biologic agents in patients with moderate to severe disease. The 2019 British Society of Gastroenterology guidelines suggest that systemic corticosteroids are still an effective initial therapy for uncomplicated luminal moderate to severe disease, regardless of disease location; however, every effort should be made to limit exposure (strong recommendation, high-quality evidence). In patients with an aggressive disease course, or high risk, poor prognostic factors, early introduction of biologics may be considered (weak recommendation, moderate-quality evidence). High risk features include extensive disease, complex (stricturing or penetrating disease), perianal fistulizing disease, age under 40 years at diagnosis, and the need for steroids to control index flare; however, the predictive power of these features is limited.

High-risk/severe CD

XIII. Patients who are considered to have severe/fulminant disease are those with persistent symptoms despite introduction of conventional corticosteroids or biologic agents as outpatients, or individuals presenting with high fevers, persistent vomiting, evidence of intestinal obstruction, significant peritoneal signs such as involuntary guarding or rebound tenderness, cachexia, or evidence of an abscess. They have endoscopic or radiographic evidence of severe mucosal disease and disease activity corresponding to CDAI score of >450.

XIV. Collective evidence suggests that initial treatment with biologics may be considered for patients with the following disease features: severe CD (CDAI >450, evidence of intestinal obstruction, abscess, stricture, or phlegmon, and endoscopic or radiographic evidence of severe mucosal disease such as deep ulcerations), perianal fistulizing disease, and pre- and post-operative CD. Additional consideration may be given to patients presenting with other poor prognostic factors (e.g., extensive bowel involvement, early age of onset) and should be evaluated on case-by-case basis.

Pediatric CD

XV. Children and adolescents with CD often present with a more complicated disease course compared to adult patients. Additionally, potential impact of CD on growth, pubertal, and emotional development warrants a specific management strategy. The goals of therapy in pediatric CD are to relieve symptoms, achieve remission, optimize growth, and improve quality of life while minimizing drug toxicity.

XVI. Oral corticosteroids are recommended for inducing remission in children with moderate to severe active luminal CD. Corticosteroids should not be used as maintenance therapy. Thiopurines (azathioprine or 6-mercaptopurine) and methotrexate are recommended options

for maintenance of steroid free remission in children at risk for poor disease outcomes. Methotrexate can be used as primary maintenance therapy or in thiopurine failure.

XVII. Anti-TNF-alpha therapy is recommended for inducing and maintaining remission in children with chronically active luminal CD despite prior optimized immunomodulator therapy or with active steroid-refractory disease. Anti-TNF-alpha therapy is recommended as primary induction and maintenance therapy for children with active perianal and fistulizing disease and can be considered for selected children with high risk for poor outcomes. According to ECCO/ESPGHAN clinical guidelines on the management of pediatric CD, early use of immunomodulators and biologics warrants selection of ideal candidates who are at high risk for developing severe disease and depends on predictive factors. Predictive factors are largely the same as the ones for adults but further include the presence of marked growth retardation (>-2.5 height Z scores) and severe osteoporosis.

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Ulcerative Colitis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), or ustekinumab (Stelara)** may be considered medically necessary when the following criteria below are met:
   A. Member is 5-17 years of age and the request is for adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)]; **AND**
      1. Member's current weight is provided; **OR**
   B. Member is 18 years of age or older; **AND**
   C. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   D. Diagnosis of **moderate to severe ulcerative colitis; AND**

E. Provider attestation or clinical documentation of at least one of the following:
    1. Treatment with systemic corticosteroids (e.g., prednisone, budesonide) has been ineffective, contraindicated, or not tolerated; **OR**
    2. Treatment with an immunomodulator (e.g., azathioprine, 6-mercaptopurine) has been ineffective, contraindicated, or not tolerated

II. **Golimumab (Simponi), ozanimod (Zeposia), mirikizumab (Omvoh), etrasimod (Velsipity), or non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
A. Criteria I(C)-I(E) above are met; **AND**
B. Member is 18 years of age or older; **OR**
    1. Member is 5 to 17 years of age and the request is for a non-preferred adalimumab biosimilar**; AND**
    2. Member's current weight is provided; **AND**
C. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], ustekinumab (Stelara), tofacitinib (Xeljanz/Xeljanz XR), and upadacitinib (Rinvoq) have been ineffective, contraindicated, or not tolerated.

III. **Vedolizumab Subcutaneous (Entyvio) and infliximab-dyyb (Zymfentra)** are considered not medically necessary when used for all conditions, including but not limited to, maintenance of remission in ulcerative colitis in place of intravenous (IV) formulations.
A. Vedolizumab (Entyvio) subcutaneous (SC) and infliximab-dyyb (Zymfentra) formulations are considered not medically necessary when used for all indications, including but not limited to maintenance of remission in ulcerative colitis. Intravenous (IV) formulations are clinically comparable in efficacy and safety to the SC formulations and are the preferred products which can be accessed via the medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

IV. **Brand Humira** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(E) above are met; **AND**
B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product; **AND**
C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
    1. The prescriber must document one or more of the following, indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage; **OR**
    2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**

3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**

D. Members 18 years of age or older: documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: ustekinumab (Stelara), tofacitinib (Xeljanz/Xeljanz XR), and upadacitinib (Rinvoq)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat ulcerative colitis or another auto-immune condition (e.g., Remicade, Cimzia, etc.); **AND**
    A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
    B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
        1. The prescriber must document one or more of the following, indicating that the reaction:
            i. Was life-threatening; **OR**
            ii. Required hospitalization; **OR**
            iii. Required intervention to prevent impairment or damage; **OR**
        2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
        3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
            i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)].

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in

promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. The above agents are FDA approved in the treatment of moderate to severe ulcerative colitis (UC) in adult patients. As of May 2021, only adalimumab (Humira) has been FDA approved in moderate to severe ulcerative colitis in pediatric patients aged 5 years and older.

III. Adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), upadacitinib (Rinvoq), mirikizumab (Omvoh), etrasimod (Velsipity), and infliximab-dyyb (Zymfentra) have not been evaluated in head-to-head trials to compare the efficacy and safety between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), upadacitinib (Rinvoq), mirikizumab (Omvoh), etrasimod (Velsipity), and infliximab-dyyb (Zymfentra) is incremental or better when evaluated against placebo.

IV. Comparative efficacy and safety data are only available for vedolizumab (Entyvio) and adalimumab (Humira) at this time. There is low certainty that vedolizumab (Entyvio) has a comparable or better net health benefit compared to adalimumab (Humira) for induction and maintenance of clinical remission and mucosal healing in patients with moderate to severe UC. Vedolizumab (Entyvio) was found to be statistically superior with respect to certain efficacy outcomes; however, efficacy and safety is regarded as clinically comparable between the two agents.

V. The safety and efficacy of adalimumab (Humira) for the treatment of moderate to severe ulcerative colitis in pediatric patients aged five years and older was evaluated in one phase 3, double-blind, randomized, historical placebo controlled clinical trial (ENVISION-1). The trial included 93 patients, majority of which were previously treated with corticosteroids and immunosuppressants at baseline and majority of patients (84%) were anti-TNF therapy naïve. Due to challenges with enrollment in the placebo arm, the trial underwent protocol amendments and was partially open label. The clinical trial studied two adalimumab (Humira) doses: 0.6 mg/kg every week (high dose) and 0.6 mg/kg every other week (standard dose). The two primary efficacy outcomes, Partial Mayo Score (PMS) and Full Mayo Score (FMS), were statistically significant against historical placebo in the high dose adalimumab (Humira) arm only, with 60% [95% CI: 44%-74%] of patients achieving PMS during induction and 45% [95% CI: 27%-64%] of patients achieving FMS during maintenance. During induction and maintenance phases, 22% and 37% of patients, respectively, experienced infections. There were 8% of patients which experienced serious infections, and 11% and 14% of patients experienced serious adverse events in the induction and maintenance phases, respectively.

VI. The 2019 American College of Gastroenterology (ACG) clinical guideline on the management of ulcerative colitis in adults recommend oral systemic corticosteroids for induction of remission in moderate to severe disease (strong recommendation, moderate quality of evidence). TNF inhibitors (adalimumab, golimumab, and infliximab), vedolizumab (Entyvio), and tofacitinib (Xeljanz) are also recommended for induction of remission (strong recommendation, moderate quality of evidence). For maintenance of remission, thiopurines are recommended if remission was achieved after corticosteroid induction (conditional recommendation, low quality of evidence). The guidelines note a systematic review of 1,632 patients with ulcerative colitis demonstrated that azathioprine and mercaptopurine had a 76% mean efficacy in maintaining remission. If remission was achieved with anti-TNF therapy, vedolizumab (Entyvio), or tofacitinib (Xeljanz), clinical guidelines support continuing with the same agent to maintain remission (strong recommendation, moderate quality of evidence). The 2020 American Gastroenterology Association (AGA) guidelines make similar recommendations. Additionally, AGA recommends early use of biologic agents, rather than gradual step up after failure of 5-ASA in moderate to severe disease at high risk for colectomy. However, overall quality of evidence supporting this recommendation was rated as very low. Guidelines also note that for patients with less severe disease, 5-ASA therapy may still be a reasonable choice of therapy to start with. For maintenance of remission, AGA makes no recommendation in favor of, or against, using biologic monotherapy, rather than thiopurine monotherapy due to absence of evidence.

VII. Patients who are primary non-responders to an anti-TNF therapy should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class. In patients with moderate to severe active ulcerative colitis who had an initial response but subsequently lost efficacy to one anti-TNF therapy, clinical guidelines recommend alternative anti-TNF therapy (but not the biosimilar to the original brand) compared with no treatment for induction of remission.

VIII. The 2018 European Crohn's and Colitis Organization and European Society of Pediatric Gastroenterology, Hepatology, and Nutrition clinical guidelines recommend treatment with oral systemic corticosteroids if patients are in the higher end of the moderate disease range and treatment with thiopurines for maintaining remission in children who are corticosteroid-dependent or relapsing frequently despite 5-ASA treatment, and 5-ASA intolerant patients. The guidelines recommend infliximab (e.g., Remicade, Inflectra) in chronically active or steroid-dependent ulcerative colitis, uncontrolled by 5-ASA and thiopurines, for both induction and maintenance of remission. Adalimumab (Humira) or golimumab (Simponi) could be considered in those who initially respond but then lose response or intolerant to infliximab (e.g., Remicade, Inflectra), based on serum levels and antibodies. Vedolizumab (Entyvio) should be considered in chronically active or steroid-dependent patients as second-line biologic therapy after anti-TNF failure.

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Behcet's Disease (i.e., Behcet Syndrome)

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), etanercept (Enbrel), or apremilast (Otezla)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a specialist that is treatment this condition (e.g., rheumatologist, dermatologist, ophthalmologist, etc.); **AND**
      1. A diagnosis of recurrent **Behcet's Disease manifesting as oral ulcers of the mouth**; **AND**
         i. One of the following have been ineffective, not tolerated, or all are contraindicated:
            a. Topical corticosteroids (e.g., triamcinolone) OR sucralfate mouthwash; **OR**
            b. Systemic therapy (e.g., colchicine, thalidomide, prednisone, benzathine penicillin); **OR**
      2. A diagnosis of **Behcet's disease manifesting as uveitis**; **AND**
         i. All of the following have been ineffective, not tolerated, or are contraindicated;
            a. Oral corticosteroids; **AND**

b. At least one non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.)

II. **Non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. Treatment with apremilast (Otezla), adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], and etanercept (Enbrel) have been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product ; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The prescriber must document one or more of the following, indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **OR**
      2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
      3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
         i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**
   D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: apremilast (Otezla) and etanercept (Enbrel)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement of disease symptoms (reduction in inflammation, and/or lesions, reduction in amount of oral glucocorticoids needed, reduction in number of flares, etc.); **AND**

IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat Behcet's Disease or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Rinvoq, etc.); **AND**
   A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
   B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The prescriber must document one or more of the following, indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **OR**
      2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
      3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
         i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)].

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Adalimumab (Humira) and Etanercept (Enbrel) are not FDA-approved for the treatment of any manifestation of Behcet's Disease; however, several studies are available to support the use of these agents for various manifestations of the disease. Notably, mouth ulcers and ophthalmic complications. Examples are provided below.
   - Trial of etanercept in Behcet's Disease, double blind, placebo-controlled trial: 40 patients with mucocutaneous disease were enrolled in a trial evaluating etancercept compared to placebo. Results indicated efficacy of etanercept on oral ulcers, nodular

lesions, papulopustular lesions, and had an increased probability of being ulcer and nodular lesion free compared to the placebo group. Although a small trial, the rarity of Behcet's Disease shall be taken into account.

- A multicenter study of refractory Behcet's Disease treated with and-TNF alpha treatments was conducted: The trial included infliximab and adalimumab. These therapies resulted in an overall 90.4% response rate for all clinical manifestations, and specifically an 88% response rate for mucocutaneous manifestations and 96.3% for severe and/or refractory ocular disease. The incidence of flares was reduced during anti-TNF alpha treatment.
- An analysis of published data in 369 patients using anti-TNF alpha agents for Behcet's Disease: This included peer-reviewed articles on Medline/PubMed and evaluated patients that were uncontrolled with or intolerant to other immunosuppressives. A rate of 90% clinical response was seen for the mucocutaneous manifestations of Behcet's disease, and a rate of 89% for ocular disease.

III. Behcet's Disease may manifest in many forms; however, it is commonly managed by rheumatology specialists; however, there may be instances when other inflammatory specialists may be managing and prescribing.

IV. Corticosteroids and oral DMARDS (typically azathioprine) have been mainstays of Behcet's Disease, with oral DMARDS having a particular role in ophthalmic manifestations.

V. For oral manifestations first line treatment is triamcinolone acetonide cream 0.1% in orabase, applied three to four times daily. High potency topical steroids may also be employed. Topical sucralfate may also be used with or as an alternative to topical corticosteroids. A strength of 1 gram/5 mL four times daily as a mouthwash is recommended to reduce pain, frequency, and healing time.

VI. In the latest 2018 EULAR recommendations in the treatment of Behcet's Disease, colchicine is used as the first-line treatment of mucocutaneous lesions. As well as benzathine penicillin, which is often added to colchicine to increase the effectiveness. Thalidomide is often helpful but should be used in caution in selected patients because of potential side effects. In acute and severe attacks of mucocutaneous lesions, oral corticosteroids can be used as an effective treatment. Additional other oral DMARDS (such as azathioprine) may be useful but are supported with less clinical evidence and are more case by case in nature of providing disease control or management.

VII. Apremilast (Otezla) was evaluated for Behcet's Disease in the following trial: Efficacy of apremilast for oral ulcers associated with active Behcet's Syndrome in a Phase III study. This indication was FDA-approved for treatment of oral ulcers of the mouth associated with Behcet's Disease in July 2019. A total of 207 patients were randomized to apremilast or placebo, and favorable treatment effect was noted. Although apremilast is an FDA-approved medication for Behcet's Disease, anti-TNF alpha therapies have equal or greater safety and efficacy data to support their use in this condition. Guidelines and key opinion leaders have consensus in regard to use of anti-TNF alpha therapies prior to use of apremilast; however, due to limited evidence of using one anti-TNF alpha agent after failure of another, trial of more than one agent is not required.

VIII. Standard dosing for adalimumab (Humira) is 40 mg every other week, and standard dosing for Etanercept (Enbrel) is 50 mg per week, either 25 mg twice weekly or 50 mg once weekly.

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Hidradenitis Suppurativa

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ), or secukinumab (Cosentyx)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **OR**
      1. Member is 12 years of age or older if prescribed adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)]; **AND**
   B. Member is being managed by, or in consultation with, a dermatologist; **AND**
   C. A diagnosis of **hidradenitis suppurativa** when the following are met:
      1. Presence of inflammatory nodules and/or abscesses; **AND**
      2. Hurley Stage III (severe) disease; **OR**
      3. Hurley Stage II (moderate) disease with:
         i. Treatment with at least one oral antibiotic (i.e., doxycycline, minocycline, tetracycline, clindamycin/rifampin, etc.) has been ineffective, contraindicated, or not tolerated

II. **Non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)] and secukinumab (Cosentyx) has been ineffective, contraindicated, or not tolerated

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product ; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The prescriber must document one or more of the following, indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **OR**
2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: secukinumab (Cosentyx)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in abscess and inflammatory nodule count, decrease in frequency of inflammatory lesions, etc.); **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat hidradenitis suppurativa or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.); **AND**

IV. **Brand Humira** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(C) above are met; **AND**
B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product ; **AND**
C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
    1. The prescriber must document one or more of the following, indicating that the reaction:
        i. Was life-threatening; **OR**
        ii. Required hospitalization; **OR**
        iii. Required intervention to prevent impairment or damage; **OR**
    2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory

complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**

3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]; **AND**

D. Documentation of treatment with all of the following have been ineffective, contraindicated, or not tolerated: secukinumab (Cosentyx)

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, inflammatory disease affecting sweat glands characterized by recurrent, painful lesions that typically develop in intertriginous areas such as the axillae, groin, vulva, or gluteal cleft/anal region. Lesions usually start small and, over weeks to months, form into nodules, abscesses, or tunnels that can lead to scarring and fistulas overtime. The disease is classified in 3 clinical stages which help guide treatment: Hurley stage I (least severe), Hurley stage II (moderate severity), and Hurley stage III (most severe).

III. Adalimumab (Humira) is FDA-approved in patients in 12 years or older with moderate to severe HS supported by results of the PIONEER I and II RCTs.

IV. In the PIONEER studies, patients were only included if they had a diagnosis of Hurley Stage II or Hurley Stage III disease, had at least three inflammatory nodules/abscesses present at baseline, and had previously had an inadequate response to at least a 3-month trial of oral antibiotics. Adalimumab met the primary end point at week 12, where the Hidradenitis Suppurativa Clinical Response (HiSCR) primary efficacy endpoint (≥50 percent reduction in the total abscess and inflammatory nodule count with no increase in the abscess or draining sinus count) was achieved with adalimumab 40mg once weekly compared to the placebo groups. A three-year, open-label, extension study that followed the PIONEER trials suggests long-term efficacy and safety of adalimumab. The OLE study found a sustained rate of response (achievement of HiSCR) over time among patients who received 40 mg of adalimumab once weekly for at least 60 weeks. No new safety concerns were raised.

V. While oral antibiotics are frequently employed in moderate to severe disease as noted above, the data for these agents primarily stems from studies in patients with Hurley Stage I and II disease. Although the combination of clindamycin/rifampin has demonstrated improvement in terms of partial or total remission, only one small study with 10 patients has examined the use in Hurley Stage III patients. Nearly 50% of patients in the PIONEER I and II studies of adalimumab had Hurley Stage III disease, and the randomized, controlled nature of the study provides greater assurance of efficacy for this more severe population than prior studies of oral antibiotics.

VI. Two phase 3, multicenter, double-blind, randomized, placebo-controlled trials (SUNSHINE and SUNRISE) evaluated the efficacy and safety of secukinumab (Cosentyx) in patients aged 18 years or older with a diagnosis of moderate to severe HS, defined as a total of five or more inflammatory lesions affecting two or more distinct anatomical areas. In both trials, this correlated to over 90 percent of participants having a diagnosis of Hurley Stage II or Hurley Stage III. Patients were randomized to secukinumab 300mg subQ every 2 weeks, every 4 weeks, or placebo. The primary endpoint evaluated the proportion of patients with a hidradenitis suppurative clinical response (HiSCR), defined as a decrease in abscess and inflammatory nodule count by 50% or more with no increase in the number of abscesses or in the number of draining fistulae compared with baseline at week 16. Key secondary endpoints include change in abscess and inflammatory nodule count, number of flares, and reduction in skin pain at week 16.
    - The primary endpoint was met in the SUNRISE trial, where 42% of participants on secukinumab every 2 weeks and 46% of those on secukinumab every 4 weeks achieved a clinically meaningful response in HiSCR, compared to 31% on placebo ($p<0.01$). In the SUNSHINE trial, the primary endpoint was not met in the secukinumab every 4 weeks, but secukinumab every 2 weeks achieved statistical and clinically significant change in HiSCR ($p=0.007$). Based on the results of the SUNSHINE trial, secukinumab every 2 weeks may be preferred over every 4 weeks dosing, especially in regard to the primary endpoint.
    - For the pooled secondary endpoints, only the SUNSHINE trial showed significantly fewer patients having flares in the secukinumab every 2 weeks group than in the placebo group during the first 16 weeks, while the SUNRISE trial showed significantly improved abscess and nodule count at week 16 in secukinumab every 4 weeks compared to placebo and statistically significant differences in the proportion of patients with flares between the secukinumab every 4 weeks group and the placebo group during the first 16 weeks. Both trials did show secukinumab improved patients' health-related quality of life (HRQoL) up to 52 weeks and many patients that did achieve a HiSCR at week 16 maintained their response at week 52.
    - No new safety concerns were raised in either trial.

VII. The Unites States and Canadian Hidradenitis Suppurativa Foundation 2019 guidelines provide recommendations for the treatment of HS. For mild-to-moderate HS, systemic antibiotics including tetracyclines are recommended as monotherapy and clindamycin and rifampin in combination is recommended in the second-line setting. For severe disease, clindamycin and rifampin may be used as a first line or adjunct treatment. For moderate-to-severe disease, moxifloxacin, metronidazole, and rifampin in combination are recommended as second- or third-line treatment. This recommendation is based on moderate-quality evidence from RCTs

and one systemic review of retrospective and prospective studies. In moderate-to-severe disease when systemic antibiotics are ineffective or insufficient, the guidelines recommend the use of biologics, with a strong recommendation for adalimumab based on high quality evidence. Limited evidence is available for infliximab, anakinra, and ustekinumab with limitations including considerable variability and validity of end points, lack of dose ranging studies, and short follow-up periods. As of June 2023, the guidelines have not been updated with regard to place in therapy for secukinumab.

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Uveitis and Panuveitis

Initial Evaluation

I. **Adalimumab-bwwd (Hadlima) or adalimumab-adaz (Adalimumab-ADAZ)** may be considered medically necessary when the following criteria below are met:
   A. Member is two years of age or older; **AND**
   B. Member is being managed by, or in consultation with, an ophthalmologist or rheumatologist; **AND**
   C. A diagnosis of **non-infectious intermediate, posterior, or panuveitis** when the following are met:
      1. Previous treatment with at least one periocular injection, implant, topical, or systemic corticosteroid (i.e., triamcinolone, dexamethasone, prednisone, fluocinolone, difluprednate, etc.) has been ineffective, contraindicated, or not tolerated; **AND**
      2. Previous treatment with at least one non-corticosteroid systemic immunomodulatory therapy (i.e., mycophenolate mofetil, tacrolimus, cyclosporine, azathioprine, or methotrexate) has been ineffective, contraindicated, or not tolerated.

II. **Non-preferred adalimumab biosimilars** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)] has been ineffective, contraindicated, or not tolerated.

III. **Brand Humira** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to a biosimilar product ; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The prescriber must document one or more of the following, indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **OR**
      2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
      3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
         i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)]

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat uveitis and panuveitis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.); **AND**
   A. If the request is for **Brand Humira**: In the absence of a drug shortage, coverage of the brand drug is to be considered medically necessary when the prescriber is requesting the brand drug due to a documented adverse reaction to the biosimilar; **AND**
   B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

1. The prescriber must document one or more of the following, indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **OR**
2. The prescriber is requesting the brand name drug due to a documented allergy to the biosimilar [i.e. skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
3. The prescriber is requesting the brand name drug due to a documented intolerance to the biosimilar which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. At least two biosimilars have been tried [e.g., adalimumab-bwwd (Hadlima) and adalimumab-adaz (Adalimumab-ADAZ)].

Supporting Evidence

I. Biosimilars are FDA-approved biological products highly similar to reference biologics. These products are valuable therapies in the pharmaceutical landscape, offering cost-effective options while maintaining comparable safety and efficacy profiles. One key aspect of their value lies in promoting competition, which can lead to reduced healthcare costs. Additionally, biosimilars play a crucial role in expanding patient access to essential biologic therapies. The FDA has established rigorous regulatory frameworks for biosimilars, ensuring that they undergo comprehensive testing to demonstrate similarity to the reference biologic. This robust regulatory oversight contributes to building confidence among healthcare professionals and patients, reinforcing the evidence supporting biosimilars are as safe and effective as the reference biologic. As a result, biosimilars offer a compelling value proposition by fostering competition, reducing healthcare expenditures, and broadening access to critical biologic treatments. As of 2023 there were 40 FDA-approved biosimilars in the U.S. The Crohn's and Colitis Foundation, American College of Rheumatology and the American Society of Clinical Oncology support biosimilar integration in clinical practice.

II. Adalimumab (Humira) is FDA-approved for patients at least two years of age with non-infectious intermediate, posterior, or panuveitis based off data from the VISUAL I and II phase 3 RCTs.

III. The Fundamentals of Care for Uveitis (FOCUS) guideline recommends that the noncorticosteroid systemic immunomodulatory therapy (NCIST) agents listed above may be indicated for patients who have a failure or lack of tolerance to regional or systemic corticosteroids. Prior to initiation of alternative medications such as biologic agents, guidelines recommend dose escalation to the maximum tolerated/effective dose of NCIST. It is noted that use of biologic agents is supported for adalimumab, infliximab, and interferon alpha-2a.

IV. A meta-analysis published recently in 2018 supports this statement of biologic utility in uveitis. The analysis included 3 RCTs and 20 non-RCTs that examined adalimumab use in patients with non-infectious uveitis, with reduced time to treatment failure and improvements in visual acuity demonstrated.

References

1. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10050):1183-1192.
2. Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in Patients with Active Noninfectious Uveitis. *N Engl J Med*. 2016;375(10):932-943.
3. Dick AD, Rosenbaum JT, Al-dhibi HA, et al. Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative. *Ophthalmology*. 2018;125(5):757-773.
4. Ming S, Xie K, He H, Li Y, Lei B. Efficacy and safety of adalimumab in the treatment of non-infectious uveitis: a meta-analysis and systematic review. *Drug Des Devel Ther.* 2018;12:2005-2016.

Giant Cell Arteritis

Initial Evaluation

I. **Tocilizumab (Actemra)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **giant cell arteritis** when the following are met:
      1. Presence of at least three of the following:
         i. Age at disease onset of at least 50 years
         ii. New onset headache at time of diagnosis
         iii. Temporary artery abnormality (tenderness to palpation or decreased pulsation)
         iv. Elevated ESR
         v. Abnormal artery biopsy

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat psoriatic arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant)

Supporting Evidence

I. Tocilizumab (Actemra) is FDA-approved for adult patients with giant cell arteritis based off results of a phase 3 RCT. In this trial, 251 patients were randomized to subcutaneous tocilizumab plus a prednisone taper or placebo plus a prednisone taper. The primary outcome of glucocorticoid-free remission statistically significant, with 53% and 56% (weekly and every other week dosing, respectively) of tocilizumab patients having sustained remission at week 52,

compared to 14% and 18% (26-week versus 52-week taper, respectively) of prednisone patients ($p < 0.001$).

II. The 1990 ACR criteria for giant cell arteritis have been demonstrated to have a sensitivity of 93.5% and a specificity of 91.2%. Newer criteria were proposed in 2012 by a collaborative effort of EULAR/ACR that aimed to reduce the need for arterial biopsy. The newer criteria thus have a lower sensitivity (68%) and specificity (78%) and has not been officially endorsed by the ACR.

III. While not entirely clear at this time what long-term effects tocilizumab use has on the underlying pathophysiology and outcomes in giant cell arteritis patients, treatment to maintain remission may prevent potential adverse effects associated with long-term glucocorticoid use. Up to 50% of patients may experience return/relapse of giant cell arteritis after a successful taper of prednisone over one to two years, and in most cases, relapses do not lead to major adverse effects such as vision loss. Glucocorticoids are thus considered standard of care as first-line therapy and the primary treatment in patients presenting with giant cell arteritis. A guideline published by the British Society for Rheumatology (BSR)/British Health Professional in Rheumatology (BHPR) recommends that adjuvant therapy with methotrexate or other immunosuppressants be considered with recurrent relapses (started at the third relapse) or in patients who are unsuccessful with glucocorticoid taper.

IV. The 2021 American College of Rheumatology guidelines for GCA recommends starting high dose daily glucocorticoids, or tocilizumab with glucocorticoids or tocilizumab alone in newly diagnosed GCA. Patients with active extracranial large vessel involvement OR disease relapse with symptoms of cranial ischemia may start tocilizumab and glucocorticoids or start methotrexate with glucocorticoids if tocilizumab is not an option due to cost or tolerability.

V. In a 2022 two-part study comparing new-onset compared to relapsing GCA treated with tocilizumab looking at 3-year timeline, 250 participants were randomized to receive tocilizumab weekly, tocilizumab every other week or placebo for 52 weeks (part 1), with a prednisone taper. In part two (open label), participants were treated at investigator discretion for 104 weeks. The primary endpoint in part 1 was portion of patients achieving sustained glucocorticoid-free remission from week 12 to 52. In part two, the primary endpoint was maintenance of remission defined as absence of flare. A total of 250 participants completed part 1 and 215 participants transitioned to part 2. Of those, 184 patients (86%) were in clinical remission [TCZ QW, 81 (95%); TCW Q2W, 36 (90%); PBO, 67 (74%)] and stopped receiving blinded injections when they entered part 2. During part 2, 7 patients (3.3%) withdrew from the study for safety reasons, and 11 patients (5.1%) withdrew for non-safety reasons. Among the patients with new-onset disease, 49% in the TCZ QW group remained flare-free compared with 27% in the TCZ Q2W group and 28% in the PBO group. Participants with added tocilizumab experienced relapse after 575 (95% CI: 463) days. Whereas participants with glucocorticoids alone experienced relapse after 224 days (95% CI: 148, 322).

VI. Tocilizumab can be used as initial treatment or as combination therapy with glucocorticoids in the first line setting. GCA is an emergent condition and patients diagnosed with GCA may be at great risk of sudden vision loss. Due to the urgency of the disease, patients are likely referred to seek urgent care and receive intravenous steroids to immediately reduce inflammation. Tocilizumab may be administered intravenously at point of care and patients may transition to subcutaneous injections thereafter.

References:

1. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med*. 2017;377(4):317-328.
2. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. *JAMA*. 2016;315(22):2442-2258.
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4. UpToDate, Inc. Treatment of giant cell arteritis. UpToDate [database online]. Waltham, MA. Last updated April 18, 2019. Available at: http://www.uptodate.com/home/index.html.
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Cryopyrin-Associated Periodic Syndromes (CAPS)

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of a **cryopyrin-associated periodic syndrome (CAPS), including neonatal-onset multisystem inflammatory disease (NOMID), familial cold autoinflammatory syndrome (FCAS) or Muckle-Wells syndrome (MWS); AND**
   C. Member has documented laboratory evidence of a genetic mutation in the Cold-Induced Auto-inflammatory Syndrome 1 (CIAS1), also known as NLRP

II. **Rilonacept (Arcalyst)** may be considered medically necessary when the following criteria below are met:
   A. Member is 12 years of age or older; **AND**
   B. Member is being managed by or in consultation with a rheumatologist; **AND**
   C. A diagnosis of **CAPS, including FCAS or MWS**; **AND**
   D. Member has documented laboratory evidence of a genetic mutation in the Cold-Induced Auto-inflammatory Syndrome 1 (CIAS1), also known as NLRP3

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat cryopyrin-associated periodic syndromes (CAPS) or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Anakinra (Kineret) is FDA approved for the treatment of CAPS, particularly neonatal-onset multisystem inflammatory disease (NOMID). Anakinra is also frequently employed in the other CAPS, including Muckle-Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS), and can lead to rapid symptom improvement and a decrease in inflammatory markers. The pivotal trial in patients with NOMID was a single arm, prospective study that examined 43 patients treated with anakinra for up to 60 months. Outcomes included the use of a disease-specific symptom diary as well as reduction in inflammatory markers, with improvement seen in both. Eleven patients also went through a withdrawal phase, in which symptoms/inflammatory markers worsened, followed by response again when anakinra was reinitiated. A retrospective review of 22 patients with CAPS (varied phenotypes), demonstrated efficacy of anakinra. All 15 patients treated with anakinra achieved serologic remission and resolution of symptoms (fever, rash, conjunctivitis, and rheumatic symptoms). Other small, observational studies have demonstrated similar improvements both serologically and symptomatically in patients with MWS and FCAS.

II. Rilonacept (Arcalyst) is FDA approved for treatment of CAPS, particularly in patients 12 years of age and older with familial cold autoinflammatory syndrome (FCAS) or Muckle-Wells syndrome (MWS). The relevant phase III trials included 47 patients who were randomized to either weekly rilonacept or placebo, with the first trial analyzing efficacy within a six-week follow-up, and the second looking at response after withdrawal of the agent in the same population. Disease activity via symptom score (0-10 scale) was significantly reduced within a few days of onset (84% rilonacept vs 13% placebo), with a decrease in inflammatory markers also observed. No data is available for analysis in the NOMID population, and no head-to-head comparison with anakinra have been identified at this time.

References

1. Kineret [package insert]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; 2016.
2. Leslie KS, Lachmann HJ, Bruning E, et al. Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations. *Arch Dermatol.* 2006;142(12):1591-1597.
3. Hoffman HM, Throne ML, Amar NJ, et al. Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. Arthritis Rheum. 2008;58(8):2443-2452.
4. UpToDate, Inc. Cryopyrin-associated periodic syndromes and related disorders. UpToDate [database online]. Waltham, MA. Last updated May 17, 2019. Available at: http://www.uptodate.com/home/index.html.
5. Kuemmerle-deschner JB, Ozen S, Tyrrell PN, et al. Diagnostic criteria for cryopyrin-associated periodic syndrome (CAPS). *Ann Rheum Dis.* 2017;76(6):942-947.
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Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:

A. Member is being managed by, or in consultation with, a rheumatologist or immunologist; **AND**
B. A diagnosis of Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS); **AND**
C. Member is 2 years of age or older; **AND**
D. Documentation of TNFRSF1A gene mutation; **AND**
    1. Member has chronic or recurrent fever flares, defined by three or more flares a year; **AND**
        i. Documentation of fever flares that last FIVE days or more; **AND**
        ii. Fever flares are accompanied by at least ONE of the following symptoms:
            a. Myalgia
            b. Rash
            c. Eye symptoms (e.g., conjunctivitis, periorbital edema)
            d. Limb pain
            e. Abdominal symptoms (e.g., pain, vomiting)
            f. Lymphadenopathy
            g. Chest pain; **AND**
E. Provider attestation that other causes of recurrent fever have been ruled out (e.g., recurrent bacterial/viral infection, cyclic neutropenia, interferonopathies, etc.)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) (e.g., Ilaris, Arcalyst, etc) or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS) is a rare genetic disorder that affects approximately one person per million. TRAPS diagnosis is confirmed by TNFRSF1A genetic mutation, in addition to prolonged fevers lasting 5 or more days and one additional clinical hallmark feature, such as myalgias, limb pain, abdominal symptoms (pain, vomiting), rash, headache, lymphadenopathy, chest pain, conjunctivitis, or periorbital edema. Underlying infections or neoplastic causes of fever must be ruled out prior to diagnosis. Given the rarity and complexity of diagnosis and management of TRAPS, the treatment of TRAPS must be initiated by, or in consultation with a rheumatologist.
II. Patients with three or more flares per year with inadequate response to oral glucocorticoids may be treated with prophylactic therapy with monoclonal antibodies that block IL-1 receptors. The 2021 European Alliance of Associations for Rheumatology (EULAR) and American College of

Rheumatology (ACR) Guidelines for Treatment of Interleukin-1 Mediated Autoinflammatory Diseases recognize both canakinumab (Ilaris) and anakinra (Kineret) as potential treatment options for prophylaxis of TRAPS over DMARDs.

III. Anakinra (Kineret) was the first IL-1 blocker successfully used in patients with TRAPS in small series and observational studies. One study was a small observational study with four children (mean age 9.1 years) and 1 adult (33 years) with TRAPS were treated with anakinra 1.5mg/kg/day. All patients had prompt responses with resolution of symptoms at 15 days. A systemic literature review identified 11 observational studies evaluating the use of anakinra (Kineret) in TRAPS. A total of 33% of patients achieved a complete response with anakinra at both short term and long-term follow-up. Other studies revealed patients with TRAPS that were successfully treated with anakinra had a complete clinical response and improvement in functional status. Studies evaluated anakinra (Kineret) at doses from 1-5mg/kg/day (max of 100mg daily) subcutaneously for pediatric patients 2 years and older with TRAPS.

IV. Given the rarity of the disease, the evidence to support efficacy and safety of anakinra (Kineret) in treatment of TRAPS is based on small series and observational studies. The guidelines do not make clear recommendations with anakinra (Kineret) as Canakinumab (Ilaris) is the only FDA-approved biologic for treatment of TRAPS but does recognize anakinra (Kineret) as a potential treatment option.

References

1. Kineret (anakinra) [prescribing information]. Stockholm, Sweden: Swedish Orphan Biovitrum AB; December 2020.
2. Gattorno M, Pelagatti MA, Meini A, et al. Persistent efficacy of anakinra in patients with tumor necrosis factor receptor-associated periodic syndrome. Arthritis Rheum. 2008;58(5):1516-1520.
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5. UpToDate, Inc. Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS). UpToDate [database online]. Waltham, MA. Last updated October 3, 2023.
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Familial Mediterranean Fever

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist, nephrologist, or gastroenterologist; **AND**
   B. A diagnosis of Familial Mediterranean Fever; **AND**
   C. Member is 2 years of age or older; **AND**
   D. Member has recurrent febrile episodes accompanied by at least ONE of the following:
      1. Peritonitis

2. Synovitis or pleuritis
3. Erysipelas-like erythema
4. First degree relative with Familial Mediterranean Fever; **AND**

E. Provider attestation that other causes of recurrent fever have been ruled out (e.g., recurrent bacterial/viral infection, cyclic neutropenia, interferonopathies, etc.); **AND**
F. Treatment with colchicine has been ineffective, contraindicated, or not tolerated

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat Familial Mediterranean Fever (e.g., Ilaris, Arcalyst etc) or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.)

Supporting Evidence

V. Familial Mediterranean Fever (FMF) is a hereditary autoinflammatory disorder characterized by recurrent bouts of fever lasting a couple of days and serosal inflammation (e.g., peritonitis, pleuritis, pericarditis, synovitis) or erysipelas-like-erythema. Untreated FMF may lead to development of secondary amyloidosis with eventual renal failure. Given the rarity and complexity of diagnosis and management of FMF, the treatment of FMF must be initiated by, or in consultation with a rheumatologist, nephrologist, or gastroenterologist.
VI. The 2016 EULAR Recommendations for the Management of Familial Mediterranean Fever recommends colchicine as first line therapy and notes colchicine should be started as soon as a clinical diagnosis is made (grade A recommendation). The guidelines note that IL-1 blockers may be a treatment option based on case reports demonstrating successful use of anakinra (Kineret).
VII. A systemic review and meta-analysis that evaluated 44 reports with 1399 FMF patients found that 60% (95% CI, 49-72%) of adults and 81% (95% CI, 72-89%) of pediatric patients achieved complete remission. At least one adverse event was observed in 25% (95% CI, 13-37%) of the adult patients and 12% (95% CI, 3-21%) of the pediatric patients. Studies evaluated anakinra (Kineret) at doses of 1-5mg/kg/day (max of 100mg daily) subcutaneously for pediatric patients 2 years and older with FMF.
VIII. Anakinra (Kineret) may be considered second line treatment after colchicine in treatment of FMF.

References

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2. Ozen S, Demirkaya E, Erer B, et al. EULAR recommendations for the management of familial Mediterranean fever. Ann Rheum Dis. 2016;75(4):644-651.
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Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD)

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD); **AND**
      1. Documentation of elevated immunoglobulin D (IgD) levels; **OR**
         i. Documentation of V3771 mutation in the mevalonate kinase gene; **AND**
   C. Member is 2 years of age or older; **AND**
   D. Documentation of fever flares that last four days or more; **AND**
   E. Fever flares are accompanied by at least ONE of the following symptoms:
      1. Chills
      2. Cervical lymphadenopathy
      3. Abdominal symptoms (e.g., pain, vomiting, diarrhea)
      4. Lymphadenopathy; **AND**
   F. Provider attestation that other causes of recurrent fever have been ruled out (e.g., recurrent bacterial/viral infection, cyclic neutropenia, interferonopathies, etc.)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) (e.g., Ilaris, Actemra, etc) or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Mevalonate Kinase Deficiency (MKD), formerly called Hyperimmunoglobulin D Syndrome (HIDS), is a rare, autosomal-recessive genetic disorder. Classic HIDS is due to compound heterozygous or homozygous V3771 mutation in the mevalonate kinase (MVK) gene. HIDS/MKD is characterized by recurrent febrile episodes lasting four or more days with chills and lymphadenopathy, abdominal pain, and elevated serum IgD levels above 14 mg/mL. Over 90% of patients have palpable lymphadenopathy during a febrile episode and 85% of patients present with abdominal pain (with or without vomiting and diarrhea). Elevated IgD levels are considered to be an epiphenomenon secondary to the inflammatory process and patients may

not present with elevated IgD levels. When patients present with HIDS/MKD symptoms but do not have elevated IgD levels, genetic testing may be completed to confirm a diagnosis of HIDS/MKD, but is not required if IgD levels are elevated. Underlying infections or neoplastic causes of fever must be ruled out prior to diagnosis. Given the rarity and complexity of diagnosis and management of HIDS/MKD, the treatment of HIDS/MKD must be initiated by, or in consultation with a rheumatologist.

II. Acute treatment for fever flares includes NSAIDs and corticosteroids. A 2015 retrospective study found that prophylactic use of anakinra (Kiineret) in HIDS/MKD resulted in 30% full response and 70% partial response in 10 patients. A systemic literature review identified 11 observational studies evaluating the use of anakinra (Kineret) in HIDS/MKD. A total of 11-30% of patients treated with anakinra achieved complete response at mid-term follow-up and 78% achieved partial response. Other observational studies revealed that anakinra decreased the AIDAI score and attained complete clinical response in 52% and functional status improvement in 81% of patients. Studies evaluated anakinra (Kineret) in pediatric patients 2 years and older with FMF.

III. The 2021 EULAR and ACR Guidelines for Treatment of Interleukin-1 Mediated Autoinflammatory Diseases recommend treatment with IL-1 antagonist as first line therapy for HIDS/MKD prophylaxis (grade C recommendation). Guidelines note that anakinra (Kineret) and canakinumab (Ilaris) have been used in children with HIDS/MKD with success, despite only canakinumab (Ilaris) having an FDA-approved indication in this space.

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Recurrent Pericarditis

Initial Evaluation

I. **Rilonacept (Arcalyst)** may be considered medically necessary when the following criteria below are met:
   A. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist; **AND**
   C. Member has a history of three or more episodes of pericarditis; **AND**
   D. Documentation that ALL of the following were ineffective, or all are contraindicated:
      1. NSAID
      2. colchicine
      3. corticosteroids

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.)

Supporting Evidence

I. Rilonacept (Arcalyst) is FDA approved for the treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and children 12 years of age and older.
II. According to the American College of Cardiology (ACC), pericarditis can be categorized as acute, incessant, recurrent, or chronic. An episode lasting ≥ 4-6 weeks without remission is defined to be incessant pericarditis, while pericarditis lasting > 3 months is defined to be chronic pericarditis. Key opinion leader input supports this classification and notes that for patients with an episode that appears to "recur" within 4 weeks is likely not a true recurrence but is still part of the initial episode or is incessant pericarditis.
III. The approval for this indication is based on findings from a phase III, multicenter, double-blind, event-driven, randomized-withdrawal design (RHAPSODY) trial (NCT03737110). Participants must have had at least one prior pericarditis episode meeting at least two of the following criteria: pericarditic chest pain, pericardial rub, new widespread ST-segment elevation/PR-segment depression, or new/worsening pericardial effusion. During the 12-week run-in period, participants received rilonacept (Arcalyst). Participants were then randomized 1:1 to monotherapy rilonacept (Arcalyst) versus placebo during the double-blind withdrawal period. A total of 86 patients were enrolled in the trial who predominantly had idiopathic pericarditis (85%) and only 15% had post–cardiac-injury pericarditis. In order for the trial to have 90% power to evaluate the primary efficacy endpoint, 22 recurrence events would be needed to detect a statistical significance. A total of 25 primary efficacy end-point events had accrued when the randomized-withdrawal period closed. The primary efficacy endpoint of the study was time to pericarditis recurrence; however, during the withdrawal period, there were too few recurrent events noted in the rilonacept (Arcalyst) group to allow for median time calculation. The median time to the first adjudicated recurrence in the placebo group was 8.6 weeks (95% CI, 4.0 to 11.7). One notable secondary endpoint was the proportion of participants who maintained clinical response at 16 weeks with 81% of the rilonacept group (95% CI; 58-95) noted compared to 20% (95% CI; 6-44) in the placebo group.
IV. According to key opinion leader input and available information from Kiniksa, the place in therapy for rilonacept (Arcalyst) is in recurrent pericarditis only. According to a Journal of American College of Cardiology (JACC) review on the management of acute and recurrent pericarditis, in acute pericarditis, the injury to the pericardium leads to a cascade of inflammatory process where IL-1 receptor (IL-1R) occupies a central role. In this process, IL-1α functions as an alarmin that is released during tissue injury and IL-1β gets released leading to

amplification of the process. The rationale for the evaluation of rilonacept (Arcalyst) for recurrent pericarditis notes that this process is thought to stimulate the production of additional IL-1α and IL-1β which induces a self-perpetuating cycle of pericardial inflammation.

V. Both the 2015 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of pericardial diseases, and the 2020 American College of Cardiology review on the management of acute and recurrent pericarditis list treatment with NSAIDs/aspirin with colchicine for both acute pericarditis and recurrent pericarditis. According to ACC, anti-inflammatory therapy is the cornerstone of acute pericarditis. NSAIDs are recommended during an acute episode. Colchicine, which has a known anti-inflammatory effect, is recommended in patients with acute pericarditis in addition to aspirin or another NSAIDs. The benefit of colchicine is well established in both acute and recurrent pericarditis through various trials including, but not limited to, the CORE trial (2005), COPE trial (2005), and ICAP (2013). The ACC also notes that the efficacy of colchicine in recurrence has been shown in various studies. Key opinion leader input also supports the use of NSAIDs/aspirin and colchicine for both acute and recurrent pericarditis and that trial of these prior to rilonacept (Arcalyst) is clinically appropriate and aligns with evidence. Currently a 3-month course of colchicine is recommended for acute pericarditis; whereas, for recurrent pericarditis, a treatment course of at least 6 months is recommended.

VI. According to available information or guidelines for recurrent pericarditis, key opinion leader input and available data for the use of rilonacept (Arcalyst) in recurrent pericarditis, NSAIDs and colchicine (≥ 6 months) remain the standard of care for the treatment for initial recurrence of pericarditis. Low-dose corticosteroids are also often used in the treatment of recurrent pericarditis and are associated with a high treatment success rate per ACC. Currently, the place in therapy for rilonacept (Arcalyst) can be considered for patients with multiple recurrence of pericarditis, and/or for patients where further use of NSAIDs, colchicine, and a low-dose corticosteroid are not clinically appropriate.

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Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

Initial Evaluation

I. **Tocilizumab (Actemra)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pulmonologist or rheumatologist; **AND**
   C. Tocilizumab (Actemra) will not be used in combination with nintedanib (Ofev) or pirfenidone (Esbriet); **AND**
   D. A diagnosis of **Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)** when all of the following are met:
      1. The diagnosis is confirmed by a high resolution computed tomographic (HRCT) scan; **AND**
      2. Treatment with immunomodulators (e.g., mycophenolate mofetil or cyclophosphamide) has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attests that member has exhibited improvement or stability of disease symptoms (e.g., sustained forced vital capacity (%FVC) decline or minimal decline in diffusing capacity of the lung for carbon monoxide (DLCO))

Supporting Evidence

I. Scleroderma-associated interstitial lung disease (SSc-ILD) is a chronic lung disease in which fibrosis builds up in the lungs in a person diagnosed with systemic sclerosis (SSc). Direct pulmonary involvement in SSc is the main cause of death in patients with SSc. Early diagnosis, severity assessment, prediction of progression, and appropriate treatment of SSc- ILD is necessary to achieve the best possible patient outcomes. Goals of treatments include optimizing therapy, slowing disease progression, and prolonging time to progression and survival.
II. The presence of SSc-ILD is defined by the identification of fibrotic features on high- resolution CT (HRCT) scan. Surgical lung biopsy is seldom performed in SSc patients, unless the HRCT pattern is atypical, there is suspicion of a different diagnosis, or there is a complication such as cancer.
III. Pulmonary function tests (PFT) in patients with SSc-ILD demonstrate a restrictive pattern, with FVC and diffusion capacity of the lung for carbon monoxide (DLCO). DLCO is a measure of the conductance of gas transfer from inspired gas to the red blood cells. A low DLCO combined with reduced lung volumes suggests interstitial lung disease (ILD).
IV. Decisions to initiate or advance treatment often take into consideration the likelihood of progression, patient comorbidities, risk of toxicities, and current data on efficacy. Patients are

treated based on expert-derived recommendations for the management of organ-specific manifestations. The European expert consensus published in 2020 recommends immunosuppressive therapies in severe or progressive ILD, including mycophenolate mofetil, cyclophosphamide, or nintedanib (Ofev) in patients requiring pharmacotherapy.

V. Nintedanib (Ofev) is approved to slow the rate of decline in pulmonary function in patients with SSc-ILD. Given its recent approval in 2019, its role in clinical practice (e.g., timing of initiation, use as add-on or monotherapy) for patients with SSc-ILD has not been well-defined.

VI. There is no evidence to suggest that combination therapy of tocilizumab (Actemra) and nintedanib (Ofev) or pirfenidone (Esbriet) will be safe or effective when used to treat Scc-ILD.

VII. The FDA has approved tocilizumab (Actemra) for slowing the rate of decline in pulmonary function in adult patients with SSc-ILD. The decision was based on the two clinical trials: the focuSSced Phase 3 trial and the Phase 2/3 faSScinate trial.

A. The focuSSed trial: A randomized, double-blind, placebo-controlled trial enrolled 212 participants >18 years of age to receive tocilizumab (Actemra) 145 mg subcutaneously once weekly (N=104) or placebo (N=106) for at least 48 weeks. Participants were excluded if they had severe restricted airway disease, including a percentage of predicted forced vital capacity (FVC% predicted) $\leq$ 55%, DLCO $\leq$45, or PAH WHO class 2 or higher. Patients were not on immunomodulating therapy (mycophenolate, cyclophosphamide) during enrollment.

a. The primary endpoint, the difference in change from baseline in modified Rodnan skin score (mRSS), was not met. Post-hoc analyses were performed to evaluate results within the subgroups of participants with and without SSc-ILD. Results of the FVC secondary endpoints support the effectiveness of tocilizumab (Actemra) in reducing the rate of progressive loss of lung function in SSc-ILD.

	Overall population		Subgroup without SSc-ILD*		SSc-ILD subgroup*	
	Placebo	Tocilizumab	Placebo	Tocilizumab	Placebo	Tocilizumab
Number of patients	106	104	36	34	68	68
Change from baseline in mRSS score						
LSM	-4.41	-6.14	-6.16	-8.56	-3.77	-5.88
Difference in LSM (95% CI)†	-1.73 (-3.78, 0.32); p = 0.10		-2.40 (-5.59, 0.79)		-2.11 (-4.89, 0.67)	
Change from baseline in ppFVC (%)						
LSM	-4.58	-0.38	-0.82	-0.32	-6.40	0.07
Difference in LSM (95% CI)†	4.20 (2.00, 6.40); p=0.0002		0.50 (-2.27, 3.27)		6.47 (3.43, 9.50)	
Change from baseline in observed FVC (mL)						
LSM	-190	-24	-53	-11	-255	-14
Difference in LSM (95% CI)†	167 (83, 250); p = 0.0001		43 (-60, 145)		241 (124, 358)	

*Post-hoc results are shown for this subgroup. Four patients had ILD status missing at baseline.
†Difference in LSM (least means squared) between tocilizumab and placebo populations at week 48

b. Subjects with SSc-ILD treated with tocilizumab (Actemra) had a smaller decline in mean ppFVC than placebo (0.07% vs. -6.4%, mean difference 6.47%), and a smaller decline in FVC compared to placebo (mean change -14mL vs. -255mL, mean difference 241mL).

B. The faSSinate trial was a randomized, double-blind, placebo-controlled trial which enrolled 87 participants > 18 years of age with SSc to receive tocilizumab (Actemra) 145 mg subcutaneously once weekly (N=44) or placebo (N=43). Participants were excluded if they had severe restricted airway disease, including a percentage of predicted forced vital capacity (FVC% predicted) ≤ 50%, DLCO ≤40, or PAH WHO class 2 or higher. Patients were not on immunomodulating therapy (mycophenolate, cyclophosphamide) during enrollment. The primary endpoint, the difference in change from baseline in modified Rodnan skin score (mRSS) at week 24, was not met. Results of the ad-hoc FVC secondary endpoints support the effectiveness of tocilizumab (Actemra) in reducing the rate of progressive loss of lung function in SSc at week 48.

	ITT population	
	Placebo	Tocilizumab
mRSS change from baseline at week 48		
Number of patients	44	43
LSM	-2.10	-5.46
Difference in LSM (95% CI)	-3.36 (-7.3,0.32); p=0.0726	
Change from baseline in ppFVC (%) at week 48		
Number of patients	26	28
LSM	-6.31	-2.04
Difference in LSM (95% CI)	4.27 (0.68,7.78); p = 0.02	
Change from baseline in observed FVC (mL) at week 48		
Number of patients	27	28
LSM	-230	-91
Difference in LSM (95% CI)	138 (-2,279); p =0.05	

VIII. No new or unexpected safety findings were observed in both studies. Adverse events observed in subjects receiving tocilizumab (Actemra) were consistent with the known safety profile in other indications.

IX. The impact of tocilizumab (Actemra) on disease involvement in lung tissue as examined by CT scans has not been evaluated.

X. Safety and efficacy of tocilizumab (Actemra) in the setting of SSc-ILD has not been established in patients <18 years of age.

XI. Safety and efficacy of tocilizumab (Actemra) has not been established in other etiologies of ILD (e.g., idiopathic pulmonary fibrosis, non-specific interstitial pneumonia) and would remain experimental or investigational in non-SSc ILD.

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Polymyalgia Rheumatica (PMR)

Initial Evaluation

I. **Sarilumab (Kevzara)** may be considered medically necessary when the following criteria are met:
   A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   B. A diagnosis of **polymyalgia rheumatica** when the following are met:
      1. Presence of the following:
         I. Age at disease onset of at least 50 years; **AND**
         II. Presence of bilateral shoulder and/or pelvic girdle pain lasting at least 2 weeks; **AND**
         III. Presence of morning stiffness > 45 minutes; **AND**
         IV. Elevated CRP or ESR; **AND**
         V. Previous treatment with at least one glucocorticoid (i.e., prednisone, hydrocortisone, methylprednisolone, etc.) and attempted dose reduction/taper has been ineffective, contraindicated, or not tolerated

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., reduction of elevated inflammatory markers the CRP and ESR, improvement of bilateral shoulder and/or pelvic girdle pain, reduction of duration of daily morning stiffness)

Supporting Evidence

I. Sarilumab (Kevzara) is FDA-approved for adult patients with Polymyalgia rheumatica based off results of the SAPHYR study (n=118), a phase 3, randomized, double-blind placebo-controlled trial evaluating the efficacy of sarilumab in patients with PMR as assessed by the proportion of subjects with sustained remission for sarilumab with a shorter corticosteroid (CS) tapering regimen as compared to placebo with a longer CS tapering regimen. Duration was approximately 62 weeks which included a 4-week screening period, 52-week treatment period and 4-week follow up period. Sustained remission rate was significantly higher in the sarilumab arm vs the placebo arm (28.3% vs 10.3%; P=0.0193). With regards to safety of sarilumab compared to placebo in the SAPHYR trial, more patients had adverse events in the sarilumab arm (94.9% vs 84.5% for sarilumab vs placebo), however, less patients experienced serious

adverse events in the sarilumab arm when compared to placebo (20.7% vs 13.6%). The common adverse reactions occurring in ≥5% of patients treated with KEVZARA were neutropenia (15.3%), leukopenia (6.8%), constipation (6.8%), rash pruritic (5.1%), myalgia (6.8%), fatigue (5.1%), and injection site pruritus (5.1%).

II. The diagnosis and management of PMR requires detailed clinical examination. Given the complexities of diagnosis and treatment of this condition, supervision of treatment by a rheumatologist is required.

III. According to the European League Against Rheumatism/American College of Rheumatology Collaborative Initiative (EULAR/ACR) classification criteria for PMR, patients are required to be age 50 years and older to be considered for a diagnosis of PMR. The typical age of onset of the disease is 60-70 years old, and it is unlikely that a patient be diagnosed with PMR under the age of 50 years old. Other diagnoses should be considered and ruled out if patient presents with symptoms under the age of 50. Additionally, the safety and efficacy of Kevzara in patients less than 50 years old have not been established in patients with PMR

IV. The presence of bilateral shoulder and/or hip pain are hallmark presenting symptoms for PMR. Within EULAR/ACR classification criteria for PMR and in the SAPHYR trial, bilateral shoulder and/or hip pain is required for diagnosis. Although morning stiffness is not mutually exclusive to PMR, the presence of morning stiffness for greater than > 45 minutes is very strong predictor of a PMR diagnosis and is commonly utilized in clinical practice.

V. Elevation of acute phase reactants such as CRP and/or ESR are strong predictors of diagnosis of PMR and are requirements for diagnosis within the EULAR/ACR classification criteria. All patients included in the SAPHYR trial must have had elevation in either CRP or ESR, defined as CRP> 10mg/L and/or ESR> 30mm/hour.

VI. Trial of a corticosteroid (e.g., prednisone) is considered first-line therapy and the standard of care for patients diagnosed with PMR. If patients exhibit a response/sustained remission with corticosteroids, a dose reduction or taper may be implemented to reduce long term exposure steroids. Sarilumab (Kevzara) is only indicated for patients who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper. Every patient within the SAPHYR trial were required to start prednisone and undergo a taper before starting sarilumab or placebo. The efficacy and safety of sarilumab in the first-line setting prior to corticosteroid use have not been established at this time.

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Investigational or Not Medically Necessary Uses

I. Cutaneous Sarcoidosis
   A. Apremilast and adalimumab have both been analyzed in this disease state. Efficacy data is limited to case reports and small studies at this time. One small RCT of adalimumab (n = 16) demonstrated a decrease in target lesion area compared to placebo. Similarly, a small observational study in 15 patients receiving apremilast demonstrated a reduction in induration at week 12 compared to baseline. Only one investigator performed the lesion assessment in this study, and similar to adalimumab, further larger scale, randomized studies are needed to fully establish efficacy of these agents.

II. Deficiency of IL-1 Receptor Antagonist (DIRA)
   A. Although anakinra (Kineret) is FDA approved for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA), the safety and efficacy data that led to FDA approval is considered to be of low quality. This approval is based on safety data from a National Institute of Allergy and Infectious Diseases (NIAID) study of nine patients with IL1RN mutations (17-I-0016). This study was neither designed nor powered to evaluate the efficacy of anakinra (Kineret) for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA). This study was part of a larger ongoing NIAID sponsored study on patients NOMID/CAPS, DIRA, CANDLE, SAVI, NLRC4-MAS, Still's Disease, and with other yet undifferentiated autoinflammatory diseases. This study is designed to identify the disease pathogenesis, including clinical, immunological, genetic and endocrinological characteristics of the disease. Currently, this indication is considered experimental and investigational due to the ongoing study and limited efficacy data for this indication.
   B. DIRA is a recently described recessively inherited autoinflammatory disease linked to activation of the IL-1 pathway. DIRA is to not be confused with DITRA (deficiency of interleukin-36 receptor antagonist) which usually results to generalized pustular psoriasis. Children with DIRA usually present with the following within the first weeks of life: symptoms of systemic inflammation (such as elevation of acute phase reactants and low-grade fever), pustular rashes, joint swelling, oral mucosal lesions and severe bone pain when being picked up. Currently, there are no other FDA approved agents approved for the treatment of DIRA. Patients who were evaluated in the NIAID sponsored study were previously treated with antibiotics, NSAIDs, corticosteroids, IVIG, and DMARDs (e.g. methotrexate, azathioprine, etc).

III. Graft Versus Host Disease (GVHD)

A. A number of observational trials have examined etanercept in acute GVHD. Treatment regimens vary significantly between these observational studies. Data from a pilot and phase II trial pooled against observational data of standard of care patients receiving standard of care with steroids observed a higher complete response rate in those treated with etanercept. The results are significantly limited, however, by the observational, nonrandomized nature and thus prospective, randomized trials are needed to fully establish possible benefit in GVHD. The use of tocilizumab has also been studied in a small population (n = 8) with refractory GVHD. While response was observed in four of the six tocilizumab treated patients, the limited sample size is insufficient to confirm efficacy at this time.
B. The safety and efficacy of the self-administered formulation of abatacept (Orencia) has not been evaluated. The intravenous form of abatacept (Orencia) is FDA-approved for the prevention or prophylaxis of acute graft vs. host disease (aGVHD). The FDA-approval of intravenous abatacept (Orencia) in aGVHD was based on two studies; a double-blind, placebo-controlled trial that showed survival benefit over placebo when used in combination with other immunosuppressive drugs; and a registry-based evaluation that compared patients that received abatacept (Orencia) in addition to conventional immunosuppressant therapy vs. conventional immunosuppressive therapy alone. The study observed to abatacept (Orencia) to have a survival benefit when used with conventional immunosuppressive treatments. The FDA-approved dose is 10 mg/kg IV over 60 minutes the day prior to stem cell transplantation, as well as days 5, 14, 28 days after transplantation, which conveniently overlaps with the expected inpatient stay following stem cell transplantation. Accurate dosing may only be achieved with the intravenous formulation. In addition to having unknown safety and efficacy, the self-administered formulation would have a greater injection burden, greater medication waste, and greater cost compared to the intravenous formulation. No other biologic therapies have been evaluated for this condition.

IV. Grave's Ophthalmopathy
A. A small, phase III RCT (n = 32) analyzed tocilizumab use compared to placebo in this disease state. A statistically significant reduction was observed in the clinical activity score from baseline by week 16, but given the small sample size, the American Academy of Ophthalmology has recommended that larger studies be completed to fully establish safety and efficacy for this indication.

V. Guttate Psoriasis
A. In this form of psoriasis, case reports suggest that the use of TNF inhibitors may induce flares when used. Typical treatment involves phototherapy and topical corticosteroids/vitamin D analogs, with tonsillectomy or antibiotics used for more refractory disease. There is no established efficacy data for the use of biologics or targeted DMARDs in this setting at this time.

VI. Interstitial Cystitis
A. TNF inhibitors such as adalimumab and certolizumab pegol have been studied in small, phase III RCTs. In the study of certolizumab pegol, no difference was observed in interstitial cystitis compared to placebo at week 2. Secondary outcomes indicate benefit may occur in this population by week 10-18 of therapy. A similar study was completed

with adalimumab, with no statistical difference observed in the primary outcome at week 12 compared to placebo. Further studies are needed to analyze efficacy in this population.

VII. Lupus Nephritis and Systemic Lupus Erythematosus (SLE)
   A. Abatacept was analyzed in a large phase III RCT (n =695) in patients with lupus nephritis and in combination with mycophenolate and steroids. No difference was observed in the primary outcome of complete renal response at one year compared to placebo. Studies utilizing ustekinumab are currently recruiting in patients with SLE.

VIII. Osteoarthritis
   A. Infliximab and adalimumab have been examined for use in patients with erosive, hand osteoarthritis. Mixed results have been seen so far. Open-label, observational studies of infliximab have shown potential benefit, while studies with adalimumab have been inconclusive. For instance, in a RCT of 60 patients, the difference in proportion of active disease in the adalimumab versus placebo group was not statistically significant. Further studies are needed to establish safety and efficacy.

IX. Palmoplantaris **Pustulosis**/Pustulosis palmaris et plantaris
   A. It is not uncommon for forms of pustulosis to coexist with plaque psoriasis/psoriasis vulgaris; however, in absence of a covered indication and when associated criteria are met, use of non-biologic and biologic therapies in the setting of pustulosis is considered experimental and investigational.
   B. A small placebo-controlled (n =15) of etanercept in palmoplantaris pustolosis supported potential efficacy of TNF inhibitors. Observations have also occurred demonstrating worsening of this disease with use of TNF inhibitors. Other biologics, such as the use of IL-12/IL-23 inhibitor ustekinumab, did not demonstrate benefit in palmoplantaris pustolosis. A phase II study has analyzed guselkumab, and case reports of IL-1 inhibitors such as anakinra have been reported, though further study is needed to confirm the use of biologics in this population.

X. Polymyositis and Dermatomyositis
   A. One phase III trial is currently recruiting to analyze abatacept in patients with polymyositis and dermatomyositis. Anakinra has also been examined in a single group study (n = 15). Decrease in certain inflammatory markers was observed, however, the clinical and patient-centered outcomes of anakinra use in this population requires further analysis. Another single-group, non-randomized trial (n = 13) looked at infliximab use in this population. None of the included patients had improvement in muscle strength by manual, and only two patients saw any improvement in disease activity scores.

XI. Pulmonary Sarcoidosis
   A. The TNF inhibitors infliximab, adalimumab, and etanercept have been studied to some extent in pulmonary sarcoidosis. A phase II study (n = 138) saw a statistically significant increase in functional vital capacity at week 24 compared to placebo, however, the effect size was small with a mean increase of just 2.5% from baseline. A small, open-label phase II study with etanercept was terminated early due to an excessive number of treatment failures. Case reports of adalimumab exist, and one study which examined 18 patients who switched after infliximab use saw improvement in just over one-third of patients,

however, further prospective, randomized trials would be needed to fully establish safety and efficacy.

XII. Pyoderma gangrenosum
    A. Case reports of the use of TNF inhibitors are available in this patient population. Most reports have involved patients with another indication for a TNF inhibitor, such as IBD or RA. A Phase III trial for this disease state is currently recruiting in Japan.

XIII. Sciatica
    A. One small RCT has examined adalimumab in patients with acute/severe radicular leg pain and imagine-confirmed lumber disc herniation. Of the 61 patients, a statistically significant, though small effect, was seen at week 6 compared to placebo. At the 6 month follow up, the statistically significant difference was lost. While a difference in surgical discectomies was also seen,

XIV. Systemic sclerosis (scleroderma)
    A. A phase III RCT (n =212) comparing tocilizumab to placebo in patients with systemic sclerosis did not observe a statistically significant difference in change from baseline to week 48 in the primary outcome in the Modified Rodnan Skin Score (mRSS).

XV. Sjogren's Syndrome
    A. Studies with TNF inhibitors etanercept and infliximab have not demonstrated benefit in Sjogren's syndrome. A RCT (n = 103) found no difference in disease activity between infliximab and placebo by week 22. Likewise, a smaller RCT (n = 28) found no statistical difference with etanercept versus placebo at 12 weeks after treatment initiation. Small, open-label studies have also been done with abatacept, though sample size has been small, and data has been mixed, with one trial demonstrating improvement in salivary gland biopsy and extraglandular manifestations, and one showing no change in tear flow or improvement in other symptoms.

XVI. Wegener's Granulomatosis
    A. One phase III RCT (n = 181) exists for the use of etanercept in patients with Wegener's Granulomatosis. Compared to standard of care (steroids plus cyclophosphamide or methotrexate), patient on etanercept demonstrated an initial sustained remission for at least six months that was not statistically different from standard of care. Likewise, a large proportion of patients lost response over the 27 months mean follow up period. An open-label study with infliximab (n = 16) has also been completed, with similar response rates to that described above in the etanercept study.

XVII. Secukinumab in Rheumatoid Arthritis
    A. Three phase III studies (NURTURE-1, REASSURE, REASSURE-2) evaluated the use of secukinumab in patients with rheumatoid arthritis. Novartis is not planning to pursue approval for secukinumab as the trials were terminated due to lack of comparative efficacy. Given the availability of other FDA approved options in this setting with established safety profiles and signals of efficacy, there is insufficient data to allow a standard path to coverage for Cosentyx in rheumatoid arthritis.

XVIII. Vedolizumab Subcutaneous (Entyvio)
    A. Vedolizumab (Entyvio) subcutaneous (SC) formulation is considered not medically necessary when used for all indications, including but not limited to maintenance of remission in ulcerative colitis. Intravenous (IV) vedolizumab (Entyvio) formulation is

clinically comparable in efficacy and safety to the SC formulation and is the preferred product which can be accessed via the medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

XIX. Infliximab-dyyb (Infliximab)

A. Infliximab-dyyb (Zymfentra) is considered not medically necessary when used for all indications, including but not limited to maintenance of remission in ulcerative colitis and Crohn's disease. Intravenous (IV) infliximab formulation is clinically comparable in efficacy and safety to the SC formulation and is the preferred product which can be accessed via the medical benefit. Preference for SC formulation over IV does not establish medical necessity for use.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy	Disease State
Systemic Janus Associated Kinase (JAK) Inhibitors in Chronic Inflammatory Disease Policy	Rheumatoid Arthritis
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)
	Psoriatic Arthritis
	Plaque Psoriasis
	Ankylosing Spondylitis
	Non-radiographic axial spondyloarthritis (nr-axSpA)
	Ulcerative Colitis
	Atopic Dermatitis
Multiple Sclerosis Policy	Multiple Sclerosis
Nintedanib (Ofev®); prifenidone (Esbriet®)	Systemic sclerosis-associated interstitial lung disease (SSc-ILD)
Tapinarof (Vtama®)	Plaque Psoriasis

Policy Implementation/Update

Action and Summary of Changes	Date
Addition of bimekizumab (Bimzelx) into policy.	03/2024
Live 04/01/2024: addition of select biosimilars (Hadlima and adalimumab-adaz) as preferred products, removal of brand Humira as a preferred product. Change to ulcerative colitis criteria to require trial of at least one corticosteroid or immunomodulator; change to Crohn's disease criteria to require trial of at least one corticosteroid or immunomodulator and change to define high-risk Crohn's disease and remove severe Chron's disease	02/2024
Added age expansions for abatacept (Orencia) and etanercept (Enbrel) in psoriatic arthritis. Added etrasimod (Velsipity) to ulcerative colitis policy. Added infliximab-dyyb (Zymfentra) as not medically necessary to ulcerative colitis and Crohn's Disease criteria. Updated Supportive evidence section and not medically necessary sections.	01/2024
Live 01/2024: Added guselkumab (Tremfya) as a preferred product.	11/2023
Added vedolizumab SC (Entyvio) to policy for ulcerative colitis as not medically necessary when used for all indications. Updated Investigational or Not Medically Necessary Uses section to include vedolizumab SC (Entyvio). Added mirikizumab (Omvoh) to policy for ulcerative colitis indication. Updated supportive evidence section accordingly.	11/2023
Added criteria for anakinra (Kineret) off-label use in TRAPS (tumor necrosis factor receptor-associated periodic syndrome), FMF (Familial Mediterranean Fever) and HIDS/MKD (hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency). Removed FMF (Familial Mediterranean Fever) from the E/I section.	10/2023
Addition of new adalimumab biosimilars into policy.	07/2023
Live 12/2023: Updated criteria for hidradenitis suppurativa to include new line indication for Cosentyx. Updated supporting evidence and references.	06/2023
Added polymyalgia rheumatica indication for Sarilumab (Kevzara) with associated criteria and supporting evidence. Removed polymyalgia rheumatica from E/I section.	06/2023
Live 06/2023: Added Rinvoq to Crohn's Disease policy, updated supportive evidence section for Crohn's Disease, updated references for Crohn's Disease, updated Related Policies section. Removed step criteria requiring trial of corticosteroids in giant cell arteritis. Added updated supporting evidence and updated guideline recommendations.	03/2023
Addition of adalimumab-atto (Amjevita) into policy.	02/2023
Updated nr-axSpA formulary agents to include new line indication for Rinvoq. Updated supporting evidence and references for AS and nr-axSpA. Updated wording of renewal criteria regarding combination biologic use to reflect specific disease state referenced. Updated related policies section.	11/2022

Added Stelara age expansion in psoriatic arthritis to include members 6 years of age or older, formatting, and supporting evidence.	10/2022
Added Skyrizi to Crohn's disease criteria, updated supporting evidence section, updated formatting. Updated AS formulary agents to include new indication for Rinvoq.	06/2022
Added Rinvoq to ulcerative colitis criteria given newly approved indication	05/2022
Updated criteria in setting of mild-moderate plaque psoriasis to require phototherapy OR treatment with only one of the list groups	04/2022
Added ERA section and created criteria for use of Cosentyx as prompted by recent FDA approval. Updated PsA criteria to include expanded age for Cosentyx and new FDA approval for Skyrizi. Refined supporting evidence for PJIA and PsA to further clarify guidelines and treatment algorithm in pediatrics.	03/2022
Added criteria for Otezla to include line extension in setting of mild to moderate psoriasis with update to supporting evidence section. Updated PsA and AS formulary agents to include new indications for Rinvoq and Xeljanz with updates to supporting evidence and references. Removed Behcet's oral corticosteroid requirement and updated to include systemic therapy to align more appropriately with guidelines. Updated Palmoplantar pustulosis E/I summary. Added Graft Vs. Host disease to E/I.	2/2022
Added Skyrizi, Rinvoq, and Xeljanz to the preferred product mix (effective 1/1/2022). Separated/removed JAK inhibitors (Xeljanz, Rinvoq, Olumiant) and created JAK Inhibitor Policy. Removed JAK inhibitors in E/I section and added Cosentyx in RA to E/I. Added Related Policies section.	12/2021
Removed criteria defining moderate to severe Crohn's disease, severe/fulminant Crohn's disease, and surgical Crohn's disease. Updated supporting evidence section accordingly.	09/2021
Added criteria for the treatment of systemic sclerosis-associated interstitial lung disease prompted by new FDA approval of Actemra for this indication.	08/2021
Updated Plaque Psoriasis, Cosentyx criteria to allow coverage in patients 6 six years of age or older	07/2021
Added criteria for treatment of recurrent pericarditis with Arcalyst	06/2021
Updated criteria for ulcerative colitis to include FDA approval of ozanimod (Zeposia) for adults with moderate to severe ulcerative colitis. Modified the weight requirement for Humira to a specific age group. Added a requirement to try and fail TNF blockers before allowing treatment with tofacitinib (Xeljanz) as recommended by FDA labeling. Supporting evidence and references updated.	06/2021
Updated criteria for ulcerative colitis to include FDA approval of adalimumab (Humira) for pediatric patients five years and older. Added the requirement for the documentation of member's current weight. Updated the language in the criterion requiring use of thiopurines only if corticosteroids were used to induce remission. Supporting evidence and references updated.	05/2021
Added DIRA indication as E/I for anakinra (Kineret); Updated the supporting evidence and references for plaque psoriasis.	04/2021
Updated PA policy to include FDA approvals for Xeljanz for PJIA. Updated supporting evidence section with clinical trial data	11/2020
Updated PA policy to include FDA approvals for Stelara and Taltz for plaque psoriasis in pediatric population. Updated supporting information section for plaque psoriasis to include clinical trial data supporting use of Stelara and Taltz in pediatric patients	09/2020
Updated the products for psoriatic arthritis to include guselkumab (Tremfya). Updated the supporting evidence section for psoriatic arthritis to reflect no changes in the guidelines with regard to guselkumab (Tremfya). Updated non-radiographic axial spondyloarthritis (nr-axSpA) criteria to include secukinumab (Cosentyx) and ixekizumab (Taltz). Updated nr-axSpA supporting evidence section to include trial information regarding new addition of secukinumab (Cosentyx) and ixekizumab (Taltz), as well as updated ACR guidelines.	08/2020
Removed Behçet syndrome from the E/I section	02/2020
Updated preferred products to also include Cosentyx, Stelara, and Otezla within their FDA label designation.	01/2020
Updated policy to add new indications for Stelara and Taltz. Included Familial Mediterranean Fever to experimental/investigational section.	11/2019
Criteria updated to new policy format. Specific changes include: <u>Rheumatoid Arthritis</u>	08/2019

• Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement
• Removed requirements for diagnosis due to varying methods to diagnose and limited value of this question from health plan standpoint
• Clarified use of oral DMARD requirement may be bypassed if all of them are contraindicated
• Added newly approved upadacitinib (Rinvoq) as a non-preferred alternative
<u>Polyarticular Juvenile Idiopathic Arthritis (PJIA)</u>
• Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement
• Added route to approval of Actemra as Actemra was previously in a separate policy
<u>Systemic Juvenile Idiopathic Arthritis (SJIA)</u>
• Separated SJIA from PJIA to have individual requirements
• Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement
• Updated route to approval to require trial of NSAIDs or indication member has severe active disease
• Routed therapy through anakinra (Kineret) over tocilizumab (Actemra) and abatacept (Orencia); followed by tocilizumab (Actemra) over abatacept (Orencia) as per
<u>Psoriatic Arthritis</u>
• Added requirement of the presence of active severe disease and provided specific indicators of severe disease
• Added clinical note: "If a patient has a diagnosis of both plaque psoriasis and psoriatic arthritis, approval of the requested medication can be made as long as the patient fulfills the criteria for at least one of the disease states and associated medication criteria."
<u>Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis</u>
• Removal of the requirement of DMARDs per the 2015 ACR guideline and 2016 ASAS/EULAR guideline
• Added requirement of a trial of two or more NSAIDS for an adequate trial of at least 4 weeks, also based on the above guidelines
<u>Plaque Psoriasis</u>
• Clarified that moderate to severe disease is needed for payment consideration
• Clarified use of oral DMARD requirement may be bypassed if all are contraindicated
 	
<u>Crohn's Disease</u>
• Added age requirement of six years of age or older
• Incorporated definition of moderate to severe Crohn's disease to help confirm disease severity
• Addition of breakdown to separate severe/fulminant Crohn's disease with definition to help confirm disease severity
  ○ Addition of IV corticosteroids as appropriate for this level of severity
• Addition of breakdown to Crohn's disease with surgical resection completed or planned
  ○ With further addition requiring presence of one additional factor demonstrating medical necessity of biologic treatment
<u>Ulcerative Colitis</u>
• Added age of 18 years or older
• Addition of trial of thiopurine for at least 8 weeks
<u>Behcet's Disease</u>
• New indication added following approval of Otezla in this setting	

• Literature supports TNF therapy in oral and ophthalmic manifestations for Behcet's. A path to approval was added to the criteria • Otezla was added as a potential option after TNF have been found inefficacious or are contraindicated <u>Hidradentitis Suppurativa</u> • Updated prescriber language to be consistent with other sections • Added requirement of a trial of antibiotics for moderate disease <u>Uveitis/Panuveitis</u> • Added age of 2 years or older • Improved trial/fail wording to state "ineffective, contraindicated, or not tolerated" ○ No changes to trial and failure requirements <u>Giant Cell Arteritis (GCA)</u> • Added age of 18 years or older • Added criteria endorsed by guidelines to confirm diagnosis of GCA • Updated terminology around steroid use to require a previous trial with steroids rather than requiring concomitant steroid use with Actemra <u>Cryopyrin-Associated Periodic Syndromes (CAPS)</u> Added requirement, of documented laboratory evidence of a genetic mutation	
Criteria update: Increased initial approval from 3 months to 6 months, updated initial QL to reflect 6 month approval duration. Added new Xeljanz IR 10mg tablet availability. Added baricitinib (Olumiant) as an option for the treatment of rheumatoid arthritis after trial and failure of a TNF antagonist.	07/2018
Criteria update: Added new Kevzara auto injector formulation, Xeljanz new indication in ulcerative colitis, added Cimzia new indication in plaque psoriasis, minor formatting edits.	06/2018
Criteria update: Align dosage and administration with quantity limit. Removal of the question pertaining to active infection.	02/2018
New Criteria Set – consolidated from all biologic agents along with Otezla and Xeljanz criteria sets. Within this new criteria set, here are the following updates: 1. 18 years of age requirement has been removed for Stelara as it has now been FDA approved for pediatric plaque psoriasis. 2. New FDA approved indication of psoriatic arthritis has been added for Xeljanz/Xeljanz XR and Taltz 3. The question regarding dual therapy has been refined to encompass the language of biologics and other non-biologics (e.g. Otezla and Xeljanz). 4. The question regarding DMARDs has been refined to only include agents that are administered non-biologic, non-specialty and that are administered orally. 5. For the indication of plaque psoriasis, the question addressing the trial of UVB has been combined with the trial of DMARDs.	01/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP090

Description
Coagulation Factor X, human is a plasma-derived human blood coagulation factor that works by temporarily replacing the missing Factor X needed for effective hemostasis.

Length of Authorization
- Initial: Six months (for on-demand treatment and prophylaxis); one month (for perioperative)
- Renewal: 12 months (for prophylaxis); 6 months (for on-demand)

Quantity limits

Product Name	Dosage Form	Indication/FDA Labeled Dosing	Quantity Limit
Coagulation Factor X, human (Coagadex)	250 IU/vial, 500 IU/vial	**Factor X deficiency:** **On-demand treatment** <12 years: 30 IU/kg/dose >12 years: 25 IU/kg/dose Repeat every 24 hours until bleeding stops. Max of 60 IU/kg/day **Routine prophylaxis** <12 years: 40 IU/kg IV twice weekly initially >12 years: 25 IU/kg IV twice weekly initially Max of 60 IU/kg/day **Perioperative management** Max of 60 IU/kg/day	**On-demand Treatment**: Amount requested OR a max of 60 IU/kg/day *(whichever value is lower)* and no more than 5 on-demand doses on hand **Routine Prophylaxis:** 480 IU/kg every 28 days **Perioperative Management:** Amount requested OR a max of 60 IU/kg/day *(whichever value is lower)* Up to the number of doses requested for 28 days

Initial Evaluation

I. Coagulation Factor X, human (Coagadex) may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by, or in consultation with a hematologist; **AND**
   B. A diagnosis of **hereditary Factor X deficiency** when the following are met:
      1. Used for on-demand treatment and control of bleeding episodes; **AND**
         i. Member does **NOT** have more than 5 on-demand doses on hand; **OR**
      2. Used for routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
         i. Member must have severe factor X deficiency (factor X level of <1%); **OR**
         ii. Member has at least two documented episodes of spontaneous bleeding into joints; **OR**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

3. Used for perioperative management of surgical bleeding in patients with mild (Factor X level 6-10%) and moderate (Factor X level 1-5%) deficiency

II. Coagulation Factor X, human (Coagadex) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent; **AND**
II. Any increases in dose must be supported by an acceptable clinical rationale (i.e. weight gain, half-life study results, increase in breakthrough bleeding when patient is fully adherent to therapy, etc.) as verified by a Moda Health pharmacist; **AND**
III. Used for on-demand treatment and control of bleeding episodes; **AND**
    - Member does **NOT** have more than five on-demand doses on hand; **OR**
IV. Used for routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
    - Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline

Supporting Evidence

I. Perioperative management of bleeding in major surgery in patients with severe hereditary Factor X deficiency has not been studied.
II. Dose and duration of the treatment depend on the severity of the Factor X deficiency, location and extent of the bleeding, the patient's age (<12 years or >12 years) and on the patient's clinical condition.
III. The dose and frequency is based on the individual clinical response. With a max dose of 60 IU/kg daily.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of coagulation Factor X, human (Coagadex) in any other condition.

References

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Policy Implementation/Update:

Date Created	January 2016
Date Effective	January 2016
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Removed age requirement as now also approved in patients less than 12 years of age. Addition of agent to be prescribed by hematologist, limited to only allow 5 doses on hand in on demand treatment setting, added requirement of severe factor X deficiency or at least two spontaneous bleeds into joints for prophylaxis use, limited perioperative use to mild or moderate deficiency as per label. Updated initial approval duration from one month to now six months. Addition of renewal criteria.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP070

Description

Cobimetinib (Cotellic) is an orally administered mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2 inhibitor. Vemurafenib (Zelboraf) is an orally administered BRAF kinase inhibitor. These agents are FDA-approved for combination use or single use.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
cobimetinib (Cotellic)	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation	20 mg tablets	63 tablets/28 days
	Histiocytic neoplasms in adults		
vemurafenib (Zelboraf)	Unresectable or metastatic melanoma with a BRAF V600E mutation	240 mg tablets	224 tablets/28 days
	Erdheim-Chester disease with a BRAF V600 mutation		

Initial Evaluation

I. **Cobimetinib (Cotellic) and vemurafenib (Zelboraf**) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medications are prescribed by, or in consultation with, an oncologist; **AND**
   C. A diagnosis of one of the following:
      1. **Unresectable, locally advanced (Stage IIIC) or metastatic (Stage IV) melanoma; AND**
         i. Documented BRAF V600E or V600K mutation; **AND**
         ii. Member has not previously received systemic anti-cancer therapy for metastatic melanoma (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy); **AND**
         iii. Cobimetinib (Cotellic) will be used only in combination with the following:

a. Vemurafenib (Zelboraf); **OR**
b. Vemurafenib (Zelboraf) AND atezolizumab (Tecentriq); **OR**

2. **Histiocytic Neoplasms (i.e., Erdheim-Chester disease, Rosai-Dorfman disease, Langerhans cell histiocytosis); AND**
   i. Documentation of prior treatment with, intolerance, or contraindication to both of the following:
      a. Cytarabine (non Erdheim-Chester disease indications)
      b. Cladribine; **AND**
   ii. Provider attestation member is not eligible or does not have access to clinical trial; **AND**
   iii. The request is for cobimetinib (Cotellic) monotherapy; **AND**
      a. Member has not previously progressed on therapy with a MEK inhibitor [i.e, binimetinib (Mektovi), selumetinib (Koselugo), or trametinib (Mekinist)];**AND**
      b. Member has had previous progression on or after BRAF inhibitor [e.g., vemurafenib (Zelboraf)]; **AND**
         i. Provider attestation that the member has an amenable MEK mutation; **OR**
   iv. The request is for vemurafenib (Zelboraf) monotherapy; **AND**
      a. Member has a diagnosis of Erdheim-Chester disease; **AND**
      b. Documented BRAF V600E mutation.

II. Cobimetinib (Cotellic) and vemurafenib (Zelboraf) are considered investigational when used for all other conditions, including but not limited to:
   A. Wild-type BRAF melanoma
   B. Melanoma in the neoadjuvant setting
   C. Breast cancer, solid tumors, colorectal cancer, thyroid cancer, central nervous system cancer, follicular/papillary cancer, and non-small cell lung cancer (NSCLC) with/without BRAF V600E mutation
   D. Hairy cell leukemia
   E. Cotellic in combination with Zelboraf for treatment of histiocytic neoplasms

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
   A. **For treatment of melanoma:** the request is for cobimetinib (Cotellic) to be used only in combination with the following:

1. Vemurafenib (Zelboraf); **OR**
2. Vemurafenib (Zelboraf) AND atezolizumab (Tecentriq); **OR**

B. **For the treatment of histiocytic neoplasms; AND**
   a. The request is for cobimetinib (Cotellic) monotherapy; **OR**
   b. The request is for vemurafenib (Zelboraf) monotherapy; **AND**
      i. Member has a diagnosis of Erdheim-Chester disease**.**

Supporting Evidence

I. **Advanced or Metastatic Melanoma**

A. Cobimetinib (Cotellic) is indicated for use in two different combinations for patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.
   i. In combination with vemurafenib (Zelboraf)– coBRIM trial
   ii. In combination with atezolizumab (Tecentriq) and vemurafenib (Zelboraf)– IMspire150 trial

B. Cobimetinib (Cotellic) was studied in a phase 3, randomized, double-blind, placebo-controlled trial (coBRIM) in 495 patients with unresectable, locally advanced stage IIIC or IV BRAF-mutated melanoma. The trial evaluated treatment with cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf) (COBI-VEM) compared to placebo with vemurafenib (Zelboraf) (PBO-VEM). The trial studied patients who were treatment-naïve defined as no prior systemic advanced/metastatic melanoma therapy (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, and biologic therapy), but did allow prior adjuvant therapy (including immunotherapy, e.g., ipilimumab).
   i. The primary endpoint was progression free survival (PFS), which resulted in 9.9 months in the COBI-VEM arm compared to 6.2 months in the PBO-VEM arm. Additionally, updated results, approximately 14 months post-trial, concluded PFS of 12.3 months in the COBI-VEM arm compared to 7.2 months in the PBO-VEM arm. Key secondary endpoints were overall survival (OS), which was 22.3 months in the COBI-VEM arm compared to 17.4 months in the PBO-VEM arm; complete response rate (CRR) of 68% in the COBI-VEM arm compared to 45% in the PBO-VEM arm; and duration of response (DoR) of 13 months in the COBI-VEM arm compared to 9.2 months in the PBO-VEM arm. Quality of life (QoL) parameters were studied; however, QoL analysis was not performed in all patients and was not studied through the entire length of the trial. QoL was evaluated until cycle 8 day 1, after which investigators report less than 25% of patients with baseline QoL scores remained enrolled in the PBO arm. There were no differences in quality-of-life scores between the two groups.
   ii. Safety results were analyzed in all patients who received at least one dose of study drug (N=254 COBI-VEM, N=239 PBO-VEM). The most common adverse events (>20% incidence) included diarrhea, nausea, vomiting, rash, photosensitivity reaction, hyperkeratosis, fatigue, pyrexia, arthralgia, alopecia, and increase creatine kinase. Cobimetinib (Cotellic) showed a 55%

discontinuation rate: 14% due to adverse events versus 7% in the PBO-VEM arm.

C. Cobimetinib (Cotellic) was also studied in a phase 3, randomized, double-blind, placebo-controlled trial (IMspire150) in 514 patients with unresectable, locally advanced stage IIIC or IV BRAF-mutated melanoma. The trial evaluated treatment with atezolizumab (Tecentriq) in combination with cobimetinib (Cotellic) and vemurafenib (Zelboraf) (ATEZO-COBI-VEM) compared to placebo, cobimetinib (Cotellic), and vemurafenib (Zelboraf) (PBO-COBI-VEM). The trial studied patients who were treatment-naïve defined as no prior systemic melanoma therapy (e.g., chemotherapy, hormonal therapy, targeted therapy, immunotherapy, or other biologic therapies); however, use with prior adjuvant therapy was allowed.
    i. The primary endpoint was PFS, which resulted in 15.1 months in the ATEZO-COBI-VEM arm compared to 10.6 months in the PBO-COBI-VEM arm. Key secondary endpoints were OS, which was 28.8 months versus 25.1 months in the PBO-COBI-VEM arm (HR 0.85, 95% CI 0.64-1.11, p=0.231); objective response rate (ORR), which was 66.3% versus 65% in the PBO-COBI-VEM arm; and DoR, which was 21 months versus 12.6 months in the PBO-COBI-VEM arm. QoL parameters were studied, which was 14.4 months to decline in QoL in the ATEZO-COBI-VEM arm, and not estimable for the comparator (HR 1.23, 95% CI 0.9-1.67).
    ii. Safety results were analyzed in all patients who received at least one dose of study drug (N=230 ATEZO-COBI-VEM, N=281 PBO-COBI-VEM). The most common adverse events (>20% incidence) included increased blood creatine phosphokinase, rash, diarrhea, arthralgia, pyrexia, increased alanine aminotransferase aspartate, increased lipase, increased aminotransferase, fatigue, nausea, pruritus, myalgia, photosensitivity, maculopapular rash, and increase amylase. Overall, 44% discontinued treatment in the ATEZO-COBI-VEM arm compared to 51% in the PBO-COBI-VEM arm: 13% in the ATEZO-COBI-VEM arm due to adverse events versus 16% in the PBO-COBI-VEM arm.

D. As of January 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for cutaneous melanoma has included cobimetinib (Cotellic) in combination with vemurafenib (Zelboraf) as first-line therapy (Category 1) or subsequent systemic therapy (Category 2A) for metastatic or unresectable disease. Additionally, triple therapy of atezolizumab (Tecentriq) in combination with cobimetinib (Cotellic) and vemurafenib (Zelboraf) were included as first-line therapy with a Category 2A recommendation.

II. **Histiocytic Neoplasms**

A. Histiocytic neoplasms are a heterogeneous group of clonal hematopoietic disorders thought to be derived from mononuclear phagocytic cells (macrophages and dendritic cells) or histiocytes. The Histiocyte Society's classification divides histiocytic disorders into five categories, based on clinical, histologic, immunophenotypic, and molecular features. Its Langerhans group includes LCH, Erdheim-Chester disease (ECD), mixed LCH/ECD, indeterminate cell histiocytosis, and extracutaneous juvenile xanthogranuloma.

B. Histiocytic neoplasms are heterogeneous, and presentation varies from localized and mild to disseminated and lethal. Initial presentation is often nonspecific but is marked by diverse mutations in the mitogen-activated protein kinase (MAPK) pathway. ERK dependence has been hypothesized to be a consistent feature across the group.
C. The evidence supporting the management of histiocytic neoplasms in adults is largely based on small retrospective studies, case series, and case reports, due to the rarity of prospective studies in adults. In addition, some of the diagnostic and treatment recommendations for adults with histiocytic neoplasms are, of necessity, extrapolated from prospective studies in children and young adults, except when stated otherwise. NCCN guidelines focus recommendations onto three of the histiocytic neoplasms: LCH, ECD, and RDD.
D. Current treatment options for LCH, ECD, and other histiocytic neoplasms include targeted therapies (BRAF: vemurafenib, PIK3CA/ALK/MAP2K1/etc: cobimetinib, trametinib, dabrafenib, ALK inhibitors), interferon alfa, glucocorticoids, methotrexate, mTOR inhibitors, systemic chemotherapy, and clinical trials. NCCN guidelines recommend first or subsequent-line therapy with vemurafenib (BRAF V600 mutation), cobimetinib (MAPK mutation or no mutation) or treatments irrespective of mutation cladribine, cytarabine (non-ECD histiocytic neoplasms), interferon alpha (ECD); other recommended regimens target identified mutations.
E. Cobimetinib (Cotellic) is FDA approved as a single agent for the treatment of adult patients with histiocytic neoplasms. Cobimetinib (Cotellic) was studied in a phase 2, single arm, open-label trial of patients with histologically confirmed histiocytic disorders. Participants (n=26) included those diagnosed with Langerhans Cell Histiocytosis (n=4), Rosai-Dorfman Disease (n=4), Erdheim-Chester Disease (n=13), Xanthogranuloma (n=2) and Mixed Histiocytosis (n=3). Of the 26 participants 6 were BRAF V600 mutant positive and 20 were BRAF V600 wild type. Those with documented BRAF V600E mutations were enrolled if they were unable to access a BRAF inhibitor or if they discontinued a BRAF inhibitor due to toxicity. Additionally, those BRAF mutated patients had to have subsequent testing to assess for amenable mutations. Other baseline characteristics included: median age 50.5 years (range, 18 to 79 years), male (65%), White (85%), Black or African American (8%), and Asian (4%). Those with prior history of therapy with MEK inhibitors [i.e, binimetinib (Mektovi), selumetinib (Koselugo), or trametinib (Mekinist)] were excluded. The primary endpoint was overall response rate (measured via PET response), which was obtained in 76.9% of participants (95% CI 56.4 – 91). The overall level of evidence is considered low given the lack of a comparator arm and overall survival data; however, given the limited options in this disease state, allowance for coverage has been outlined in the criteria section above.
F. Vemurafenib (Zelboraf) was studied in one single-arm, open-label, and multiple cohort basket trial of patients with non-melanoma BRAF V600 mutation-positive disease (n=26), including 22 patients with ECD and four with Langerhans Cell Histiocytosis, a similar but distinctly different type of histiocytic neoplasm. Population characteristics were as follows: median age 58.5 years (range 34-77 years), 55% male, 68% previous systemic therapy. Primary endpoint was overall response rate, which was obtained in 54% of participants (95% CI 32.2 – 75.6). Given the study design, and the inability to

distinguish between the effect of vemurafenib (Zelboraf) and the natural history of ECD, the evidence is considered low quality; however, given the limited options in this disease state, allowance for coverage has been outlined in the criteria section above.

G. Combination therapy with cobimetinib (Cotellic) and vemurafenib (Zelboraf) has not been evaluated for use in histiocytic neoplasms.

Investigational or Not Medically Necessary Uses

I. Cobimetinib (Cotellic) has not been sufficiently evaluated outside of unresectable or metastatic melanoma and histiocytic neoplasms. Limited evidence is available consisting of early phase studies evaluating use in other cancers; however, safety and efficacy have not been established in these conditions:
   A. Wild-type BRAF melanoma
   B. Melanoma in the neoadjuvant setting
   C. Breast cancer, solid tumors, colorectal cancer, thyroid cancer, central nervous system cancer, follicular/papillary cancer and non-small cell lung cancer (NSCLC) with/without BRAF V600E mutation
   D. Hairy cell leukemia
   E. Cotellic in combination with Zelboraf for histiocytic neoplasms

References

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3. Zelboraf [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated May 2020. Accessed June 2022.
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9. Diamond EL, Durham BH, Ulaner GA, et al. Efficacy of MEK inhibition in patients with histiocytic neoplasms. Nature. 2019;567(7749):521-524.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
trametinib (Mekinist®), dabrafenib (Tafinlar®)	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy
	Melanoma, BRAF V600E or K mutated, adjuvant therapy for malignant disease as combination therapy and for malignant unresectable or metastatic disease as monotherapy in treatment-naïve patients
	Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy
encorafenib (Braftovi®), binimetinib (Mektovi®)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy
	Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy
selumetinib (Koselugo™)	Neurofibromatosis type 1 (NF1)

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication for cobimetinib (Cotellic) in histiocytic neoplasms with supporting evidence. Combined initial criteria and renewal criteria sections to include ECD under histiocyctic neoplasms. Updated E/I section to disallow combination use of cobimetinib (Cotellic) and vemurafenib (Zelboraf) for histiocytic neoplasms. Removed RDD and LCH from E/I. Updated related policies criteria to include selumetinib (Koselugo).	06/2023
Revised initial and renewal criteria to align standard verbiage/formatting. Removed requirement for oncologist prescriber/consultation in renewal criteria. Updated supporting evidence for Erdheim-Chester disease. Added cobimetinib (Cotellic) monotherapy or combination with vemurafenib (Zelboraf) for ECD to E/I section with supporting evidence. Added Related Policies table.	06/2022
Cobimetinib (Cotellic) criteria transitioned to policy format. Consolidated cobimetinib (Cotellic) and vemurafenib (Zelboraf) criteria. Addition of E/I and supporting evidence section. Updated length of initial approval from three to six months. Addition of the following to initial criteria: age requirement (18+yrs); not to be used in combination with any other oncology therapy unless outlined in criteria; disease is unresectable/locally advanced (Stage IIIC) or metastatic (Stage IV); provider attestation to all the following: member has not previously received systemic anti-cancer therapy for melanoma (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy), or if previously received immunotherapy, treatment was for use in the adjuvant setting only; additional combination agent option (atezolizumab [Tecentriq] and vemurafenib [Zelboraf]). Addition of the following to renewal criteria: member has received a previous prior authorization approval for this agent through this health; not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; medication prescribed by, or in consultation with, an oncologist; not to be used in combination with any other oncology therapy unless outlined in criteria. In consolidation, removed verbiage requiring BRAF V600E mutation "by an FDA-approved test" from vemurafenib (Zelboraf) criteria. Updated QL for vemurafenib (Zelboraf) to align with cobimetinib (Cotellic), from 240 tablets per 30 days to 224 tablets per 28 days.	01/2021
Policy created	02/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP286

Description

Colchicine (Lodoco) is an orally administered alkaloid. The mechanism of action of colchicine (Lodoco) in prevention of major cardiovascular events is not well understood at this time.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
colchicine (Lodoco)	Cardiovascular risk reduction in patients with established atherosclerotic cardiovascular disease (ASCVD) or with multiple risk factors for cardiovascular disease	0.5mg tablet	30 tablets/30 days

Initial Evaluation

I. **Colchicine (Lodoco)** may be considered medically necessary when the following criteria are met:
   A. Member is 35 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a provider specializing in heart disease (i.e., cardiology, lipidology); **AND**
   C. A diagnosis of **established Atherosclerotic Cardiovascular Disease (ASCVD)** when the following are met:
      1. Diagnosis is confirmed by one of the following:
         i. Primary prevention failure (e.g., member has had a stroke, myocardial infarction, percutaneous coronary intervention [PCI], etc.); **OR**
         ii. Evidence of clinical atherosclerotic disease on invasive or non-invasive testing (e.g., coronary angiography, CT angiography, etc.); **AND**
      2. Blood pressure is controlled and stable on current antihypertensive therapy; **AND**
      3. Provider attestation that member does not have any of the following comorbidities:
         i. Renal failure (i.e., CrCl <15 mL/min)
         ii. Severe liver impairment
         iii. Pre-existing blood dyscrasias
         iv. Concurrent use of strong CYP3A4 or P-gp inhibitors; **AND**
      4. Member will continue background therapy with maximally tolerated statin (e.g., atorvastatin, rosuvastatin, simvastatin, etc.); **OR**

i. If statin intolerant, member will continue background therapy with maximally tolerated non-statin lipid-lowering agents (e.g., ezetimibe, Repatha, Praluent, fenofibric acid, etc.) unless contraindicated or not tolerated; **AND**

5. Treatment with colchicine 0.6mg (Colcrys) has been ineffective, contraindicated, or not tolerated

II. Colchicine (Lodoco) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Gout
   B. Familial Mediterranean fever

III. Colchicine (Lodoco) is considered investigational when used for all other conditions, including but not limited to:
   A. Actinic Keratosis
   B. Amyloidosis
   C. Behcet's syndrome
   D. Pericarditis, acute or recurrent
   E. Post-pericardiotomy syndrome

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has not experienced a major cardiovascular event (e.g., stroke, myocardial infarction); **OR**
   - If member has experienced a major cardiovascular event, the provider attests continuation of therapy is medically necessary AND clinical rationale of medical necessity has been provided and reviewed by a Moda Health clinician; **AND**

IV. Member will continue background therapy with maximally tolerated statin (e.g., atorvastatin, rosuvastatin, simvastatin, etc.); **OR**
   - If statin intolerant, member will continue background therapy with maximally tolerated non-statin lipid-lowering agents (e.g., ezetimibe, Repatha, Praluent, fenofibric acid, etc.) unless contraindicated or not tolerated; **AND**

V. Treatment with colchicine 0.6mg (Colcrys) has been ineffective, contraindicated, or not tolerated

Supporting Evidence

I. Colchicine (Lodoco) 0.5mg tablets was evaluated in one pivotal phase 3, randomized, double-blind, placebo-controlled trial (LoDoCo2) to evaluate the safety and efficacy in patients with chronic coronary artery disease in 5,522 adult patients aged 35 to 82 years old. The primary

composite endpoint of time to first cardiovascular (CV) death, spontaneous (non-procedural) myocardial infarction (MI), ischemic stroke, or ischemia-driven coronary revascularization was statistically significant compared to placebo, with an incidence rate per 100 person-years of 2.5 and 3.6 events, respectively [(hazard ratio, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P<0.001)]. The key secondary endpoint of composite of CV death, spontaneous MI, or ischemic stroke was also met, with incidence rates of 1.5 and 2.1 events per 100 person-years in the colchicine and placebo groups, respectively [hazard ratio, 0.72; 95% CI, 0.57 to 0.92; P = 0.007)].

II. The most commonly adverse event reported during the LoDoCo2 clinical trial was myalgia, which occurred in 21.2% of colchicine (Lodoco) treated patients and 18.5% of patients in the placebo group. Colchicine (Lodoco) also carries labeled contraindications for use in patients with renal failure (e.g., CrCl <15 mL/min), severe hepatic impairment, and pre-existing blood dyscrasias due to higher risk of toxicity in this population.

III. Insight from cardiology specialists indicate that diagnosis of clinical ASCVD in the absence of a cardiovascular event can be achieved by angiography, ischemia on stress test, or stenosis of 50% or more using other imaging techniques. The inclusion trial for the LoDoCo2 clinical trial also included patients who had proven coronary disease by a Coronary Artery Calcium score ≥400; Although coronary calcium scores are not typically used as a diagnostic tool for ASCVD, this could be accepted as a verification of ASCVD based on the population colchicine (Lodoco) was studied in.

IV. Emerging data has shown that inflammation, in addition to hyperlipidemia, contributes to the risk of future atherothrombotic events. A collaborative analysis of three randomized trials observed that inflammation of high-sensitivity C-reactive protein (CRP) was a stronger predictor for risk of future CV events and death than cholesterol assessed by low-density lipoprotein cholesterol (LDL-C). The 2021 ESC guidelines for secondary prevention of CV events indicates that colchicine is an appropriate therapy to consider in patients with established ASCVD (secondary prevention) who remain at very high risk of future CV events, particularly if other risk factors are insufficiently controlled or if recurrent CV events occur under optimal therapy (i.e., controlled blood pressure, controlled hyperlipidemia, etc.). Guidelines indicate that statins continue to provide the strongest level LDLC reduction and protection against CV events; however, in those who do not tolerate statin therapy, use of other anti-hyperlipidemic therapy is appropriate to reduce LDL.

V. Although colchicine 0.6mg tablet has not specifically been studied in the setting of CV prevention, this is likely due to the lack of availability of this formulation in the geography of the clinical trial (i.e., Europe). There is no anticipated clinically meaningful difference in the effect of colchicine 0.5mg (Lodoco) compared to 0.6mg; therefore, the off-label use of colchicine 0.6mg tablets is required as cost-effective step therapy.

Investigational or Not Medically Necessary Uses

I. Colchicine (Lodoco) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Gout
      i. Colchicine 0.6mg (Colcrys) is currently FDA-approved for the treatment of gout. Although there is no anticipated clinically meaningful difference in the effect of

colchicine 0.5mg (Lodoco) compared to 0.6mg, therapies are only considered medically necessary when prescription drug or prescription drug dose recommended for this condition is cost-effective compared to alternative interventions, including no intervention. Since colchicine 0.6mg tablets are considered a cost-effective therapy, use of colchicine 0.5mg (Lodoco) is considered not medically necessary for this indication.

B. Familial Mediterranean fever
    i. Colchicine 0.6mg (Colcrys) is currently FDA-approved for the treatment of familial mediterranean fever. Although there is no anticipated clinically meaningful difference in the effect of colchicine 0.5mg (Lodoco) compared to 0.6mg, therapies are only considered medically necessary when prescription drug or prescription drug dose recommended for this condition is cost-effective compared to alternative interventions, including no intervention. Since colchicine 0.6mg tablets are considered a cost-effective therapy, use of colchicine 0.5mg (Lodoco) is considered not medically necessary for this indication.
C. Actinic Keratosis
D. Amyloidosis
E. Behcet's syndrome
F. Pericarditis, acute or recurrent
G. Post-pericardiotomy syndrome

Appendix

I. Table 1: Examples of CYP3A4 and P-gp inhibitors

Strong CYP3A4 inhibitors	Atazanavir
	Clarithromycin
	Darunavir/ritonavir
	Indinavir
	Itraconazole
	Ketoconazole
	Lopinavir/ritonavir
	Nefazodone
	Nelfinavir
	Ritonavir
	Saquinavir
	Telithromycin
	Tipranavir/ritonavir
Moderate CYP3A4 inhibitors	Amprenavir
	Aprepitant
	Diltiazem
	Erythromycin
	Fluconazole
	Fosamprenavir (prodrug of amprenavir)
	Verapamil

P-gp inhibitors	Cyclosporine
	Ranolazine

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Related Policies

Policy Name	Disease state
Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitor Policy	Atherosclerotic cardiovascular disease (ASCVD)
Bempedoic acid, bempedoic acid/ezetimibe (Nexletol™, Nexlizet™)	As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with established atherosclerotic cardiovascular disease who require additional lowering of LDL-C

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	09/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP107

Description
Continuous Glucose Monitors (CGMs) are blood glucose monitoring systems used to manage patients with diabetes mellitus that are insulin dependent.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
Dexcom G6	Diabetes Mellitus	System meter	1 meter per 365 days
		Transmitter	1 transmitter per 90 days
		Sensors	3 sensors (1 kit) per 30 days
Dexcom G7		System meter	1 meter per 365 days
		Sensors	3 sensors (1 kit) per 30 days
Freestyle Libre		Reader	1 reader per 365 days
		Sensor (14 day)	2 sensors per 28 days
Medtronic Guardian CGM		Transmitter	1 transmitter per 365 days
		Sensor	5 sensors per 30 days
Eversense CGM system		Transmitter	1 transmitter per 365 days
		Sensor	1 sensor per 90 days

Initial Evaluation

I. **Dexcom** and **Freestyle Libre CGM products** may be considered medically necessary when the following criteria are met:
   A. Member is less than 19 years of age; **OR**
   B. Member is 20 years of age or older with diagnosis of one of the following:
      1. **Type I Diabetes**; **OR**
      2. **Type II Diabetes; AND**
         i. Unable to achieve A1c goal despite adherence to an appropriate glycemic management plan; **AND**
            a. Member is currently on intensive insulin therapy; **AND**
            b. Member is testing glucose more than 4 times per day; **OR**
         ii. Experiencing one or more severe (blood glucose < 50 mg/dl or symptomatic) episodes of hypoglycemia despite adherence to an appropriate glycemic management plan (e.g. frequent adjustments in medication regimen; testing blood glucose 4 or more times per day); **OR**
         iii. Unable to recognize, or communicate, symptoms of hypoglycemia; **OR**
      3. **Diabetes in pregnancy**; **AND**
         i. Type II Diabetes with use of insulin prior to pregnancy; **OR**

ii. Type II or gestational diabetes requiring insulin therapy during pregnancy due to uncontrolled blood glucose (e.g HbA1c above target, hyperglycemic or hypoglycemic episodes).

II. **All other CGM products (e.g. Medtronic, Eversense, etc.)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) are met; **AND**
   B. Use of Dexcom AND Freestyle Libre products have been ineffective, not tolerated, or not indicated; **OR**
   C. Member uses an insulin pump not compatible with preferred Dexcom or Freestyle Libre CGM products (e.g Medtronic MiniMed).

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [i.e., HbA1c within target, improved hypoglycemic awareness, or decreased hypoglycemic episodes].

Supporting Evidence

I. In a study conducted by the Effective Health Care Program of the US Agency for Healthcare Research and Quality, where they conducted comparative effectiveness research assessing glucose monitoring (GM) methods and intensive insulin therapy methods, noted a lower A1c by 0.3% in patients who used CGM compared to conventional blood glucose monitoring (BGM). Although this method of glucose monitoring did not affect patient quality of life overall, the positive outcome of a lowered A1c was consistent in patients <18 years of age, thereby supporting the recommendation for CGM in adolescent patients and children.
II. The 2016, the American Association of Clinical Endocrinologists and American College of Endocrinology glucose monitoring consensus recommends the use of a CGM in adults with Type 1 diabetes. In adults with type 2 diabetes, the consensus recommends a structured blood glucose management (BGM) in patients receiving insulin, sulfonylureas, or glinides (prandial glucose regulators) , the consensus does not have a recommendation for the use of CGM in these patients but note that data for a CGM in patients with type 2 diabetes is limited.
III. The American Diabetes Associated International Consensus on Use of Continuous Glucose Monitoring recommended a CGM system to patients with type 1 diabetes and patients with type 2 diabetes treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia.
IV. In a randomized controlled trial (CONCEPTT) of CGM systems in addition to standard care on pregnant women with type 1 diabetes, the value of CGM in pregnancy was demonstrated by showing a mild improvement in A1c without an increase in hypoglycemia and reductions in large-for-gestational-age births, length of stay, and neonatal hypoglycemia.

V. According to Dexcom, the G6 system is compatible with the t:slim X2™ Insulin Pump and Omnipod®.
Minimed™ offers 2 insulin pump systems that are compatible with select CGMs. The Minimed™ 770G System which can be used with Medtronic products (e.g. reservoir, infusion sets, Guardian™ Link 3 Transmitter, Guardian™ Sensor 3) and Accu-Chek® Guide Link Blood Glucose Meter. On the other hand, the Minimed™ 630G insulin pump is only compatible with the Contour® NEXT LINK 2.4 meter.

VI. The UMP Policy for Continuous Glucose Monitoring systems aligns with the Washington Health Care Authority (HCA) Health Technology Clinical Committee (HTCC) policy. The determinations of the HTCC are required to be followed by state purchased health care programs including Uniform Medical Plan. Glucose monitoring | Washington State Health Care Authority

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7. Eversense CGM system website. Accessed June 11, 2021. https://www.eversensediabetes.com/
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Policy Implementation/Update:

Action and Summary of Changes	Date
Update to Medtronic sensor QL from 5 sensors in 35 days to 5/30	10/2023
Added requirement that member must test 4x/day and have intensive insulin therapy to qualify for CGM use	07/2023
Added Medtronic Gaurdian 4 to the policy	06/2023
Effective 04/01/2023: Added Dexcom G7 CGM system to policy	03/2023
Updated language to better capture intent; updated non-preferred criteria to be more encompassing to all non-formulary products	08/2022
Added Eversense CGM system to policy under non-preferred status	07/2021
Policy created	12/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP268

Description

Pasireotide diaspartate (Signifor) is a subcutaneous somatostatin analog solution that exerts its activity by binding to somatostatin receptors causing adrenocorticotropic hormone (ACTH) secretion to be inhibited thereby leading to decreased cortisol secretion.

Osilodrostat (Isturisa) is an orally administered cortisol synthesis inhibitor. It inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland.

Levoketoconazole (Recorlev), the 2S,4R enantiomer of ketoconazole, is an orally administered steroidogenesis inhibitor that reduces endogenous cortisol levels.

Mifepristone (Korlym) is a cortisol receptor blocker indicated for hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pasireotide diaspartate (Signifor®)	Cushing's Disease	0.3 mg/mL ampule	60 ampules/30 days
		0.6 mg/mL ampule	
		0.9 mg/mL ampule	
osilodrostat (Isturisa®)		1 mg tablets	180 tablets/30 days
		5 mg tablets	
		10 mg tablets	
levoketoconazole (Recorlev®)	Cushing's Syndrome	150 mg tablets	240 tablets/30 days
mifepristone (Korlym®)	Hyperglycemia secondary to hypercortisolism in Cushing's syndrome	300 mg tablets	120 tablets/30 days (not to exceed 20 mg/kg/day)
Provider Administered Agents*			
pasireotide pamoate (Signifor LAR®)	Acromegaly, Cushing's disease	10 mg vial	1 vial/28 days
		20 mg vial	
		30 mg vial	
		40 mg vial	
		60 mg vial	

**Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit*

Initial Evaluation

I. **Pasireotide diaspartate (Signifor) and osilodrostat (Isturisa)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. Will not be used in combination with other agents listed in this policy (e.g., pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and/or mifepristone (Korlym)); **AND**
   D. A diagnosis of **Cushing's disease** when the following are met:
      1. Member had inadequate response to pituitary surgical resection; **OR**
         i. Member is not a candidate for pituitary surgery; **AND**
      2. Treatment with TWO of the following has been ineffective, not tolerated, or all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
         i. Ketoconazole; **OR**
         ii. Cabergoline (Dostinex); **OR**
         iii. Metyrapone (Metopirone)*; **OR**
         iv. Mitotane (Lysodren); **AND**
      3. The request is for pasireotide diaspartate (Signifor); **OR**
      4. The request is for osilodrostat (Isturisa); **AND**
         i. Treatment with pasireotide diaspartate (Signifor) has been ineffective, contraindicated, or not tolerated

II. **Levoketoconazole (Recorlev)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. Levoketoconazole (Recorlev) will not be used in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or mifepristone (Korlym); **AND**
   D. A diagnosis of **Cushing's syndrome** when the following are met:
      1. Member had inadequate response to pituitary surgical resection; **OR**
         i. Member is not a candidate for pituitary surgery; **AND**
      2. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of oral ketoconazole; **OR**
         i. Documentation of serious adverse effect or allergy with oral ketoconazole; **AND**
      3. Treatment with ALL of the following has been ineffective, not tolerated, or all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
         i. Cabergoline (Dostinex); **AND**
         ii. Metyrapone (Metopirone)*; **AND**
         iii. Mitotane (Lysodren); **AND**
         iv. Pasireotide diaspartate (Signifor)*

III. **Mifepristone (Korlym)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. Mifepristone (Korlym) will not be used in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or levoketoconazole (Recorlev); **AND**
   D. A diagnosis of **hyperglycemia secondary to hypercortisolism in members with endogenous Cushing's syndrome** when the following are met:
      1. Member had inadequate response to pituitary surgical resection; **OR**
         i. Member is not a candidate for pituitary surgery; **AND**
      2. Member has a diagnosis of type 2 diabetes OR glucose intolerance; **AND**
         i. Baseline hemoglobin A1c (HbA1c) has been provided in this request; **AND**
      3. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of generic oral mifepristone tablets; **OR**
         i. Documentation of serious adverse effect or allergy with generic oral mifepristone; **AND**
      4. Treatment with ALL of the following has been ineffective, not tolerated, or all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
         i. Ketoconazole; **AND**
         ii. Cabergoline (Dostinex); **AND**
         iii. Metyrapone (Metopirone)*; **AND**
         iv. Mitotane (Lysodren); **AND**
         v. Pasireotide diaspartate (Signifor)*

IV. Pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), mifepristone (Korlym) are considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. Hypertension associated with Cushing's syndrome
   B. Termination of pregnancy
   C. Induction of labor
   D. Treatment of fungal infections

V. Pasireotide diaspartate (Signifor), Osilodrostat (Isturisa), levoketoconazole (Recorlev), mifepristone (Korlym) are considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Use in combination with other agents used for Cushing's syndrome
   B. Exogenous (Iatrogenic) Cushing's syndrome
   C. Acromegaly
   D. Pancreatic fistula, postoperative/prophylaxis
   E. Carcinoid syndrome
   F. Neuroendocrine tumor

G. VIPoma
H. Hyperglycemia secondary to Type 2 diabetes (not associated with endogenous Cushing's Syndrome)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication requested will not be used in combination with other agents listed in this policy (e.g., pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and/or mifepristone (Korlym)); **AND**
IV. The request is for one of the following:
    A. **Pasireotide diaspartate (Signifor)**; **AND**
        1. Member has exhibited improvement or stability of disease symptoms (e.g. cortisol level has decreased from baseline); **OR**
    B. **Osilodrostat (Isturisa); AND**
        1. Member has exhibited improvement or stability of disease symptoms (e.g. cortisol level has decreased from baseline); **OR**
    C. **Levoketoconazole (Recorlev); AND**
        1. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of oral ketoconazole; **OR**
            i. Documentation of serious adverse effect or allergy with oral ketoconazole; **AND**
        2. Member has exhibited improvement or stability of cortisol levels and disease symptoms (e.g., improvement in cushingoid appearance, acne, hirsutism, psychiatric symptoms, body weight); **OR**
    D. **Mifepristone (Korlym); AND**
        1. Documentation cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of generic oral mifepristone tablets; **OR**
            i. Documentation of serious adverse effect or allergy with generic oral mifepristone; **AND**
        2. Member experienced a reduction in HbA1c from baseline; **AND**
        3. Member has exhibited improvement in Cushing's syndrome symptoms (e.g., cushingoid appearance, acne, hirsutism, psychiatric symptoms, and excess total body weight).

Supporting Evidence

I. Cushing's disease is a disorder that leads to excess cortisol (hypercortisolemia) and is usually due to a corticotropin (ACTH)-producing pituitary (Cushing's disease). In Cushing's syndrome, ACTH levels are not always elevated, and symptoms of high cortisol can be caused by

corticosteroid or an adrenal tumor. Diagnosis and management of Cushing's syndrome is complex and requires confirmatory tests (e.g., urinary free cortisol (UFC), salivary cortisol) as well as close monitoring by, or in consultation with, an endocrinologist.

II. Cushing's disease and Cushing's syndrome are caused by pathological hypercortisolism that includes demonstrable clinical features. Hallmark symptoms of high levels of cortisol include clinical features such as weight gain, hypertension, high blood glucose, and depression. The goals of treatment are to eliminate its primary cause and achieve remission so as to eliminate the associated signs, symptoms, and comorbidities and to improve quality of life (QOL).

III. According to the Endocrine Society Clinical Practice Guidelines and Pituitary Society Consensus Guidelines for Cushing's disease, first line treatment for excess cortisol production due to Cushing's syndrome is transsphenoidal surgery (TSS) regardless of the cause. Although surgical treatment is optimal with a success rate of 80-85%, second-line medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Repeat TSS is indicated in patients with recurrent Cushing's syndrome symptoms and have evidence of residual visible tumor on MRI. There is low quality evidence recommending systemic therapy to treat Cushing's syndrome in the pre-operative setting. Pre-operative therapy with systemic treatment or targeted radiation may be considered for patients with aggressive Cushing's syndrome, defined as those with life-threatening severe clinical features to rapidly reduce or stabilize cortisol levels.

IV. Systemic therapy options for Cushing's consist of steroidogenesis inhibitors (i.e., ketoconazole, metyrapone, mitotane, osilodrostat, etomidate), pituitary-directed agents (i.e., cabergoline, pasireotide), and glucocorticoid antagonists (i.e., mifepristone). Only levoketoconazole (Recorlev), osilodrostat (Isturisa), and pasireotide (Signifor) are FDA-approved to treat Cushing's in patients which pituitary surgery is not an option or has not been curative. Ketoconazole, metyrapone, mitotane, etomidate, and cabergoline are used off-label.

V. Guidelines recommend steroidogenesis inhibitors (i.e., ketoconazole, osilodrostat, metyrapone, etomidate) as first-line pharmacologic therapy following non-curative surgery or in patients for whom surgery was not an option. Among these therapies, ketoconazole is strongly recommended due to ease of dose titration and availability. Efficacy of ketoconazole in Cushing's syndrome is based on several retrospective trials that report UFC normalization in 45-50% of patients. IV anesthetic, etomidate, has a rapid onset of action, but use is limited to acute treatment of severe hypercortisolism due to Cushing's syndrome. Second-line systemic therapies may include any of the remaining agents (i.e., pituitary-directed agents, glucocorticoid antagonists, etc.) as treatment selection is individualized based on severity of disease, clinical manifestations, cost, drug accessibility, and safety profile. As of February 2023, guidelines have not been updated with regard to place in therapy for osilodrostat (Isturisa) or levoketoconazole (Recorlev) for the treatment of Cushing's syndrome.

VI. Guidelines do not specify a preferred treatment algorithm, nor do they indicate that treatment failure to one agent precludes treatment with another agent in the same class. The Pituitary Society guidelines recommend switching therapies when cortisol levels remain elevated despite treatment on maximum tolerated dose for 2-3 months.

VII. There is a lack of head-to-head trials showing superior safety or efficacy comparing levoketoconazole to ketoconazole, cabergoline (Dostinex), metyrapone (Metopirone), mitotane (Lysodren), or pasireotide diaspartate (Signifor). Given the known safety, established efficacy,

and cost-effectiveness of these therapies, pasireotide diaspartate (Signifor) remains the preferred specialty agent by this plan due to efficacy, safety, and cost. Osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) are significantly more costly than pasireotide diaspartate (Signifor), despite not having any evidence of improved clinical efficacy or safety.

VIII. The safety and efficacy of pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) has been studied in patients 18 years of age or older, and there is no published data to support its use in pediatric patients.

IX. The efficacy of pasireotide was demonstrated in a 12-month, randomized, Phase III study. The study looked at 162 patients with Cushing's disease with persistent or recurrent disease despite pituitary surgery or new patients whom surgery was not indicated or who had had refused surgery. Cushing's disease was defined by a mean 24-hour urinary free cortisol (UFC) level of at least 1.5 times the upper limit of the normal range (ULN). Patients enrolled were randomized to receive pasireotide at 0.6 mg twice daily (n = 82) or 0.9 mg twice daily (n = 80). Three months after randomization patients were reassessed for efficacy, which was defined as having a 24-hour UFC ≤2.0 ULN or equal to their baseline values. If they were considered responders they were continued at their randomized dose until month six. If the patient did not fall into those responder parameters the patient and provider were unblinded and their dose was increased by 0.3 mg bid. At month six all the patients were transferred into the open label portion of the study, where their dose of pasireotide could be increased (to a max of 1200 mg bid) to achieve UFC under the upper limit of the normal range. At this time doses could also be decreased if needed for adverse events.

- The primary outcome was the proportion of patients who achieved normalization of mean 24-hour UFC levels (UFC ≤ULN) after 6 months of treatment without a dose increase of pasireotide. Secondary outcomes included signs and symptoms of Cushing's disease including morning cortisol levels, blood pressure, LDL and weight changes (please review study for others).
- Results showed after 6 months, 15% (12 patients) and 26% (21 patients) of patients in the 0.6 mg and 0.9 mg groups respectively reached the primary endpoint (normalization of mean 24-hour urinary free cortisol UFC levels). Secondary outcomes also showed statistically significant changes including: diastolic blood pressure: −3.7 mm Hg P=0.03, LDL cholesterol: −15 mg/deciliter P<0.001 and weight: −6.7 kg P<0.001.
- The open label portion of the study showed continuing benefits with 13% of patients in the 0.6 mg group and 25% of those in the 0.9 mg group had urinary free cortisol levels at or below the upper limit of the normal range at month 12.

X. The safety and efficacy of osilodrostat (Isturisa) was assessed in one 48-week, prospective, multicenter, open-label, phase III trial with a double-blind, placebo-controlled, randomized withdrawal period in 137 patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative. The trial included patients who were previously treated (87.6% had previous pituitary surgery and 74.5% had previous medical therapy for Cushing's disease, including ketoconazole, metyrapone, cabergoline, and pasireotide (Signifor/Signifor LAR).

- The primary efficacy outcome was the proportion of patients maintaining complete response a mean urinary free cortisol (mUFC) ≤ upper limit of normal (ULN) without

a dose increase during the randomized withdrawal period at week 34. At the time of the randomization (Week 26) all (100%) randomized patients were biochemically controlled (mUFC ≤ ULN).

- At the end of the 8-week randomized withdrawal period (Week 34 of study), the complete response rate in the osilodrostat (Isturisa) group dropped to 86.1% but was higher than that in the placebo group (29.4%).
- About 53% of patients met the key secondary endpoint, the proportion of patients with mUFC≤ULN at week 24 (end of open-label osilodrostat treatment period 2) without dose-up titration weeks 13-24.
- Most common adverse reactions (incidence >20%) were adrenal insufficiency, fatigue, nausea, headache, and edema.
- Although osilodrostat (Isturisa) showed a statistically significant improvement in the control of the cortisol levels, clinical significance, durability of response, meaningfulness of these results are unknown and the quality of evidence is low.

XI. Ketoconazole is a racemic mixture of two enantiomers, one of which is levoketoconazole. Levoketoconazole (Recorlev) is the pure (2S, 4R) enantiomer and is FDA approved for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom pituitary surgery is not an option or has not been curative.

XII. Levoketoconazole (Recorlev) has not been evaluated against ketoconazole for the treatment of hypercortisolemia in patients with Cushing's syndrome, therefore comparative safety and efficacy remain uncertain. However, the chemical entity in ketoconazole is the same as levoketoconazole (Recorlev); therefore, both products are expected to produce a similar efficacy and safety profile for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome, even in the absence of an FDA-labeled indication for ketoconazole. Furthermore, medical necessity for levoketoconazole (Recorlev) is limited to members that have a documented serious intolerance (e.g., allergy reaction, serious adverse event, life-threatening reaction that required hospitalization) or treatment failure with generic oral ketoconazole. If a member has a contraindication to ketoconazole, it is presumed that treatment with levoketoconazole would also be contraindicated, given similar warnings and side effect profile.

XIII. Levoketoconazole (Recorlev) has been studied in two phase 3 studies for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom pituitary surgery is not an option or has not been curative.

- The SONICS trial was a 6-month open-label, single arm, dose-titration study (n=95) with a 21-week run-in period; patients who did not achieve a stable therapeutic dose during this dose titration phase did not continue in the study. The primary efficacy endpoint was the proportion of patients with normalized mean urinary free cortisol (mUFC) response of at the end of a 6-month maintenance phase without a dose increase. About 30% of patients on levoketoconazole achieved a normalized mUFC (95% CI: 21.7%- 41.2%; p=0.0154) at 6 months. Significant mean improvements in comorbidity biomarkers and clinical signs and symptoms were also seen (glucose metabolism, total cholesterol, LDL, HDL, body weight, and hirsutism (women)). Approximately 15% of patients had at least one treatment-related serious adverse event, which include reversible liver-related adverse events, QT prolongation, and adrenal insufficiency. Routine laboratory assessments showed ALT increases above the ULN in 41% of patients at any time. Notably, 51% of study

participants discontinued therapy with the most common reasons being adverse events and inefficacy.

- The LOGICS trial was 6-month double-blind, randomized, placebo-controlled withdrawal and rescue/restoration study of patients who completed the SONICS trial (n=12) or were treatment-naïve (n=72). A total of 84 patients were enrolled in the study, of whom 44 entered the randomized withdrawal phase and were assigned 1:1 to placebo or levoketoconazole. The primary outcome was the proportion of patients with loss of mUFC response, which was met with a 40% loss of response in the levoketoconazole group compared to 95% of patients in the placebo group (p=0.0002). A secondary endpoint, mUFC normalization, was met with 50% of patients achieving normalized mUFC in the levoketoconazole group compared to 4.5% of patients on placebo (95% CI: 19.2-67.9; P=0.0015). Approximately 48% of patients discontinued the study before the double-blind phase due to treatment related adverse events. Additionally, 95% of patients required rescue therapy due to high mUFC levels during the randomized withdrawal phase.

XIV. Long term safety and efficacy of levoketoconazole has not been established; however, an ongoing trial (OPTIC study) is currently evaluating long-term use of levoketoconazole in patients that have completed the SONICS and LOGICS trials.

XV. The overall quality of evidence for levoketoconazole (Recorlev) is considered low due to open-label study design, lack of an active or meaningful comparator given high volume of concomitant rescue therapy, and high attrition rate. While UFC is a clinically meaningful, objective endpoint correlated with improvement of hypercortisolism in Cushing's syndrome, concerns listed above limit confidence that medication is providing a clinically meaningful benefit over available treatments for Cushing's syndrome. Additionally, levoketoconazole use was associated with serious safety concerns including hepatotoxicity and QT prolongation.

XVI. It is known that patients with Cushing's have various lab abnormalities and may develop type 2 diabetes secondary to elevated cortisol levels. The difference between mifepristone (Korlym) and the other agents for Cushing's is that mifepristone (Korlym) was evaluated for treating hyperglycemia secondary to hypercortisolism in patients with CS who have T2DM. Korlym has not been evaluated to lower cortisol levels, however mifepristone has been used off-label for this; no other drugs approved for CS have such an indication.

XVII. Mifepristone acts as a rapid acting glucocorticoid receptor antagonist. The safety and efficacy of mifepristone (Korlym) for the treatment of endogenous Cushing's syndrome was studied in an uncontrolled, open-label, 24-week, multicenter clinical study that enrolled 50 participants. Those participants exhibited clinical and biochemical evidence of hypercortisolemia despite first-line intervention via surgical treatment and radiotherapy. Per label, the reasons for medical treatment was failed surgery, recurrence of disease, and a poor medical candidate for surgery. The study was split into two cohorts: diabetes and hypertension. The primary efficacy endpoint for the diabetes cohort was a ≥25% reduction from baseline in glucose AUC and was conducted in the modified intent-to-treat population (n=25); 15 of 25 patients (60%) were treatment responders (95% CI: 39%, 78%) and were found to have a mean A1c reduction of 1.1% at 24 weeks. As for the hypertension cohort, there were no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21). Participants in the study showed varying degrees of improvement in Cushing's syndrome manifestations such as cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight.

XVIII. The overall quality of evidence for mifepristone (Korlym) is considered low due to open-label study design, small sample size, lack of an active or meaningful comparator, high attrition rate, and absence of a statistically significant different in the hypertension cohort. While reduction in glucose AUC is a clinically meaningful, objective endpoint correlated with improvement of hypercortisolism in Cushing's syndrome, concerns listed above limit confidence that medication is providing a clinically meaningful benefit over available treatments for Cushing's syndrome. In clinical trials for Signifor, Isturisa, and Recorlev, metabolic lab values, including glucose, were evaluated as secondary outcomes with improvements in glucose lowering, blood pressure, and weight. Close monitoring for severe hypokalemia, clinical signs of adrenal insufficiency, and QT prolongation may limit the use of mifepristone in clinical practice.

XIX. Mifepristone (Korlym) has not been evaluated against generic mifepristone for the treatment of hyperglycemia secondary to hypercortisolism in Cushing's syndrome, therefore comparative safety and efficacy remain uncertain. However, the chemical entity in generic mifepristone tablets is the same as mifepristone (Korlym) therefore, both products are expected to produce a similar efficacy and safety profile for the treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome, even in the absence of an FDA-labeled indication for mifepristone. Documentation of medical necessity for mifepristone (Korlym) is required, as the recommended dose can be obtained with the generic mifepristone, providing a significant price differential (6 – 10x difference). Medical necessity for mifepristone (Korlym) is limited to members that have a documented serious intolerance (e.g., allergy reaction, serious adverse event, life-threatening reaction that required hospitalization) or treatment failure with generic oral mifepristone. If a member has a contraindication to mifepristone, it is presumed that treatment with mifepristone (Korlym) would also be contraindicated, given similar warnings and side effect profile.

Investigational or Not Medically Necessary Uses

I. The agents referenced in this policy have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Exogenous (Iatrogenic) Cushing's syndrome
      i. The treatment of Cushing's syndrome due to exogenous therapy is to stop the glucocorticoid. Safety and efficacy of pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) has only been established for endogenous Cushing's (e.g. ACTH dysregulation caused by tumor, etc), there is currently limited evidence to suggest the use of the agents in this policy in the setting of exogenous (iatrogenic) Cushing's syndrome.
   B. Agents in the policy used in combination
      i. Approved treatments are not to be used in combination with other specialty medications listed in this policy used to treat Cushing's given lack of scientific evidence to safely recommend their use as dual therapy. Sufficient data is not currently available to support the safety and efficacy of pasireotide diaspartate (Signifor), osilodrostat (Isturisa), levoketoconazole (Recorlev), and mifepristone (Korlym) use in combination with other agents listed in these criteria. Osilodrostat (Isturisa) and Pasireotide diaspartate (Signifor) have not been studied in

combination with one another or with agents used for Cushing's syndrome (levoketoconazole (Recorlev) and/or mifepristone (Korlym), etc.). Levoketoconazole (Recorlev) has not been studied in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), or mifepristone (Korlym).

ii. In practice, ketoconazole has been used in combination with metyrapone or osilodrostat to maximize cortisol level lowering when monotherapy has been ineffective; triple therapy (ketoconazole/pasireotide/cabergoline and ketoconazole/metyrapone/mitotane) has also been used in patients with uncontrolled cortisol levels and presence of visible tumor post-resection. However, quality of evidence supporting combination use is low and there are significant safety concerns due to additive toxicity (QT prolongation, hepatotoxicity).

C. Acromegaly
    i. Pasireotide diaspartate (Signifor) subcutaneous syringe does not carry an FDA approval in the setting of acromegaly; however, Pasireotide pamoate (Signifor LAR) product is approved in this setting. Notably, coverage of pasireotide pamoate (Signifor LAR) under the pharmacy benefit is excluded due to provider administration exclusion. Other somatostatin agents used in acromegaly include Sandostatin LAR, Sandostatin, and somatuline.
D. Pancreatic fistula, postoperative; prophylaxis
    i. Limited data evaluating pasireotide diaspartate (Signifor) demonstrated reduction in relative risk only, therefore use of pasireotide diaspartate (Signifor) for prophylaxis or postoperative treatment of pancreatic fistula is considered experimental and investigational.
E. Carcinoid syndrome
    i. Pasireotide diaspartate (Signifor) failed to demonstrate statistically significant benefit for the treatment of carcinoid syndrome. Additionally, use is not recognized by NCCN guidelines, therefore use of pasireotide diaspartate (Signifor) for carcinoid syndrome is considered experimental and investigational.
F. Neuroendocrine tumor (NETS)
    i. Pasireotide diaspartate (Signifor) failed to improve symptom control or tumor response in clinical trials evaluating treatment for NETS. Additionally, use is not recognized by NCCN guidelines, therefore use pasireotide diaspartate (Signifor) for NETs is considered experimental and investigational.
G. Vasoactive intestinal peptide tumors (VIPomas) [pancreatic neuroendocrine (islet cell) tumor, insulinoma, glucagonoma, somatostatinoma, and gastrinoma]
    i. Pasireotide diaspartate (Signifor) failed to improve symptom control or tumor response in clinical trials evaluating treatment for VIPoma. Additionally, use is not recognized by NCCN guidelines, therefore use pasireotide diaspartate (Signifor) for VIPoma is considered experimental and investigational. Appropriate treatment options may include injectable octreotide (e.g. generic octreotide acetate, Sandostatin, Bynfezia Pen).
H. Treatment of fungal infections

i. Safety and efficacy of levoketoconazole (Recorlev) has not been established for treating fungal infections and should not be substituted for ketoconazole when used to treat fungal infections. Additionally, drugs or interventions that a treating licensed health care provider recommends are considered medically necessary if the level of service, intervention, or prescription drug recommended for the condition is cost-effective compared to alternative interventions. Therefore, it is considered not medically necessary.

I. Type 2 diabetes unrelated to endogenous Cushing's Syndrome
    i. Safety and efficacy of mifepristone (Korlym) has only been established for hyperglycemia secondary to hypercortisolism in members with endogenous Cushing's syndrome; therefore, hyperglycemia due to type 2 diabetes alone is considered experimental and investigational.

J. Hypertension associated with Cushing's syndrome
    i. In the SEISMIC clinical trial evaluating mifepristone, the hypertension cohort demonstrated no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21). Therefore, use of mifepristone is considered not medically necessary for any symptoms outside of hyperglycemia (e.g. hypertension, weight loss, cortisol induced-psychosis) related symptoms secondary to hypercortisolism.

K. Termination of pregnancy and induction of labor
    i. Although the active ingredient, mifepristone, at a lower strength is indicated for both termination of pregnancy and induction of labor, mifepristone (Korylm) has not been approved by the FDA or studied in those indications. Therefore, mifepristone (Korylm) is considered not medically necessary.

Appendix

I. Levoketoconazole (Recorlev)
    A. The recommended initial dosing of levoketoconazole is 150 mg twice daily and dosing is titrated by 150 mg daily every 2-3 weeks until an adequate clinical response is achieved based on cortisol levels and patient tolerability. The maximum recommended dosage is 1,200 mg per day in divided doses.
    B. Levoketoconazole (Recorlev) carries black box warning for hepatotoxicity and is contraindicated in patients with cirrhosis, elevated LFT defined as baseline AST or ALT > 3 times the upper limit of normal, acute liver disease or poorly controlled chronic liver disease, extensive metastatic liver disease, or recurrent symptomatic cholelithiasis. Cases of serious hepatoxicity were reported in patients taking levoketoconazole (Recorlev) and therefore treatment with levoketoconazole (Recorlev) is contraindicated in patients with a prior history of drug induced liver injury with ketoconazole or any azole antifungal therapy that required treatment discontinuation (serious and fatal hepatotoxicity have been reported in patients taking oral ketoconazole). Baseline liver function tests should be obtained prior to starting therapy and continuously monitored throughout treatment.
    C. Levoketoconazole (Recorlev) also carries a black box warning for QT prolongation and is contraindicated with other drugs that prolong the QT interval, in patients with a

prolonged QTcF interval of greater than 470 msec at baseline, and in patients with a history of torsade's de pointes, ventricular tachycardia, ventricular fibrillation, or long QT syndrome (including first-degree family history). A baseline electrocardiogram (ECG) function test should be obtained prior to starting therapy.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
octreotide (Sandostatin, Bynfezia Pen, Mycapssa)	Acromegaly
	Metastatic carcinoid tumor
	Vasoactive intestinal peptide tumor (VIPoma)
pegvisomant (Somavert)	Acromegaly

Policy Implementation/Update

Action and Summary of Changes	Date

Created new Cushing's Syndrome Policy, combining Isturisa, Signifor, Recorlev, and Korlym policies: Added criteria to avoid combination Cushing's agent use in initial and renewal. Updated E/I (added VIPoma), supporting evidence, references. Added related policies.
• Isturisa policy
  ○ Removed documentation of baseline UFC level.
• Korlym policy
  ○ Updated from trial of 2 to trial of all generic available agents in Cushing's, including generic mifepristone and trial of Signifor. Require documentation of medical necessity for generic mifepristone in renewal criteria.
	02/2023

Previous reviews
• Pasireotide diaspartate (Signifor)
  ○ Changed criteria regarding previous therapy to require treatment with two agents to have been ineffective, not tolerated, or contraindicated. Updated the example for improvement or stability of disease symptoms
  ○ Removal of UFC 24-hour urinary free cortisol level (UFC). Addition of age requirement and addition of previous trial of ketoconazole, metyrapone, or mitotane.
• Mifepristone (Korlym)
  ○ Changed criteria regarding previous therapy to require treatment with two agents to have been ineffective, not tolerated, or contraindicated. Updated renewal language to reflect new standard language. Updated supporting evidence.
  ○ Transitioned criteria to policy with the following updates: defined surgery in the policy, removed pregnancy question, addition of supporting evidence, and addition of investigational diagnoses along with supporting evidence.
	08/2020
	12/2019
	08/2020
	10/2019

Policy created • Levoketoconazole (Recorlev) • Osilodrostat (Isturisa) • Pasireotide diaspartate (Signifor) • Mifepristone (Korlym)	03/2022 07/2020 07/2013 09/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP050

Split Fill Management* [Applies to abemaciclib (Verzenio) ONLY]

Description

Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) are orally administered cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors, which suppress the activity of CDK 4/6 enzymes in tumor cells leading to the inactivation of certain tumor suppressor genes.

Length of Authorization

- Initial: Six months; (first three months split fill for abemaciclib (Verzenio) only)
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
abemaciclib (Verzenio)	Breast cancer, HER2-negative, HR-positive, advanced or metastatic; early-stage breast cancer	50 mg tablets	56 tablets/28 days
		100 mg tablets	
		150 mg tablets	
		200 mg tablets	
palbociclib (Ibrance)	Breast cancer, HER2-negative, HR-positive, advanced or metastatic	75 mg capsules/tablets	21 capsules or tablets/28 days
		100 mg capsules/tablets	
		125 mg capsules/tablets	
ribociclib (Kisqali)	Breast cancer, HER2-negative, HR-positive, advanced or metastatic	200 mg tablet dose pack	21 tablets/28 days
		400 mg tablet dose pack	42 tablets/28 days
		600 mg tablet dose pack	63 tablets/28 days
ribociclib/letrozole (Kisqali/Femara)		200 mg and 2.5 mg tablet dose pack	49 tablets/28 days
		400 and 2.5 mg tablet dose pack	70 tablets/28 days
		600 and 2.5 mg tablet dose pack	91 tablets/28 days

Initial Evaluation

I. **Abemaciclib (Verzenio), palbociclib (Ibrance), ribociclib (Kisqali), and ribociclib/letrozole (Kisqali/Femara)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Member has <u>not</u> previously progressed on, or after, treatment with another CDK4/6 inhibitor (e.g., ribociclib [Kisqali], abemaciclib [Verzenio]); **AND**

D. Member has a diagnosis of hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer; **AND**

E. The request is for **adjuvant therapy of early-stage (stage I- III) breast cancer (EBC)**; **AND**

1. Provider attests the member has high-risk breast cancer based on one the following:
    - **i.** Histopathological tests showing four or more (≥ 4) axillary lymph nodes are affected (pALN N2 or N3 disease); **OR**
    - ii. Histopathological tests showing one to three axillary lymph nodes are affected (N1 disease), and one of the following:
        a. Tumor size is ≥ 5 cm; **OR**
        b. Histopathological grade 3 disease (G3); **OR**
        c. The member has a Ki-67 score ≥ 20% as determined by an FDA-approved test; **AND**
2. The member has undergone definitive surgical resection of the primary tumor; **AND**
3. The member has received therapy using one of the following treatment modalities:
    - i. Radiotherapy; **OR**
    - ii. Taxane (e.g., docetaxel) and/or anthracycline (e.g., doxorubicin) based chemotherapy; **AND**
4. The request is for abemaciclib (Verzenio); **AND**
    - i. Abemaciclib (Verzenio) will be used in combination with an aromatase inhibitor (e.g., letrozole, anastrozole, exemestane) or tamoxifen; **AND**
    - ii. Will not be used in combination with any additional oncology therapy; **OR**

F. The request is for **systemic therapy of recurrent, advanced, or metastatic breast cancer**; **AND**

1. Member has a diagnosis of advanced (stage III), or metastatic (stage IV) breast cancer; **AND**
2. The medication is being prescribed as a first-line systemic therapy; **AND**
    - i. Treatment will be used in combination with an aromatase inhibitor (e.g., letrozole, anastrozole, exemestane) or fulvestrant; **AND**
    - ii. Will not be used in combination with any additional oncology therapy; **AND**
    - iii. The member is a postmenopausal female, premenopausal or perimenopausal female receiving ovarian suppression/ablation (e.g., surgical ablation, suppression with GnRH therapy [e.g., leuprolide], etc.); **AND**
        a. The request is for abemaciclib (Verzenio) or ribociclib (Kisqali) or ribociclib/letrozole (Kisqali/Femara Co-Pack); **OR**
        b. The request is for palbociclib (Ibrance); **AND**
            i. Documentation that treatment with abemaciclib (Verzenio) or ribociclib (Kisqali) is contraindicated or not tolerated; **OR**
    - iv. The member is hormone suppressed male (e.g., GnRH therapy [e.g., leuprolide] used concomitantly); **AND**
        a. The request is for abemaciclib (Verzenio) or ribociclib (Kisqali) or ribociclib/letrozole (Kisqali/Femara Co-Pack); **OR**
        b. The request is for palbociclib (Ibrance); **AND**

i. Documentation that treatment with abemaciclib (Verzenio) or ribociclib (Kisqali) is contraindicated or not tolerated; **OR**

3. The medication is being prescribed as second-line systemic therapy; **AND**
    i. Treatment will be used in combination with fulvestrant (Faslodex); **AND**
    ii. Will not be used in combination with any additional oncology therapy; **AND**
    iii. The member had disease progression on, or after primary endocrine therapy (as adjuvant or first-line systemic therapy); **AND**
    iv. The member is a postmenopausal female, premenopausal or perimenopausal female receiving ovarian suppression/ablation (e.g., surgical ablation, suppression with GnRH therapy [e.g., leuprolide], etc.); **AND**
        a. The request is for abemaciclib (Verzenio) or ribociclib (Kisqali) or ribociclib/letrozole (Kisqali/Femara Co-Pack); **OR**
        b. The request is for palbociclib (Ibrance); **AND**
            i. Documentation that treatment with abemaciclib (Verzenio) or ribociclib (Kisqali) is contraindicated or not tolerated; **OR**
    v. The member is a hormone suppressed male (e.g., GnRH therapy [e.g., leuprolide] used concomitantly); **AND**
        a. The request is for abemaciclib (Verzenio) or ribociclib (Kisqali) or ribociclib/letrozole (Kisqali/Femara Co-Pack); **OR**
        b. The request is for palbociclib (Ibrance); **AND**
            i. Documentation that treatment with abemaciclib (Verzenio) or ribociclib (Kisqali) is contraindicated or not tolerated; **OR**
4. The medication is being prescribed for subsequent-line (3rd line or later) systemic therapy in metastatic (stage IV, M1) setting; **AND**
    i. Member had disease progression on, or after endocrine therapy AND systemic chemotherapy (not containing a CDK 4/6 inhibitor) in the metastatic (stage IV) setting; **AND**
    ii. The request is for abemaciclib (Verzenio) monotherapy

II. Abemaciclib (Verzenio), palbociclib (Ibrance) and ribociclib (Kisqali) are considered investigational when used for all other conditions, including but not limited to:
    A. In combination with, or following progression on or after, another CDK4/6 inhibitor (e.g., ribociclib [Kisqali], abemaciclib [Verzenio])
    B. Adjuvant therapy of early stage breast cancer (palbociclib (Ibrance) and ribociclib (Kisqali))
    C. Pancreatic neuroendocrine tumors (pNET)
    D. Ovarian or endometrial cancer
    E. Central nervous system cancers (e.g., glioma, astrocytoma, head and neck, etc.)
    F. Colorectal cancer
    G. Urothelial or renal cell carcinoma
    H. Leukemias and lymphomas

I. Non-small-cell lung cancer
J. Liposarcoma
K. Biliary tract carcinoma
L. Head and neck cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication will not be used in combination with any other oncolytic medication with the exception of an aromatase inhibitor (e.g., anastrozole, letrozole) or estrogen receptor antagonist (e.g., tamoxifen, fulvestrant); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., decrease in tumor size, or tumor spread)

Supporting Evidence

I. Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) were not studied in patients under 18 years of age; therefore, their efficacy and safety in the pediatric population is unknown.
II. Many treatment options exist for advanced and metastatic breast cancer. Initial and subsequent therapies in this setting are contingent upon patient specific characteristics. Given the complexities surrounding the diagnosis and treatment options, targeted drug therapies such as cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors should be prescribed by, or in consultation with, an oncologist.
III. **Abemaciclib (Verzenio):** Abemaciclib (Verzenio) was evaluated as a early-stage adjuvant therapy, first-line or subsequent-line systemic chemotherapy in adult, female subjects with HR+, HER2-, advanced or metastatic breast cancer. The following studies were pivotal trials for the approved indications:
    a. MONARCH-E: Abemaciclib (Verzenio) was studied in the setting of adjuvant therapy for early-stage breast cancer with high risk of recurrence or metastasis, in an open-label, randomized, phase 3 trial (MONARCH-E) in 5,637 patients. Efficacy and safety of adding abemaciclib (Verzenio) to endocrine therapy (aromatase inhibitor or tamoxifen) was compared with conventional endocrine therapy. Abemaciclib (Verzenio) was administered for 2 years following a definitive tumor reduction surgery and chemotherapy with taxane and/or anthracycline in adjuvant or neoadjuvant setting. High risk was defined based on the following key factors: ≥ 4 pALN disease; or 1 to 3 positive ALN in the setting of a tumor of at least 5 cm or larger, or histologic grade 3 disease. A Ki-67 index ≥ 20% in untreated breast tissue as determined by an FDA approved test was required as a marker for high-risk of recurrence (Ki-67 is a cancer antigen protein and serves as a marker for tumor cell mitosis). Invasive disease-free survival (IDFS) was the primary endpoint. As of Oct. 2021, IDFS data for 2,003 patients in cohort 1, who had Ki-67 scores ≥ 20% (1,017 in abemaciclib (Verzenio) arm and 986 in comparator ET arm) was

reported, which exhibited significant improvement in IDFS for abemaciclib (Verzenio) over conventional endocrine therapy alone with a 36-month IDFS of 86.1% (82.8, 88.8) versus 79% (75.3, 82.3) (HR = 0.626; [95% CI, 0.48, 0.80]; p= 0.0042). Results published December 2022 from a preplanned interim analysis noted an increase in absolute invasive disease–free survival and distant recurrence–free survival benefit at 4 years benefit of abemaciclib (Verzenio), regardless of Ki-67 score. The overall survival (OS) data was immature.

i. While statistically significant improvements in IDFS for patients in cohort 1 with Ki-67 score ≥ 20% at the final IDFS analysis was favorable for the indicated subpopulation, it was not favorable for the ITT population. Although OS data was immature, the ITT population observed hazard ratios for OS was 1.091 (95% CI, 0.818 to 1.455) and HR = 0.767 (95% CI, 0.511 to 1.152) in the FDA-approved population (cohort 1) appear to have influenced the label indication. The FDA labeled indication for adjuvant abemaciclib (Verzenio) was limited to the subset of patients with a worse prognostic risk on the basis of a higher anatomic stage (cohort 1) and with higher tumor proliferation based on Ki-67 biomarker expression (>20 %).
ii. As of December 2022, the NCCN guidelines for invasive breast cancer (version 4.2022) define high risk breast cancer as those with ≥ 4 positive lymph nodes, or 1–3 positive lymph nodes with one or more of the following: Grade 3 disease, tumor size ≥5 cm, or a Ki-67 score of ≥20%), which is consistent with the inclusion criteria for MONARCH-E trial design. The guideline recommends two years of adjuvant therapy with abemaciclib (Verzenio) in combination with endocrine therapy in patients with HR+/HER2-, high-risk breast cancer that meet that definition, thus suggesting broader consideration of treatment than the FDA label.
iii. Furthermore, the American Society of Clinical Oncology (ASCO) has updated their guideline and is consistent with the NCCN guideline recommendation, in that adjuvant abemaciclib (Verzenio) may be offered to patients with either ≥ 4 positive lymph nodes (regardless of Ki-67 score) or 1-3 lymph nodes with high-risk features (grade 3 disease or tumor ≥ 5 cm or Ki-67 ≥ 20%) – in line with the definition/inclusion criteria of the MONARCH-E trial.
iv. Upon outreach to a key opinion leader specializing in oncology, practical considerations exist outside of using Ki-67 score as a sole marker for high-risk status in breast cancer. There are moderate quality data to suggest Ki-67 testing as an accepted clinical measure to guide therapy decisions for patients with early breast cancer; however analytical validity of Ki-67 testing remains poor. Analytical validity, standardization, and interobserver reproducibility have been cited as limitations of using this biomarker to drive patient-care decisions. There remain challenges in implementing Ki-67 scoring as a standard of care, and given individual circumstances such as when Ki-67 testing may not be readily available in situations where there is absence of tissue sample, and when all other criteria are met for patients that meet the definition of high-risk early breast cancer, treatment with adjuvant abemaciclib (Verzenio) may be appropriate.

b. MONARCH 3: Abemaciclib (Verzenio) in combination with an aromatase inhibitor. The trial evaluated postmenopausal women and with no prior systemic therapy, and was a randomized, double-blinded, placebo-controlled trial. Premenopausal women were administered GnRH therapy for at least two weeks prior to initiation of therapy for ovarian suppression and continued throughout the trial. The primary efficacy outcome was Progression-Free Survival (PFS), which favored abemaciclib (Verzenio). A secondary outcome was objective response rate (ORR), which also favored abemaciclib (Verzenio); however, overall survival (OS) data is not yet available.
c. MONARCH 2: Abemaciclib (Verzenio) in combination with fulvestrant. The trial evaluated subjects with disease progression on or after adjuvant metastatic endocrine therapy, and was a randomized, placebo-controlled trial. The primary and secondary outcomes mirror that of MONARCH 3, in favor of abemaciclib (Verzenio); however, OS data was not mature at time of FDA-approval.
    i. At the final interim data cut-off reported in 2020, the ITT population (n=446) analysis reported median OS of 46.7 months for abemaciclib (Verzenio) plus fulvestrant and 37.3 months for placebo plus fulvestrant (HR= 0.757; 95% CI, 0.606-0.945; P = 0.01). Improvement in OS was consistent across all stratification factors. Among stratification factors, more pronounced effects were observed in patients with visceral disease (HR 0.675; 95%CI, 0.511-0.891) and primary resistance to prior ET (HR 0.686; 95%CI, 0.451-1.043). Time to second disease progression (median, 23.1 months vs 20.6 months) was also statistically significantly improved.
d. MONARCH 1: Abemaciclib (Verzenio) administered as a monotherapy in metastatic breast cancer. The trial, a single-arm, open-label, phase II trial, evaluated women who received prior endocrine therapy and one-to-two lines of chemotherapy in the metastatic setting. The primary outcomes were ORR and median duration of response (DOR). Abemaciclib (Verzenio) induced partial response in 19.7% and demonstrated an ORR of 19.7% (95% CI: 13.3–27.5). Median PFS was 6 months (95% CI: 4.2–7.5). At the final analysis, at 18 months, median OS was 22.3 months (95% CI: 17.7–not reached).

IV. **Palbociclib (Ibrance):** Palbociclib (Ibrance) was evaluated as a first-line or subsequent-line systemic chemotherapy in adult male and female subjects with HR+, HER2-, advanced or metastatic breast cancer. The following studies were trials have evaluated the safety and efficacy of palbociclib (Ibrance) for the approved indications:
    a. PALLAS: Prospective, randomized, phase III trial evaluated patients with HR+/HER- early breast cancer were randomly assigned to receive 2 years of palbociclib (Ibrance) with adjuvant endocrine therapy or adjuvant endocrine therapy alone (for at least 5 years). The primary end point of the study was iDFS. The study concluded the addition of adjuvant palbociclib (Ibrance) to standard endocrine therapy did not improve outcomes over endocrine therapy alone in patients with early HR+/HER2- eBC. At a median follow-up of 31 months, IDFS events occurred 8.8% patients who received palbociclib (Ibrance) plus endocrine therapy vs. 9.1% patients who received endocrine therapy alone, with similar results between the two treatment groups (iDFS at 4 years: 84.2% v 84.5%; HR= 0.96; 95% CI 0.81 to 1.14, p=0.65).

b. PALOMA-2: Palbociclib (Ibrance) plus aromatase inhibitor (letrozole) vs. placebo and letrozole in postmenopausal women receiving first-line treatment for HR+/HER2- mBC. This was a Phase III, randomized, double-blind, trial where subjects had no prior treatment in the metastatic setting. The results showed that palbociclib (Ibrance) plus letrozole resulted in an improved median PFS of 24.8 months compared to letrozole+placebo at 14.5 months (HR =0.58; 95% CI, 0.46 to 0.72; p <0.0001). The final OS analysis published June 2022 reported no significant survival benefit with palbociclib (Ibrance) plus letrozole over letrozole and placebo. After a median follow-up of 90 months, patients receiving palbociclib (Ibrance) + letrozole had numerically longer OS compared to letrozole monotherapy (median 53.9 months vs median 51.2 months), however the results were not statistically significant (HR=0.96; 95% CI: 0.78-1.18; *P*=0.3378).
c. PALOMA-3: Palbociclib (Ibrance) and fulvestrant vs. fulvestrant in pre- or post-menopausal HR+, HER2- advanced breast cancer patients, whose disease progressed on prior endocrine therapy in the adjuvant or metastatic setting. The median PFS was 9.5 months for the combination compared to 4.6 months for fulvestrant (HR= 0.46; 95% CI: 0.36 to 0.59; p< 0.0001). Key secondary endpoints were ORR and OS. ORR was achieved by 24.6% patients on palbociclib (Ibrance) + fulvestrant vs 10.9% on fulvestrant. An OS difference of 6.9 months was seen; median OS was 34.9 months with palbociclib (Ibrance) + fulvestrant vs 28.0 months with fulvestrant (HR=0.81; 95% CI: 0.64-1.03; p=0.09). At the updated non-prespecified OS analysis with a data cut off August 2020, data showed a numerical difference in median OS in favor of palbociclib (Ibrance), but did not reach statistical significance.
d. PENELOPE-B: Palbociclib (Ibrance) for 1 year was examined as adjuvant therapy in the metastatic setting in women who still had residual disease after undergoing neoadjuvant chemotherapy versus placebo. The study did not meet the primary endpoint of improved IDFS in women with HR+/HER- eBC.
e. P-REALITY X: Real-world effectiveness of 1L use of palbociclib (Ibrance) + letrozole vs letrozole monotherapy in HR+/HER2- mBC. This was an observational, retrospective analysis of electronic health records (EHRs) of 2888 postmenopausal women and men. The primary endpoint was OS. After stabilized inverse probability treatment weighting, median OS was 49.1 months among palbociclib (Ibrance) vs. 43.2 months vs letrozole (HR=0.76; 95% CI, 0.65-0.87; p<0.0001). Progression-free survival was 19.3 months vs versus 13.9 months, respectively (HR= 0.70; 95% CI, 0.62-0.78; p<0.0001).

V. **Ribociclib (Kisqali):** Ribociclib (Kisqali) was evaluated in adults with HR-positive, HER2-negative, advanced, or metastatic breast cancer.
a. MONALEESA-2: Randomized, double-blind, placebo-controlled trial comparing ribociclib (Kisqali) in combination with letrozole versus placebo with letrozole in 1L postmenopausal patients with HR/HER2- mBC. Subjects were treatment naïve for their disease. The outcomes were PFS and ORR, which were found to be statistically significant in favor of ribociclib (Kisqali) plus letrozole. Median OS data was published March 2022, showed OS 64 months with ribociclib (Kisqali) plus letrozole and 51 months with placebo plus letrozole (HR =0.76; 95% CI, 0.63 to 0.93; P = 0.008).

b. MONALEESA-7: Ribociclib (Kisqali) in combination with an aromatase inhibitor in 1L premenopausal patients. Randomized, double-blind, placebo-controlled trial of pre-perimenopausal subjects evaluating ribociclib (Kisqali) plus an aromatase inhibitor or tamoxifen with goserelin versus an aromatase inhibitor or tamoxifen and goserelin. The outcomes included PFS and ORR, which were statistically significant in favor of ribociclib (Kisqali). Overall survival data was reported in June 2019 and showed a hazard ratio (HR) of 0.712 (0.535-0.948; p=0.00973).
c. MONALEESA-3: Randomized, double-blind, placebo-controlled study of ribociclib (Kisqali) in combination with fulvestrant for 1L/2L treatment of postmenopausal women who had received zero to one line of prior endocrine therapy. This was compared to placebo plus fulvestrant. Efficacy primary outcomes were PFS and ORR which were statistically significant in favor of ribociclib (Kisqali). At 42 months, estimated survival rates among patients who received first-line therapy were 66.9% with ribociclib (Kisqali) plus fulvestrant versus 56.3% with fulvestrant alone. The median OS among patients in the early-relapse and second-line subgroup was 40.2 months with ribociclib (Kisqali) plus fulvestrant and 32.5 months with fulvestrant alone.

VI. **Treatment of breast cancer in men:** few men have been included in breast cancer clinical trials. As such natural incidence of breast cancer in men is rare (<1%), which has also reflected in the clinical trials' sample population. Therefore, recommendations regarding management of breast cancer in men are generally extrapolated from the findings of clinical trials in women.
a. Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) have received FDA-approval in the setting of treatment of breast cancer in men. For abemaciclib (Verzenio), this indication also extends in the adjuvant setting for the treatment of early breast cancer with high risk of recurrence.
b. Palbociclib (Ibrance) was FDA-approved for breast cancer in men in 2019. The approval was based on data from electronic health records and post marketing reports of real-world use in male patients. The sources of data included the following: IQVIA Insurance database, Flatiron Health Breast Cancer database, and the Pfizer global safety database. NCCN Guidelines recommend that men on an aromatase inhibitor and palbociclib (Ibrance) be administered a GnRH analog concurrently.
c. In the preoperative/adjuvant therapy setting, chemotherapy with or without HER2-targetted therapy is recommended in the male population. Typical adjuvant endocrine therapy options for men with breast cancer include tamoxifen, or if tamoxifen is contraindicated, an aromatase inhibitor in combination with a GnRH analog. In men, single-agent adjuvant treatment with an aromatase inhibitor has been associated with inferior outcomes compared to tamoxifen monotherapy, likely due to inadequate estradiol suppression.
d. Similarly, when aromatase inhibitor is used in combination with a CDK 4/6 inhibitor for the treatment of advanced or metastatic breast cancer in men, additional therapy with a GnRH analog (e.g., leuprolide) is recommended by NCCN guidelines for breast cancer. However, few retrospective studies involving treatment of men with metastatic breast cancer using aromatase inhibitors with or without GnRH analog showed that concurrent use of GnRH analog or type of aromatase inhibitor used did not provide statistically

significant advantage in outcomes- progression free survival (PFS), and overall survival (OS).

VII. Clinical trials to date have not included significant numbers of subjects previously treated with other CDK4/6 inhibitors; thus, safety and efficacy of subsequent administration is unknown at this time. Additionally, CKD4/6 inhibitors have been evaluated as monotherapy, and sufficient safety and efficacy evidence, in combination with therapies outside of aromatase inhibitors and fulvestrant, remain unknown. The NCCN notes a lack of data to support use of an additional CKD4/6 inhibitor after progression on a CDK4/6 regimen. As of December 2022, NCCN guidelines stated "If there is disease progression while on a CDK4/6 inhibitor, there is are limited data to support the use of another CDK4/6 inhibitor."

VIII. Endocrine therapies include, but may not be limited to, the following: tamoxifen, anastrozole, letrozole, and exemestane. Chemotherapy regimens include, but may not be limited to, the following: doxorubicin, paclitaxel, capecitabine, gemcitabine, cyclophosphamide, carboplatin, docetaxel, cisplatin, and combinations of these therapies.

IX. There is lack of scientific evidence from randomized controlled trials supporting the safety and/or efficacy for increased dosing or frequency of palbociclib (Ibrance). The dosing recommendation is one capsule once daily, with various doses for tolerability and dose adjustments for safety considerations, in 21 out of 28-day cycles. Increasing the dose beyond 125 mg per day or dosing more than 21 out of every 28 days has not been evaluated.

X. Postmenopausal status may be reached in women via ovarian suppression through GnRH therapy (pharmacotherapy-induced) for several weeks prior to palbociclib (Ibrance) administration, bilateral oophorectomy (surgically-induced), ovarian irradiation, or natural menopause. Any of these routes is considered acceptable for the aforementioned criteria.

XI. As of December 2022, the NCCN guidelines do not currently distinguish a preference between currently available CDK4/6 inhibitors (abemaciclib, palbociclib, and ribociclib) and no evidence is currently available indicating that one of these agents is superior to the other. A prospective analysis of the efficacy data of abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali) as first- or second-line therapies in ER-positive advanced breast cancer noted that these agents had similar efficacy. To date, no large head-to-head comparison is currently available to support or oppose this conclusion.

Investigational or Not Medically Necessary Uses

I. Clinical trials to date have not included significant numbers of subjects previously treated with other CDK4/6 inhibitors; thus, safety and efficacy of subsequent administration is unknown at this time. Additionally, CKD4/6 inhibitors have been evaluated as monotherapy, and sufficient safety and efficacy evidence in combination with therapies outside of aromatase inhibitors (e.g. anastrozole) and estrogen receptor antagonists (e.g. tamoxifen, fulvestrant) remain unknown. National Comprehensive Cancer Network (NCCN) acknowledges there are limited data to support use of an additional CKD4/6 inhibitor after progression on a CDK4/6 regimen.

II. There is currently no evidence supporting the use of CDK4/6 inhibitors for other types of cancer, other than the indications listed in this policy.

III. Abemaciclib (Verzenio) received FDA approval in the setting of adjuvant therapy of high-risk early stage breast cancer (EBC). Clinical trials are ongoing for palbociclib (Ibrance) and ribociclib (Kisqali). However, these agents have not been FDA approved in this setting.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

Appendix

I. The tumor, node, metastasis (TNM) TNM system is the most common method of cancer staging in breast cancer. Numbers or letters after T, N, and M give more details about each characteristic. Higher numbers mean the cancer is more advanced.
   a. T refers to the size and extent of the main (primary) tumor.
      i. Tis: non-invasive cancer found only in ducts (carcinoma in situ)
      ii. TX: Main tumor cannot be measured
      iii. T0: Main tumor cannot be found
      iv. T1, T2, T3, T4: Refers to the size and/or extent of the main tumor. The higher the number after the T, the larger the tumor or the more it has grown into nearby tissues. T's may be further divided to provide more detail, such as T3a and T3b.
   b. The N refers to the number of nearby lymph nodes involved that have cancer
      i. NX: Cancer in nearby lymph nodes cannot be measured (e.g., previously removed, etc.)
      ii. N0: There is no cancer in nearby lymph nodes
      iii. N1, N2, N3: Refers to the number and location of lymph nodes that contain cancer. The higher the number after the N, the more lymph nodes that contain cancer
   c. The M refers to whether the cancer has metastasized
      i. MX: Metastasis cannot be measured
      ii. M0: Cancer has not spread to other parts of the body
      iii. M1: Cancer has spread to other parts of the body (distant metastasis)

II. Breast cancer is often staged before and after surgery. Clinical staging (c) is referred to staging before treatment (cTNM) and pathologic stage (p) is based on the results of tissue samples removed during surgery (pTNM).

III. Tumor grade is dependent on tumor histology. A low-grade tumor has a lower risk of recurrence. A high-grade tumor tend to grow/spread faster and have a higher risk for recurrence.
   a. GX: Grade cannot be determined
   b. G1: Low grade
   c. G2: Intermediate grade

d. G3: High grade

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Olaparib (Lynparza)	Early, high-risk breast cancer
Everolimus (Afinitor)	Advanced breast cancer
Talazoparib (Talzenna)	Locally advanced or metastatic breast cancer
Gonadotropin-releasing hormone (GnRH)	Advanced prostate cancer
	Advanced breast cancer in premenopausal women
Alpelisib (Piqray)	Advanced or metastatic breast cancer
Lapatinib (Tykerb)	Advanced or metastatic breast cancer
Tucatinib (Tukysa)	Metastatic breast cancer
Neratinib (Nerlynx)	Early breast cancer
	Advanced, metastatic breast cancer

Policy Implementation/Update

Action and Summary of Changes	Date
Effective 01/01/2023 - Updated criteria in early breast cancer to allow coverage when Ki-67 <20% to align with definition of high-risk breast cancer NCCN/ASCO guidelines. Updated criteria requiring trial of Verzenio or Kisqali prior to Ibrance in setting of systemic therapy of recurrent, advanced, or metastatic breast cancer due to new OS data from PALOMA-2 trial. Updated criteria formatting. Updated supporting evidence and references. Added related policies and appendix.	12/2022
Updated requirement of palbociclib (Ibrance) and abemaciclib (Verzenio) prior to Kisqali to an or, in setting of systemic therapy of recurrent, advanced, or metastatic breast cancer.	10/2022
Added expanded indication for Abemaciclib (Verzenio) for adjuvant therapy of high-risk early stage breast cancer; added and rearranged relevant supporting information; updated policy to categorize adjuvant therapy for EBC vs systemic chemotherapy for advanced and metastatic breast cancer; aligned use of Verzenio and Ibrance in male population with current FDA approval and recommendations; removed specialist prescribing criteria for renewal; added split fill requirement for Verzenio	11/2021
Addition of wording related to GnRH therapy to induce menopause in order to clarify the FDA approval for Kisqali in pre/perimenopausal setting	03/2021
Transitioned criteria to policy format and merged into one policy and added add step through abemaciclib (Verzenio) and palbociclib (Ibrance) for Kisqali, effective 1/1/2021.	12/2020
Previews reviews • Verzenio: Updated to include age, specialist, limit concurrent therapy, with renewal criteria to align with current practice and removal of subgroup analysis exclusions, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2019); added new indication: first-line treatment in combination with an aromatase inhibitor (2018); clarified use of concomitant medication (2017) • Kisqali: Updated to include age, specialist, limit concurrent therapy, with renewal criteria to align with current practice (2019); updated product availability with Kisqali-Femara dose pack, added new indication for pre/perimenopausal setting in combination with aromatase inhibitor, as well as postmenopausal setting in combination with fulvestrant as first or second line endocrine	03/2020 10/2019 05/2019 09/2018 08/2018 03/2018

therapy, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2018) • Ibrance: Updated QL box to inform about transition to tablets (2020), Added new indication and FDA-approval of breast cancer in men, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2019); updated criteria to allow treatment after disease progression on prior endocrine therapy (2016)	09/2017 01/2016
Criteria created • Verzenio • Kisqali • Ibrance	 10/2019 04/2017 02/2015

Policy Type: PA Pharmacy Coverage Policy: UMP092

Description

Cyproheptadine is an orally administered antihistamine.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
cyproheptadine	4 mg tablets	Appetite stimulation; Migraine prophylaxis	120 tablets/30 days	005604
cyproheptadine	2 mg/5mL		1,200 mL/30 days	005603

Initial Evaluation

I. Cyproheptadine may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      1. Loss of appetite; **AND**
         i. Member is less than 18 years of age
      2. Headache or migraine prophylaxis; **AND**
         i. Member is less than 18 years of age; **OR**
         ii. Member is 18 years of age or older; **AND**
            a. Documentation of history of trial and failure of prophylactic therapy with at least one agent listed in each of the following groups (of note, if a group of agents is contraindicated, a trial and failure of at least three agents listed in the remaining groups is required):
               i. Group 1: propranolol, metoprolol, atenolol, timolol, nadolol
               ii. Group 2: amitriptyline, venlafaxine
               iii. Group 3: topiramate, sodium valproate, divalproex sodium; **AND**
            b. Documentation of use of each of the prophylactic therapies at therapeutic doses for at least 3 months

II. Cyproheptadine is considered not medically necessary when criteria above are not met and/or when used for:
   A. Use for other indications as there are over the counter alternatives for antihistamine products.

III. Cyproheptadine is considered investigational when used for all other conditions, including but not limited to:
   A. Functional abdominal pain
   B. Weight loss with cancer
   C. Combination therapy or monotherapy for ADHD
   D. Fatigue post stroke

Renewal Evaluation

I. Confirmed diagnosis of:
   A. Appetite stimulation; **AND**
      1. Documentation of treatment benefit as indicated by weight stability or gain.
   B. Migraine prophylaxis; **AND**
      1. Documentation of treatment benefit as indicated by a decrease in the number or severity of migraines.

Supporting Evidence

I. Plan covers use for appetite stimulation in pediatric population.
II. Guidelines recommend select beta blockers, antidepressants, anticonvulsants, and onabotulinumtoxinA, as efficacious or probably efficacious (Level A and B, respectively) for the prophylactic treatment of migraine in adults. If onabotulinumtoxinA has been stated, this may be used as one qualifier of the three required agents to meet payment consideration for a quantity exception. Agents not listed here have lower level, or conflicting evidence. This includes, but is not limited to SSRIs, cyproheptadine, clonidine, guanfacine, nebivolol, pindolol, carbamazepine, lisinopril, candesartan, duloxetine, calcium channel blockers, gabapentin, pregabalin, lamotrigine, oxcarbazepine, clomipramine, telmisartan, and benzodiazepines. There is limited evidence for efficacy for any class of agents for pediatric patients. Coupled with safety concerns of many of the convention migraine agents in pediatric patients, trial and failure of other conventional agents prior to coverage of cyproheptadine is not indicated at this time.
III. Guidelines label a “treatment success” as a 50% reduction in migraine after three months or prophylactic therapy utilization. Additionally, some agents take one-to-three months to begin working. If the prophylactic therapies have not been trialed for three months, this does not constitute an adequate trial of that agent. Of note, adverse effects and contraindications may limit ability to utilize an agent, or class of agents for three months, and this should be taken into consideration when determining if criteria coverage has been met.
IV. Antihistamines are not covered in adults due to over-the-counter products.

Investigational or Not Medically Necessary Uses

I. Clinical trials are ongoing for the following indications:
   A. Indication of functional abdominal pain
   B. Indication of weight loss with cancer
   C. Indication of combination therapy for ADHD
   D. Indication of fatigue post stroke.

References

1. Lewis DW, Diamond S, Scott D, Jones V. Prophylactic treatment of pediatric migraine. Headache. 2004;44(3):230-7.
2. Worawattanakul M, Rhoads JM, Lichtman SN, Ulshen MH. Abdominal migraine: prophylactic treatment and follow-up. J Pediatr Gastroenterol Nutr. 1999;28(1):37-40.
3. Watemberg NM, Roth KS, Alehan FK, Epstein CE. Central anticholinergic syndrome on therapeutic doses of cyproheptadine. Pediatrics. 1999;103(1):158-60.
4. Couluris M, Mayer JL, Freyer DR, Sandler E, Xu P, Krischer JP. The effect of cyproheptadine hydrochloride (periactin) and megestrol acetate (megace) on weight in children with cancer/treatment-related cachexia. J Pediatr Hematol Oncol. 2008;30(11):791-7.
5. Epifanio M, Marostica PC, Mattiello R, et al. A randomized, double-blind, placebo-controlled trial of cyproheptadine for appetite stimulation in cystic fibrosis. J Pediatr (Rio J). 2012;88(2):155-60.
6. Gilmore B, Michael M. Treatment of acute migraine headache. Am Fam Physician. 2011;83(3):271-80.
7. Weatherall MW. The diagnosis and treatment of chronic migraine. Ther Adv Chronic Dis. 2015;6(3):115-23.

Policy Implementation/Update:

Date Created	January 2013
Date Effective	January 2013
Last Updated	May 2018
Last Reviewed	05/2018, 06/2019

Action and Summary of Changes	**Date**
Converted to policy	06/06/2019
Criteria update: Added indication of migraine prophylaxis in pediatric patients, updated document to standard format, and updated questions to yes/no format for systematic implementation into criteria builder for Cover My Meds programming.	05/30/2018
Criteria update: Excluded samples and updated renewal language to general improvement.	1/11/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP119

Description

Cysteamine (Cystaran; Cystadrops) is a cystine depleting ophthalmic solution agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
cysteamine (Cystaran)	0.44% ophthalmic solution	Corneal cystine crystals	60 mL (4 bottles)/28 days
cysteamine (Cystadrops)	0.37% ophthalmic solution		20 mL (4 bottles)/28 days

Initial Evaluation

I. Cysteamine (Cystaran; Cystadrops) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an ophthalmologist; **AND**
   B. A diagnosis of **cystinosis** when the following are met:
      1. Diagnosis has been confirmed with ONE of the following:
         i. Presence of corneal cysteine accumulation; **OR**
         ii. CTNS gene analysis; **OR**
         iii. Elevated intracellular cystine levels (>1nmol cystine/mg protein)

II. Cysteamine (Cystaran; Cystadrops) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms

Supporting Evidence

I. Cystinosis is a rare, multisystem genetic disorder characterized by the accumulation of cystine in various bodily organs and tissues leading to the potential for severe organ dysfunction. Cystinosis is further classified into three different forms, known as nephropathic cystinosis, intermediate cystinosis, and non-nephropathic (or ocular) cystinosis. Corneal cystine crystal accumulation may present in all three types.

II. Topical cysteamine is prescribed to prevent corneal deposits, as the oral formulation does not reach the cornea due to a lack of corneal vascularization.

III. The diagnosis of cystinosis is confirmed by elevated intraleukocyte cystine content, (i.e. measuring cystine levels in polymorphonuclear leukocytes), detection of CNTS gene mutation, or demonstration of cystine corneal crystals by the slit lamp examination.

IV. Per the package insert, each bottle of both Cystaran and Cystadrops lasts only 7 days after opening and the remaining contents should be discarded.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of cysteamine (Cystaran; Cystadrops) in any other condition.

References

1. Cystaran [Prescribing Information]. Gaithersburg, MD: Sigma Tau Pharmaceuticals; October 2012.
2. Cystadrops [Prescribing Information]. Lebanon, NJ: Recordati Rare Diseases Inc.; August 2020.
3. UpToDate, Inc. Cystinosis. UpToDate [database online]. Waltham, MA. Last updated February 27, 2019 Available at: http://www.uptodate.com/home/index.html.
4. National Organization for Rare Disorders. Cystinosis. Available at: https://rarediseases.org/rare-diseases/cystinosis/
5. Liang H, Labbé A, Le Mouhaër J, Plisson C, Baudouin C. A new viscous cysteamine eye drops treatment for ophthalmic cystinosis: an open-label randomized comparative phase iii pivotal study. Invest Ophthalmol Vis Sci. 2017;58(4):2275-2283.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new formulation, Cystadrops	01/2021
Policy created	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP041

Description

Ivacaftor (Kalydeco) is an orally administered cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. Ivacaftor/lumacaftor (Orkambi) combines the potentiating mechanism of ivacaftor with lumacaftor which improves the conformational stability of F508del-CFTR. Ivacaftor/tezacaftor (Symdeko) includes tezacaftor, which is a CFTR modulator that acts as a CFTR corrector. Elexacaftor/tezacaftor/ivacaftor (Trikafta), adds an addition CFTR corrector with elexacaftor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
ivacaftor (Kalydeco)	Cystic fibrosis, one mutation in the CFTR gene[a] that is responsive to ivacaftor[b]	150 mg tablet	56 tablets/28 days
		5.8 mg/ packet oral granules	56 packets/28 days
		13.4 mg/packet oral granules	56 packets/28 days
		25 mg/packet oral granules	56 packets/28 days
		50 mg/packet oral granules	56 packets/28 days
		75 mg/packet oral granules	56 packets/28 days
ivacaftor/ lumacaftor (Orkambi)	Cystic fibrosis, homozygous for F508del mutation	125/200 mg tablet	112 tablets/28 days
		125/100 mg tablet	112 tablets/28 days
		94/75 mg oral granule packet	28 packets/28 days
		125/100 mg oral granule packet	56 packets/28 days
		188/150 mg oral granule packet	56 packets/28 days
ivacaftor/ tezacaftor (Symdeko)	Cystic fibrosis, homozygous F508del mutation or at least one mutation in the CFTR gene[a] that is responsive to ivacaftor/tezacaftor[b]	Kit: (ivacaftor; ivacaftor/tezacaftor) 150mg; 150/100mg	56 tablets/28 days
		Kit: (ivacaftor; ivacaftor/tezacaftor) 75mg; 75/50 mg	56 tablets/28 days
elexacaftor/ tezacaftor/ ivacaftor (Trikafta)	Cystic fibrosis, one F508del mutation or at least	Kit (elexacaftor/ tezacaftor/ ivacaftor; ivacaftor) 100/50/75mg; 150 mg	84 tablets/28 days

	mutation if the CFTR gene[a] that is responsive[b]	Kit (elexacaftor/ tezacaftor/ ivacaftor; ivacaftor) 50/37.5/25mg; 75 mg	84 tablets/28 days
		Kit (elexacaftor/ tezacaftor/ ivacaftor; ivacaftor) 100/50/75mg; 75mg	56 packets/28 days
		Kit (elexacaftor/ tezacaftor/ ivacaftor; ivacaftor) 80/40/60mg; 59.5mg	56 packets/28 days

[a] Specific mutations listed below in policy criteria

[b] Based on clinical and/or *in vitro* assay data

Initial Evaluation

I. **Agents listed in this policy** may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   B. The medication is not used in combination with other agents in this policy (i.e., use of only one of the following at a given time: Kalydeco, Orkambi, Symdeko, Trikafta) (*please note: if a previous approval has been granted for one of these agents, and criteria is met for another, the previous PA approval will be discontinued)*; **AND**
   C. A diagnosis of **cystic fibrosis** when the following are met:
      1. For ivacaftor (Kalydeco):
         i. The member is one month of age or older; **AND**
         ii. Documentation that the member has a mutation that is eligible for treatment with ivacaftor (Kalydeco) as defined in the FDA label; **AND**
         iii. Member Gene Mutation supported by Table in Package Insert: KALYDECO® (ivacaftor); OR
      2. For ivacaftor/lumacaftor (Orkambi):
         i. The member is one year of age or older; **AND**
         ii. The member is homozygous (two copies) for the F508del mutation in the CFTR gene; **OR**
      3. For ivacaftor/tezacaftor (Symdeko):
         i. The member is six years of age or older; **AND**
         ii. The member has **ONE** of the following:
            a. The member is homozygous (two copies) for the F508del mutation (*please note: one copy of F508del in the absence of a responsive mutation listed below does not meet criteria)*; **OR**
            b. Documentation that the member as a mutation that is eligible for treatment with ivacaftor/tezacaftor (Symdeko) defined in the FDA label; **AND**
         iii. Member Gene Mutation supported by Table in Package Insert: SYMDEKO® (tezacaftor/ivacaftor and ivacaftor); **OR**
      4. For elexacaftor/tezacaftor/ivacaftor (Trikafta):
         i. The member is two years of age or older: **AND**

ii. The member has **ONE** of the following:
    a. The patient has at least one copy of the F508del mutation; **OR**
    b. Documentation that the member as a mutation that is eligible for treatment with elexacaftor/tezacaftor/ivacaftor (Trikafta) defined in the FDA label; **AND**
iii. Member Gene Mutation supported by Table in Package Insert: TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor)

II. Medications listed in this policy are considered investigational when used for all other conditions, including but not limited to:
    A. Cystic fibrosis outside of the specific mutations listed above for each medication.
    B. Cystic fibrosis outside of ages listed above for each medication
    C. Chronic obstructive pulmonary disease and/or asthma
    D. Hyperglycemia or diabetes mellitus
    E. Premature termination codon mutations

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Clinical documentation of response to therapy as indicated by disease stability or improvement as defined by **one** of the following:
    A. Improvement in FEV1
    B. Decrease in pulmonary exacerbations
    C. Decrease in rate of hospitalizations
    D. Decrease in pulmonary infections
    E. Increased weight
    F. Improvement in sweat chloride

Supporting Evidence

I. Cystic fibrosis is an autosomal recessive disease that manifests primarily with pulmonary complications and may often affect several other organ systems. Treatment and management of cystic fibrosis is complex and requires a myriad of treatment modalities. A specialist should direct, or at least be consulted, at every stage of the member's care.
II. The use of the CFTR agents has not been studied in combination with other CFTR modulators, and due to lack of safety and efficacy data with a combination regimen, these agents should not be used together.
III. The safety of efficacy of Ivacaftor (Kalydeco) has been evaluated in several clinical trials.
    - Originally approved in 2012, two trials evaluated ivacaftor (Kalydeco) in patients with G551D mutation in the CFTR gene. The primary outcome in both studies was absolute change from baseline in percent predicted pre-dose FEV1 through 24

weeks of treatment. Trial one evaluated patients 12 years of age and older (10.6%; p<0.0001), and Trial 2 evaluated patients six to 11 years of age (12.5%; p<0.0001). Additional outcomes included change in body weight, change in sweat chloride, and relative risk of pulmonary exacerbation, all of which were statistically significant.

- In 2014, efficacy and safety of ivacaftor (Kalydeco) was evaluated in patients ages six and older with R117H mutation which showed a statistically significant change from baseline in FEV1 and CFQ-R score.
- Between 2015 and 2018, the efficacy and safety of ivacaftor (Kalydeco) expanded into patients with G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, and S549R mutations. Outcomes included absolute change in percent predicted FEV1, change in body weight, and CFQ-R Respiratory Domain Score, all of which had statistically significant outcomes; although, there was much variability among the responses per mutation type. Continued rare mutations were further added in 2020.
- In April 2019, the FDA approved ivacaftor (Kalydeco) as the first CFTR modulator to treat eligible infants from six months of age. This was supported by data from the Phase 3 ARRIVAL study. This was based on 11 patients with cystic fibrosis. Furthermore, in September 2020, the FDA approved ivacaftor (Kalydeco) to treat patients four months of age and older. This was supported by a 24-week open-label cohort of the ARRIVAL trial, showing a similar safety profile to other FDA-approved age groups.
- In May 2023, the FDA approved an age expansion down to one month of age or older. This data was based on Trial 8 (ARRIVAL), a phase 3, 24-week, open-label, 2-part study that included patients one month of age or older. Oral granules were mixed with 5mL of age-appropriate soft food or liquid and administered with syringe or spoon (bottle use not recommended). The primary endpoint was safety, assessed by adverse events and clinical laboratory assessments, with secondary endpoints looking at absolute change from baseline in sweat chloride concentration at week 24. This data showed similar safety profile of those two years and older.
- Ivacaftor (Kalydeco) has not been shown to have efficacy in those with the F508del mutation or any of the following: A46D, G85E, E92K, P205S, R334W, R347P, T338I, S492F, I507del, V520F, A559T, R560S, R560T, A561E, L927P, H1054D, G1061R, L1065P, R1066P, R1066C, R1066H, R1066M, L1077P, H1085R, M1101K, W1282X, N1303K.

IV. The efficacy and safety of ivacaftor/lumacaftor (Orkambi) has been evaluated in patients homozygous for the F508del mutation in the CFTR gene across several clinical trials.

- Trials 1 and 2 were 24-week, Phase 3, randomized, double-blind, placebo-controlled studies of patients aged 12 years and older with CF who were homozygous for the *F508del-CFTR* mutation. The primary endpoint in both trials was an absolute change in $ppFEV_1$ from baseline at Week 24 assessed as the average of the treatment effects at Week 16 and at Week 24. The treatment difference between ORKAMBI and placebo for the mean absolute change in ppFEV1 from baseline at Week 24 was 2.6 percentage points [95% CI (1.2, 4.0)] in Trial 1 (P=0.0003) and 3.0 percentage points [95% CI (1.6, 4.4)] in Trial 2 (P<0.0001). Additional key second endpoints were also met for relative change in percent predicted FEV1 at week 24, absolute change in BMI at week 24 in trial 2.
- Trials 3 and 4 was an expansion in ages 6 to 12; both open-label studies assessing safety and tolerability of ivacaftor/lumacaftor (Orkambi) in younger patients with

stable CF and the homozygous *F508del-CFTR* mutation. There were no new safety markers and an additional lung function measurement of precent predicted FEV1 at week 24 supported a 2.5% within group improvement.

- Trial 6 was an open-label study evaluating safety, tolerability and pharmacokinetics of patients aged 2-5 with stable CF and the homozygous*F508del-CFTR* mutation. This study reported same similar safety and tolerability in the 24 weeks as the prior studies
- Trial 7 was a similar open-label study assessing safety in those aged 1-2 with stable CF and homozygous *F508del-CFTR* mutations. No new safety signals were found in the studies' 24 weeks.

V. Ivacaftor/tezacaftor (Symdeko) has been evaluated in several trials.

- Trial 1 evaluated ivacaftor/tezacaftor (Symdeko) against placebo in patients 12 years of age and older that were homozygous for F508del, with the primary endpoint of change in FEV1 (4% vs 0% [3.1-4.8]; p<0.0001). Notable secondary outcomes included number of pulmonary exacerbations from baseline, absolute change in BMI from baseline, and change in CFQ-R Respiratory Domain Score from baseline. The change in number of pulmonary exacerbations was significantly reduced (0.65 [CI 0.48-0.88; p<0.0054).
- Trial 2 evaluated patients heterozygous for F508del and a second mutation predicted to be responsive to Ivacaftor/tezacaftor (Skydeko). Outcomes evaluated were similar to Trial 1. The change in FEV1 was 6.8 percentage point (CI 5.7-7.8; p<0.0001), while the change in CF-R Reparatory Domain Score was 11.1 points 9CI 8.7-13.6); p<0.0001).
- Trial 3 evaluated patients who were heterozygous for F508del mutation and a second mutation not predicted to be responsive to tezacaftor/Ivacaftor (Symdeko). The primary efficacy endpoint, a change in FEV1 compared to baseline, was 1.2 percentage points (CI -0.3-2.6), and was not significant. The study was terminated early.
- The efficacy of ivacaftor/tezacaftor (Symdeko) for patients aged six to 12 years was supported by data from a 24-week, open-label treatment period of 70 patients. Observations of safety were noted to be similar to that of the data available for ages 12 years and above.

VI. Elexacaftor/tezacaftor/ivacaftor (Trikafta) safety and efficacy was evaluated in the following clinical trials:

- Trial 1: 24-week, randomized, double-blind, placebo-controlled trial in patients 12 and older (n=403). Subjects had an F508del mutation and a second mutation that resulted in no CFTR protein or a CFTR protein that was nonresponsive to ivacaftor (Kalydeco) or ivacaftor/tezacaftor (Symdeko). A change of 13.8% ppFEV1 (primary endpoint) compared to placebo was seen in this trial.
- Trial 2: 4-week, randomized, double-blind, active-controlled trial in 107 patients, homozygous for F508del. A change of 10% ppFEV1 (primary endpoint) compared to Symdeko was seen in this trial.
- Statistical and clinical improvement in sweat chloride, body mass index, and reduction in pulmonary exacerbations occurred in the both trials.Trial 3: a 24-week phase 3 open label, multicenter study, enrolled 66 children ages six to 11 years old with CF who had either two copies of the *F508del* mutation or one copy of the *F508del* mutation and one minimal function mutation to evaluate safety,

pharmacokinetics, and efficacy. The treatment was generally well tolerated, and safety data was similar to those 12 and older.

- Trial 4: Phase 3, 24-week, open label study which enrolled patients 2-5 years (n=75). The primary endpoint was safety profile and secondary endpoints looked at change in sweat chloride concentration and change in lung clearance index. Both of these showed clinical improvement and there were no new safety signals that were not seen in the rest of the clinical program for Trikafta.

VII. In a published update from 12/2020, Vertex released that the FDA approved updated CFTR gene mutations that were shown to be responsive from *in vitro* data for ivacaftor (Kalydeco), elexacaftor/tezacaftor/ivacaftor (Trikafta), and ivacaftor/tezacaftor (Symdeko). The package inserts have all been included in each drug policy section.

Investigational or Not Medically Necessary Uses

I. The aforementioned indications listed as experimental and investigational are currently being evaluated in clinical trials and/or have not yet shown efficacy and safety in moderate or high-quality clinical trials.

References

1. Kalydeco [Prescribing Information]. Vertex Pharmaceuticals. Boston, MA. May 2023.
2. Orkambi [Prescribing Information]. Vertex Pharmaceuticals. Boston, MA. May 2023.
3. Symdeko [Prescribing Information]. Vertex Pharmaceuticals. Boston, MA. June 2022.
4. Trikafta [Prescribing Information]. Vertex Pharmaceuticals. Boston, MA. May 2023.
5. Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. N Engl J Med. 2017. 377(21): 2013-2023. DOI: 10.1056/NEJMoa1709846.
6. Rowe SM, Daines C, Ringshausen RC, et al. Tezacaftor-Ivacaftor in Residual-Function Heterozygous with Cystic Fibrosis. 377(21): 2024-2035. DOI: 10.1056/NEJMoa1709847.
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9. Vertex Pharmaceuticals. [Media Release]. FDA Approves Orkambi (lumacaftor/ivacaftor) - the First Medicine to Treat the Underlying Cause of Cystic Fibrosis for People Ages 12 and Older with Two Copies of the F508del Mutation Retrieved from: http://investors.vrtx.com/releasedetail.cfm?ReleaseID=920555 Accessed 7/10/2015.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated age expansion for Kalydeco and Trikafta with new approvals. Updated supporting evidence to mirror other age expansions.	6/2023
Updated age expansion for Orkambi with new approval. Updated supporting evidence to mimic other age expansion trial data.	10/2022
Updated age for Trikafta with new FDA approval. Updated links to the PI to reflect a link to each manufacturer page	08/2021
Updated *CFTR* gene mutation indications with new *in vitro data,* adding additional attestation and PI for verification to that mutation.	02/2021
Kalydeco age requirement updated to four months of age (previous six) based on updated FDA-approval.	10/2020
New FDA-approved therapy, Trikafta, added to the policy. Grammatical changes and formatting edits.	02/2020
Criteria combined, transitioned to policy format for all medications. Added new indication for Kalydeco for ages 6 months and older. Symdeko now approved down to six years of age.	06/2019
Criteria update: New indication for Orkambi, approved in CF patients two years of age and older. New approval in CF for patients between the ages of 12 and 24 months for Kalydeco, previously approved only for 24 months and older. Criteria added to not allow concomitant use.	09/2018
Updated criteria to new format, removed question assessing liver enzymes levels, added references, added question regarding combination therapy with other CFTR modulating medications. Symdeko criteria created.	05/2018
Criteria update: Excluded samples and updated renewal language to general improvement.	01/2016
Policy created	02/2012

Cystine Depleting Agents

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP118

Description

Cysteamine bitartrate (Cystagon; Procysbi) is a cystine-depleting agent that lowers cystine levels within cells.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
cysteamine IR (Cystagon)	50 mg capsule	Nephropathic cystinosis	60 capsules/30 days
	150 mg capsule		1.95 g/m^2/day
cysteamine DR (Procysbi)	25 mg DR capsule		60 capsules/30 days
	75 mg DR capsule		1.95 g/m^2/day
	75 mg DR granule packet		1.95 g/m^2/day
	300 mg DR granule packet		1.95 g/m^2/day

Initial Evaluation

Cysteamine bitartrate IR (Cystagon) is the preferred cystine-depleting agent.

- **Patients must have failed, have contraindication to, or intolerance of cysteamine bitartrate IR (Cystagon) prior to the consideration of cysteamine bitartrate DR (Procysbi).**
  - There is no prior authorization required for cysteamine bitartrate IR (Cystagon) when used for nephropathic cystinosis unless requesting above the quantity limit noted above.

I. **Cysteamine bitartrate DR (Procysbi)** may be considered medically necessary when the following criteria below are met:

A. A diagnosis of **nephropathic cystinosis** when the following are met:

1. Diagnosis has been confirmed with ONE of the following:
   i. Presence of corneal cysteine accumulation; **OR**
   ii. CTNS gene analysis; **OR**
   iii. Elevated intracellular cystine levels (>1nmol cystine/mg protein); **AND**
2. Documentation member has an intolerance or contraindication to cysteamine bitartrate IR (Cystagon); **OR**
   i. Documentation of unavoidable non-adherence to cysteamine IR (Cystagon) that prevents the achievement of optimal white blood cell (WBC) cystine levels (<1 nmol ½ cystine per mg protein); **AND**
3. Dose requested does not exceed 1.95 g per m^2 per day

II. Cysteamine bitartrate (Cystagon, Procysbi) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in leukocyte cystine concentration]; **AND**
IV. If request is for a dose increase, the new dose does not exceed 1.95 g per m^2 per day.

Supporting Evidence

I. Cystinosis is a rare, multisystem genetic disorder caused by mutations within the CTNS gene on chromosome 17p13, which is characterized by the accumulation of cystine in different organs and tissues, increasing the potential for severe organ dysfunction. It is further classified into three forms known as infantile (nephropathic) cystinosis, late-onset (juvenile) cystinosis, and adult (benign or ocular nonnephropathic) cystinosis. Corneal cystine crystal accumulation may be present in all three types of cystinosis. Treatment of cystinosis is comprised of the amelioration of symptoms, the administration of cysteamine, and renal transplantation for those who progress to end-stage renal disease (ESRD). Ophthalmic cysteamine is prescribed to prevent corneal deposits, because the oral formulation does not reach the cornea due to absent corneal vascularization.
II. Diagnosis of cystinosis is confirmed by elevated intraleukocyte cystine content, (i.e. measuring cystine levels in polymorphonuclear leukocytes), detection of *CTNS* gene mutation, or demonstration of cystine corneal crystals by the slit lamp examination.
III. The immediate-release preparation of cysteamine bitartrate (Cystagon) is the most used formulation. The dose should be progressively increased from 10 to 50 mg/kg per day (maximum dose of 1.95 gm/m2 per day), given in divided doses every six hours. Cystine levels are measured in white blood cells once a maintenance dose is reached, this is then followed by monitoring monthly for three months, quarterly for one year, and then twice a year. Blood sampling should be obtained six hours after taking a dose of cysteamine. The goal of cysteamine therapy is to lower WBC cystine levels to an optimal target level of less than 1 nmol half-cystine/mg protein.
IV. The safety and efficacy of cysteamine bitartrate IR (Cystagon) was demonstrated in the National Collaborative Cysteamine Study (NCCS) which treated 94 children with nephropathic cystinosis with increasing doses of cysteamine HCl (mean dose 54 mg/kg/day) to attain white cell cystine levels of <2 nmol ½ cystine per mg protein 5 to 6 hours post-dose in comparison with an historical control group of 17 children who had been in the placebo group of a randomized placebo-controlled trial of ascorbic acid. The average median white cell cystine level attained during treatment in the NCCs was 1.7 ± 0.2 nmol ½ cystine per mg protein. Among cysteamine

patients, glomerular function was maintained over time despite the longer period of treatment and follow-up (up to 5 years vs. 2 years with placebo).

V. Cysteamine bitartrate (Procysbi) is a delayed-release formulation of cysteamine bitartrate (Cystagon). The delayed-release (Procysbi) formulation is dosed twice daily, while the immediate release (Cystagon) is dosed four times daily. Currently, there is insufficient evidence to support an additional adherence benefit from taking cysteamine DR (Procysbi) when considered together with the extensive increase in cost (estimated 90x increase). Additionally, in the pivotal trial for cysteamine DR (Procysbi), there was a higher incidence of adverse reactions in patients taking the delayed release product compared to patients taking immediate-release cysteamine (Cystagon).

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Removed PA for cysteamine bitartrate (Cystagon) in favor of RDx edit programming. Adjusted policy to reflect programming change. Updated supporting evidence.	02/2024
Addition of Procysbi granule packets	04/2020
Policy created	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP103

Description

Dalfampridine ER (Ampyra) is an orally administered broad-spectrum potassium channel blocker with an unknown mechanism of action for its therapeutic effect.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
dalfampridine ER (Ampyra)	Improve walking in patients with multiple sclerosis	10 mg tablets	60 tablets/30 days

Initial Evaluation

I. **Dalfampridine ER (Ampyra)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Must be prescribed by, or in consultation with, a neurologist; **AND**
   C. A diagnosis of **multiple sclerosis** when the following are met:
      1. Member does not have a history of seizures; **AND**
      2. Member has a creatinine clearance (CrCl) >50 mL/min; **AND**
      3. Member has difficulty walking or leg weakness; **AND**
         i. Member must be able to ambulate (i.e., not wheelchair bound); **AND**
      4. Member is taking concurrent disease modifying therapy for multiple sclerosis (i.e., glatiramer acetate, dimethyl fumarate, interferon beta-1a, etc.) unless contraindicated.; **AND**
      5. If request is for brand Ampyra, documentation of treatment with generic dalfampridine ER has been ineffective, contraindicated, or not tolerated

II. Dalfampridine ER (Ampyra) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute spinal cord injury
   B. Disorder of neuromuscular transmission
   C. Alzheimer's disease, dementia
   D. Botulism
   E. Reversal of neuromuscular blockade
   F. Toxicity of calcium channel blockers

G. Non-ambulating members with multiple sclerosis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member is taking concurrent disease modifying therapy for multiple sclerosis (i.e., glatiramer acetate, dimethyl fumarate, interferon beta-1a, etc.) unless contraindicated.; **AND**
IV. Member has demonstrated disease stability or improvement (e.g improvement in walking distance or speed); **AND**
V. If request is for brand Ampyra, documentation of treatment with generic dalfampridine ER has been ineffective, contraindicated, or not tolerated

Supporting Evidence

I. Multiple sclerosis (MS) is a common immune-mediated inflammatory disease of the central nervous system, and is characterized by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. However, because symptoms are non-specific and there are no clinical findings that are unique to MS, evaluation and care of patients with MS should be conducted by a specialist.
II. Dalfampridine ER (Ampyra) was studied in two randomized controlled trials that evaluated improvement in the timed 25-foot walk using percentage of timed walk responders as the primary outcome. Patients included in the clinical trials were required to be able to ambulate. Dalfampridine ER (Ampyra) had a significantly greater number of responders compared to placebo in both trials. Trial one had 42.9% vs 9.3% responders ($p<0.0001$) for dalfampridine ER (Ampyra) and placebo respectively. Trial two had 35% vs 8% responders ($p<0.0001$) for dalfampridine ER (Ampyra) and placebo respectively.
III. Dalfampridine ER (Ampyra) has only been studied in patients aged 18 years and older; therefore, safety and efficacy of dalfampridine ER (Ampyra) in the pediatric population remains undefined.
IV. Use of dalfampridine ER (Ampyra) is contraindicated in patients with a prior history of seizure and in those with a CrCl less than 50 mL/min. Seizures have been reported in patients with no history of seizure, and minor renal impairment (CrCl 51 to 80 mL/min) may increase risk of seizures. Permanent discontinuation is advised if seizures occur.
V. Dalfampridine ER (Ampyra) is typically seen as a complementary therapy to disease modifying therapy (DMT), which remains the standard of care for MS patients to prevent progression of disease. This position is supported by the Guidelines and Best Practices for Appropriate Use of Dalfampridine in Managed Care Populations published in the American Journal of Managed Care. However, multiple clinical trials and meta analyses have identified that the efficacy of dalfampridine is not dependent on DMT or any other medication. The FDA label notes that in the pivotal trials, the majority of patients (63%) were using DMT (interferons, glatiramer acetate, or natalizumab), but the magnitude of improvement in walking speed was independent

of concomitant treatment with these agents. Notably, dalfampridine has the highest utility when initiated in the early stages of MS, and thus initiation soon after diagnosis is imperative to preserve motor function and ambulation. Although there may be instances where monotherapy with dalfampridine ER (Ampyra) may be appropriate based on patient specific characteristics, the use of dalfampridine ER (Ampyra) as complementary therapy to DMT remains appropriate to ensure all facets of MS are addressed.

Investigational or Not Medically Necessary Uses

I. Dalfampridine ER (Ampyra) has not been adequately studied for the following conditions and does not have established safety and efficacy in these populations:
   A. Acute spinal cord injury
   B. Disorder of neuromuscular transmission
   C. Alzheimer's disease, dementia
   D. Botulism
   E. Reversal of neuromuscular blockade
   F. Toxicity of calcium channel blockers

II. Dalfampridine ER (Ampyra) was only studied in patients able to ambulate and is not indicated for non-ambulating members with multiple sclerosis

References

1. Dalfampridine ER [Prescribing Information]. Basking Ridge, NJ: Micro Labs USA, Inc. March 2019.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Annual review completed. Adjusted length of initial duration to six months. Added requirement that member has difficulty walking to initial criteria and member is using in combination with DMT to renewal criteria. Updated supporting evidence.	03/2023
Added requirement to trial generic dalfampridine ER prior to branded Ampyra on continuation	05/2022
Transitioned criteria to policy	10/2019
Previous reviews	10/2011;

	05/2013; 01/2016; 11/2018;

Policy Type: PA/SP Pharmacy Coverage Policy: UMP016

Split Fill Management*

Description

Dasatinib (Sprycel) is an orally administered tyrosine kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
dasatinib (Sprycel)	20 mg tablets	Philadelphia chromosome-positive (Ph+) Chronic myeloid leukemia (CML)/ Ph+ Acute lymphoblastic leukemia (ALL)	90 tablets/30 days
	50 mg tablets		30 tablets/30 days
	70 mg tablets		30 tablets/30 days
	80 mg tablets		30 tablets/30 days
	140 mg tablets		30 tablets/30 days
	100 mg tablets	Chronic phase CML	30 tablets/30 days
	70 mg tablets	Gastrointestinal Stromal Tumors (GIST)	60 tablets/30 days

Initial Evaluation

I. Dasatinib (Sprycel) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in coordination with, an oncologist; **AND**
   B. A diagnosis of one of the following:
      1. **Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL); AND**
         i. Adult member with resistance or intolerance to prior therapy; **AND**
            a. If resistance to prior TKI therapy:
               i. Member does not have BCR-ABL mutations T315I, V299L, or F317L; **OR**
         ii. Newly diagnosed pediatric member ≥1 year of age; **AND**
         iii. Used in combination with chemotherapy; **OR**
      2. **Ph+ Chronic myeloid leukemia (CML)**; **AND**
         i. Adult or pediatric member with newly diagnosed Ph+ CML in chronic phase; **OR**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

ii. Adult or pediatric member with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy; **AND**
    a. If resistance to prior TKI therapy:
        i. Member does not have BCR-ABL mutations T315I, V299L, and F317L; **OR**

3. Gastrointestinal Stromal Tumors (GIST); AND

i. BCR-ABL KD mutational status contains PDGFRA D842V mutation; **AND**

ii. Member has tried and failed imatinib (Gleevec) AND sunitinib (Sutent) AND regorafenib (Stivarga) for the treatment of gastrointestinal stromal tumors

II. Dasatinib (Sprycel) is considered investigational when used for all other conditions, including but not limited to:
    A. Pancreatic cancer - Metastatic

Renewal Evaluation

I. No increase in the rate of disease progression while on therapy

Supporting Evidence

I. Per NCCN guidelines dasatinib (Sprycel) is not active against cells harboring the ABL mutations T315I, V299L, and F317L. Thus for patients with disease resistant to TKI therapy it becomes important to identify potential ABL mutations that may underlie the observed resistance to treatment.

II. The efficacy of Sprycel was investigated in open label trials in adult patients with Ph+ CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib: 1,158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. Overall, 80% of patients had imatinib-resistant disease and 20% of patients were intolerant to imatinib. The primary efficacy endpoint of major cytogenetic response (MCyR) in chronic phase CML was met in 63% of patients. The primary efficacy endpoint of major hematologic response (MaHR) in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was met in 44% of Sprycel patients by 7 years.

III. Prior therapy includes a minimum of 30 to 60 day trial of imatinib 400mg or more per day without a complete hematologic response or discontinuation of imatinib therapy due to toxicity. Dosing may be escalated to 180 mg once daily in patients who do not achieve a hematologic or cytogenic response at the recommended dosage.

IV. In clinical trials imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

V. The approval for Sprycel for pediatric patients with Ph+ ALL was based on findings from a phase II trial (NCT01460160), which demonstrated a 3-year event-free survival (EFS) 64.1% (95% CI, 52.4%-74.7%) in 78 pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. This trial compared dasatinib (Sprycel) plus chemotherapy versus chemotherapy alone in the external

historical control trial. Another TKI, Gleevec, was approved for this same patient population in 2013. There is no head to head study comparing Gleevec to Sprycel for Ph+ ALL in pediatric patients. NCCN guidelines recommend all tyrosine kinase inhibitors within the same 2a recommendation.

VI. Dasatinib (Sprycel) in the setting of newly diagnosed chronic phase CML in adults was approved based on the DASISION trial (NCT00481247) an open label, randomized trial comparing Sprycel to imatinib. The primary endpoint of rate of confirmed complete cytogenetic response (CCyR) within 12 months was achieved in 76.8% of Sprycel patients versus 66.2% of imatibib patients. After 60 months follow-up, median time to confirmed complete cytogenetic response was 3.1 months in 215 Sprycel responders and 5.8 months in 204 imatinib responders.

VII. Treatment of Ph+ CML in chronic phase in pediatric patients ≥1 year of age was evaluated in two pediatric studies: an open-label, non-randomized dose-ranging trial (NCT00306202) and an open label, non-randomized, single-arm trial (NCT00777036). With a median follow-up of 4.5 years in newly diagnosed patients, the median durations of CCyR, MCyR, and major molecular response (MMR) could not be estimated as more than half of the responding patients had not progressed at the time of data cut-off. With a median follow-up of 5.2 years in imatinib-resistant or -intolerant patients, the median durations of CCyR, MCyR, and MMR could not be estimated as more than half the responding patients had not progressed at the time of data cut-off.

VIII. In the setting of GIST, NCCN guidelines recommend following imatinib and sutinib, therapy with regorafenib (Cat 1). Regorafenib may then be followed by dasatinib (Sprycel) (Cat 2a). Dasatinib (Sprycel) is thus recommended as a fourth line agent in the setting of D842V mutation status.

Investigational or Not Medically Necessary Uses

I. Pancreatic Cancer Metastatic
   A. Sprycel is currently being evaluated for use in metastatic pancreatic cancer and is the subject of ongoing clinical trials. A phase 2 study of dasatinib (Sprycel) added to gemcitabine for subjects with locally-advanced pancreatic cancer (LAPC) was recently completed.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to new format. Added new indication in pediatric patients with newly diagnosed Ph+ ALL. Added patient specific mutation assessment in the relapsed CML and ALL settings.	02/2019
Removed pregnancy question and adult only language as this is now approved for pediatric indications. Added regorafenib as an additional prior agent in GIST indication, as well as assessing patient specific mutation that received benefit in GIST in the salvage setting.	01/2018
Previous Reviews	03/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP202

Description

Decitabine/cedazuridine (Inqovi) is an orally administered combination of DNA methylation inhibitor and cytidine deaminase inhibitor.

Length of Authorization

I. Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
decitabine/cedazuridine (Inqovi)	35/100 mg tablet	Myelodysplastic Syndrome (MDS); Chronic myelomonocytic leukemia (CMML)	5 tablets/28 days

Initial Evaluation

I. Decitabine/cedazuridine (Inqovi) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. Decitabine/cedazuridine (Inqovi) will be used as monotherapy; **AND**
   D. Provider attests that member's bone marrow blast count is less than (<) 20%; **AND**
   E. Member has a diagnosis of **Myelodysplastic syndrome (MDS)**; **AND**
      I. Member has one of the following French-American-British (FAB) subtypes of **myelodysplastic syndrome (MDS)**:
         a. Refractory anemia; **OR**
         b. Refractory anemia with ringed sideroblasts; **OR**
         c. Refractory anemia with excess blasts; **OR**
         d. Chronic myelomonocytic leukemia (CMML); **AND**
      II. Documentation of the members International Prognostic Score (IPSS) denoting whether the member has intermediate or high risk (e.g. IPSS Intermediate-1; Intermediate-2, or high risk); **AND**
      III. Treatment with IV azacitidine (Vidaza) OR IV decitabine (Dacogen) has been ineffective, contraindicated, or not tolerated

II. Decitabine/cedazuridine (Inqovi) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute myeloid leukemia (AML)

B. Lower risk myelodysplastic syndrome (e.g. IPSS low; IPSS-R Very low, low; WPSS very low, low)
C. Refractory anemia with del(5q) abnormality
D. Chronic myelogenous leukemia (CML)
E. Acute lymphoblastic leukemia (ALL)
F. Multiple myeloma (MM)
G. Ovarian cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited response to treatment defined by complete or partial response to treatment, disease stabilization, or achieving transfusion independence

Supporting Evidence

I. Decitabine/cedazuridine (Inqovi) is FDA-approved for use in patients aged 18 years and older. Decitabine/cedazuridine (Inqovi) is a combination of DNA methylation inhibitor and cytidine deaminase inhibitor, indicated for the treatment of MDS, including previously treated and untreated, de novo and secondary MDS, and CMML.
II. Myelodysplastic syndrome is a heterogeneous disease involving ineffective, dysplastic hematopoiesis leading to cytopenias, bleeding, infections, and in one-third of patients ultimately progressing to acute AML. CMML is a related hematopoietic condition involving peripheral blood monocytosis. MDS may be classified in to seven subtypes as per French-British-American (FAB) system. Decitabine/cedazuridine (Inqovi) received FDA-approved for four of the seven subtypes, namely: refractory anemia; refractory anemia with ringed sideroblasts; refractory anemia with excess blasts; and CMML**.** Additionally, approval of decitabine/cedazuridine (Inqovi) was limited to intermediate-1 (Int-1), Int-2, and high-risk MDS according to the IPSS classification.
III. Based on symptoms at presentation (fatigue, bone pain, frequent infections, and bleeding), MDS may be misdiagnosed as other conditions such as anemia, HIV infection, autoimmune disorder or osteomyelitis. Proper diagnosis and treatment of MDS requires histochemical and cytogenetic studies; therefore, decitabine/cedazuridine (Inqovi) must be prescribed by, or in consultation with an oncologist or hematologist.
IV. The only FDA-approved therapies for Int-1, Int-2, and high-risk MDS and CMML are IV administered hypomethylating agents (HMA): azacitidine (Vidaza) and decitabine (Dacogen). Lenalidomide (Revlimid) oral capsule also has FDA approval for treatment of MDS; however, use of this drug is limited to transfusion-dependent anemia in low-risk MDS with 5q deletion. Decitabine/cedazuridine (Inqovi) tablet is the first oral HMA and provides the advantage of self-

administration for patients. Decitabine/cedazuridine (Inqovi) may be considered an alternative first-line therapy option for MDS and CMML treatment.

V. Regimens involving combination of IV administered HMA (azacitidine and decitabine) with other agents such has ruxolitinib (Jakafi), and venetoclax (Venclexta) have been studied and recommended by NCCN guidelines in the settings of MDS, CMML, and AML. Limited low quality clinical data are also available with respect to combinations of IV HMA with lenalidomide (Revlimid), vorinostat (Zolinza), phenylbutyrate or valproic acid. However, efficacy and safety of decitabine/cedazuridine (Inqovi) in combination with other drugs for the treatment of MDS and CMML has not been studied and remains unknown. Additionally, decitabine/cedazuridine (Inqovi) has not received FDA-approval for any other indications (e.g. CLL, AML).

VI. Decitabine/cedazuridine (Inqovi) was studied in two (Phase 2 ASTX727-1-B trial, and Phase 3 ASCERTAIN), open-label, randomized, crossover trials in 222 patients with Int-1 or Int-2 or high risk MDS or CMML. Patients with de novo or secondary MDS or CMML were included. Additional inclusion criteria consisted of absence of secondary hematological malignancy and a bone marrow blast count of ≤ 20% (of note, a bone marrow blast count of >20% is a parameter used in differential diagnosis of AML versus MDS). One prior cycle of decitabine or azacitidine was allowed, but no other chemotherapy within two weeks before randomization was permitted.

VII. The primary efficacy outcome was pharmacokinetic (PK) measurement of five-day exposure of oral decitabine/cedazuridine (Inqovi) vs IV decitabine, using area under the curve (AUC) during first two cycles of treatment. Decitabine/cedazuridine (Inqovi) showed comparable PK data to that of IV decitabine during cycles one and two of the treatment. For Phase 3 (ASCERTAIN) study, five-day oral/IV decitabine exposure was 98.9% (90% CI; 92.7, 105.6). Additionally, overall response rates (ORR) were reported in 60% patients across all cohorts during Phase 2 trial, with 21% patients exhibiting complete response (CR) to decitabine/cedazuridine (Inqovi).

VIII. Safety data was pooled from both studies. Reported treatment emergent adverse events (TEAE) were similar between oral and IV decitabine patient populations with neutropenia, thrombocytopenia, leukopenia, anemia, pneumonia, and sepsis as the most common. Gastro-intestinal (GI) adverse reactions were comparable between oral and IV formulations of decitabine. Thirteen (6.1%) deaths were reported during treatment period, among which, 11 (5.2%) were associated to adverse events. Overall, 30-day mortality rate was 0.5%.

IX. Decitabine/cedazuridine (Inqovi) has not been compared with IV azacitidine (Vidaza) or IV decitabine (Dacogen) in head-to-head clinical trials. The majority of the safety and efficacy data for hypomethylating agents in the MDS treatment space are rooted in the trials for the IV therapies. Approval of decitabine/cedazuridine (Inqovi) was based off of comparative pharmacokinetic exposure to decitabine between oral and IV formulations. Although this trial showed comparable efficacy and safety, there is lack of data to show superiority of the oral decitabine/cedazuridine (Inqovi) over IV decitabine (Dacogen). Weighing the safety, efficacy, cost, and clinical experience, IV therapies are considered standard and appropriate high-value treatment options for MDS and CMML and are preferred over decitabine/cedazuridine (Inqovi).

Investigational or Not Medically Necessary Uses

I. Decitabine/cedazuridine (Inqovi) has not been sufficiently studied for safety and efficacy for any other condition to date.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP018

Description

Deflazacort (Emflaza) is an orally administered corticosteroid prodrug whose active metabolite exerts anti-inflammatory and immunosuppressive effects. Vamorolone (Agamree) is an orally administered dissociative steroid that suppresses the inflammatory pathway.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
deflazacort (Emflaza)	Duchenne Muscular Dystrophy	6 mg tablets	0.9 mg/kg/day (round to nearest tablet size)
		18 mg tablets	
		30 mg tablets	
		36 mg tablets	
generic deflazacort		22.75 mg/mL oral suspension	
vamorolone (Agamree)		40 mg/mL	225 mL/ 30 days

Initial Evaluation

I. **Deflazacort (Emflaza)** and **vamorolone (Agamree)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a neuromuscular specialist or neurologist; **AND**
   B. Must not be used in combination with each other for treatment of Duchenne Muscular Dystrophy (DMD); **AND**
   C. A diagnosis of **Duchenne Muscular Dystrophy (DMD)** when the following are met**:**
      1. Documentation of DMD gene mutation; **OR**
         i. Documentation of total absence of dystrophin confirmed by muscle biopsy; **AND**
      2. Member is two years or older; **AND**
      3. Member displays delayed motor milestones (e.g., child not walking by 18 months, toe walking, poor head control, not running by three years old, struggling to hop, abnormal gait, difficulty ambulating without assistance, etc.); **AND**
   D. Member's current weight is documented; **AND**
   E. Treatment with oral prednisone for six months or greater has been ineffective, not tolerated, or contraindicated ; **AND**
   F. Treatment with generic deflazacort has been ineffective, not tolerated, or contraindicated

II. Deflazacort (Emflaza) and vamorolone (Agamree) are considered investigational when used for all other conditions, including, but not limited to:
   A. Dysferlinopathies: including Miyoshi Myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B)
   B. Ulcerative Colitis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication requested will not be used in combination with another corticosteroid (e.g., prednisone, deflazacort, etc.); **AND**
IV. Member has responded to therapy, defined as stability or improvement in net motor function, compared to pretreatment baseline (e.g., stability or improvement in gait, muscle strength, etc)

Supporting Evidence

I. DMD (Duchenne Muscular Dystrophy) is a rare X-linked genetic disorder characterized by progressive muscle degeneration and weakness due to alterations in DMD genes required to synthesize a protein called dystrophin. Dystrophin is a major component of the cytoskeleton structure that prevents contraction-induced damage. Muscles with low levels of dystrophin are more sensitive to damage, resulting in progressive muscle loss and function. DMD initially presents as developmental delay and weakness in proximal limb muscle in young male s ages three to five years old. Although rare, DMD may affect girls. Due to its gradual progression, if left untreated, most patients with DMD will lose ambulation before the age of 12 years and require noninvasive ventilation. Treatment in DMD target improving motor function, delaying the onset of cardiac and respiratory complications. Given the rarity and complexity of diagnosis and management of DMD, the treatment of DMD must be initiated by, in or consultation with a neurologist or neuromuscular specialist.
II. Suspected cases of DMD should be referred to a neuromuscular specialist to evaluate creatinine kinase levels. If these are elevated, the diagnosis of DMD should be confirmed by dystrophin genetic testing. In rare cases genetic testing may be negative, but a diagnosis can still be confirmed by a muscle biopsy and dystrophin analysis.
III. There are no curative therapies for DMD. Supportive care is crucial for optimizing health and quality of life for patients with DMD. The 2016 American Academy of Neurology Recommendation on Corticosteroid Use in Duchenne Muscular Dystrophy note that glucocorticoids may be used to improve physical functioning and should be started prior to substantial physical decline. Prednisone and deflazacort have been shown to improve motor and pulmonary function and improve survival. Guidelines have not been updated to include vamorolone (Agamree).
IV. Per the American Academy of Neurology 2016 Guideline on Corticosteroid Use in Duchenne Muscular Dystrophy:
   - Prednisone

i. Should be offered for improving strength (Level B) and pulmonary function (Level B)
ii. The preferred dosing regimen of prednisone is 0.75 mg/kg/d (Level B); though this regimen is associated with significant risk of weight gain, hirsutism, and cushingoid appearance (Level B).
iii. Prednisone 10 mg/kg/weekend is found equally effective at 12 months (Level B).
iv. Prednisone may be offered for improving timed motor function, reducing the need for scoliosis surgery, and delaying cardiomyopathy onset by 18 years of age (Level C for each).
v. Retrospective studies and the Duchenne Natural History Study (DNHS) demonstrated that patients with advanced DMD on any steroid regimen for 6 months or greater had significantly longer preserved ambulation.

- Deflazacort
  i. May be offered for improving strength and timed motor function, and delaying age at loss of ambulation (Level C)
  ii. May be offered for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival (Level C for each.)
  iii. Deflazacort (Emflaza) does not provide clinically significant efficacy advantages compared to prednisone, but it is disproportionally more expensive.
- Prednisone and deflazacort are possibly equally effective for improving motor function in patients with DMD. However, there is insufficient evidence to directly compare the effectiveness of prednisone vs deflazacort in cardiac function in patients with DMD.
- Both prednisone and deflazacort have been shown to improve muscle strength compared with placebo.
- There may be differences in weight gain-related adverse events between prednisone and deflazacort.
  i. Central obesity was seen as an adverse event in 25.0% and 24.6% of deflazacort patients compared to 42.9% of prednisone patients and cushingoid appearance was seen in 60.3% and 69.2% of deflazacort patients compared to 77.8% of prednisone patients.

V. Deflazacort (Emflaza) was evaluated in two multicenter, randomized, double-blind, placebo-controlled trials in 225 patients. Study 1 consisted of 196 male pediatric patients, five to 15 years of age with documented mutation of the dystrophin gene, and onset of weakness before five years of age. The primary endpoint was the average change in muscle strength score between baseline and week 12. The average change was 0.15 (95% CI 0.01, 0.28) and -0.10 (95% CI -0.23, 0.03) for the deflazacort (Emflaza) and placebo groups, respectively. Study 2 consisted of 29 male pediatric patients, six to 12 years of age with documented mutation of the dystrophin gene. The primary endpoint was the average muscle strength score at two years. The results were not statistically significant.

VI. Vamorolone is an FDA approved dissociative steroid indicated for treatment of DMD. Vamorolone is available as a 40mg/mL suspension and dosing is weight-based. Per label, the

recommended dose of vamorolone is 6mg/kg, with a max of 300mg daily for those >50kg. A dissociative steroid retains a selective anti-inflammatory profile and assumed to have a favorable side effect profile compared to traditional corticosteroids with reduced bone fragility, metabolic disturbance, and immune suppression.

VII. Vamorolone was studied in a phase IIb, multicenter, double-blinded, randomized, placebo- and prednisone-controlled trial (VISION-DMD phase IIb) in 121 boys ages ≥ 4 years and <7 years old with confirmed DMD via DMD gene mutation or muscle biopsy. Participants were randomized to receive low or high dose vamorolone (2mg/kg [N=30] or 6mg/kg [N=30]), prednisone (0.75mg/kg [N=30]) or placebo (N=31) daily. Patients that received prior treatment with oral glucocorticoids or other immunosuppressants or clinically significant cardiac disease were excluded. Baseline characteristics were similar between all groups with a mean age of 5.4 years, weight of 20kg, 82.9% Caucasian, and baseline time to stand (TTSTAND) velocity of 1.7m/s.

VIII. The primary endpoint was TTSTAND from supine velocity in the vamorolone 6 mg/kg per day group vs placebo. Treatment with vamorolone 6 mg/kg/day resulted in statistically significant lower TTSTAND scores relative to placebo at week 24, least square mean (LSM) 0.05 m/s in high dose vamorolone compared to -0.01 m/s in the placebo group, LSM difference 0.06m/s, p=0.002 (95% CI, 0.02-0.10). Secondary endpoints included TTSAND velocity in the vamorolone 2mg/kg per day group vs placebo, 6-minute walk test (6MWT) and time to run/walk (TTRW) between high dose vamorolone compared to placebo and low dose vamorolone compared to placebo.

- TTSTAND velocity in the vamorolone 2mg/kg per day 0.03 m/s vs placebo -0.01 m/s, LSM difference 0.05 m/s, p=0.02 (95% CI, 0.01-0.08)
    i. TTSTAND is a validated outcome measure for DMD. A difference of 0.05 m/s in TTSTAND velocity is indicative of clinically meaningful changes. Strength testing is reliable and reflects differences between steroid-treated and naive populations between the ages of 4 and 9 years and for stronger and more mobile subpopulations aged 10 and older. However, strength testing has limited continuity across the entire age range of affected individuals from young children to adults.
- 6MWT in the vamorolone 6mg/kg per day 28.3m vs placebo -13.3m LSM difference 41.6m, p=0.003 (95% CI, 14.2-68.9); vamorolone 2mg/kg per day 23.9 m vs placebo -13.3m, LSM difference 37.1, p=0.009 (95% CI, 9.6-64.7)
- TTRW velocity in the vamorolone 6mg/kg per day 0.26m/s vs placebo 0.01m/s LSM difference 0.024 m/s, p=0.024 (95% CI, 0.09-0.39); vamorolone 2mg/kg per day 0.16 m/s vs placebo 0.01 m/s, LSM difference 0.02 m/s, p>0.05 (95% CI, -0.03-0.28)

IX. The number of participants reporting at least one adverse event (AE) was similar between all groups. Participants in the prednisone group experienced linear growth delay, which was not present in the vamorolone group. There were 2 treatment-emergent vertebral fractures at week 24; 1 participant in the prednisone group had a total of 4 incident vertebral fractures, and 1 participant in the placebo group had a single incident vertebral fracture.

X. Additionally, 41 participants enrolled in a 30-month open label extension trial. Participants were matched and compared with participants from the DNHS. Participants in DNHS were first eligible for inclusion in the control group after they had experienced 6 months of continuous glucocorticoid exposure. There was a decrease in mean TTSTAND velocity from baseline to 30 months (0.206 rises/s vs 0.189 rises/s), which was not a statistically significant change (−0.011 rises/s; CI, −0.068 to 0.046 rises/s). There were no statistically significant differences between

participants receiving high dose vamorolone and matched participants in the historical control groups receiving glucocorticoid treatment.

XI. The clinical program for vamorolone (Agamree) consisted of a moderate to well-designed randomized clinical trial reporting consistent improvement in TTSTAND score, which is an objective, validated measure of muscular function in DMD. Milestones of disease progression, such as loss of ability to rise from floor, ambulate 10 m and self-feed occur in a predictable order, and loss of those abilities can be predicted by timed functional evaluations. The generalizability of current clinical data may be limited due to exclusion of patients with severe disease. However, in the absence of substantial physical decline, vamorolone (Agamree) may provide potential clinical benefit similar to standard of care glucocorticoids.

XII. DMD treatment guidelines have not been updated to include vamorolone (Agamree). The FDA-label for vamorolone (Agamree) has similar warnings and precautions as prednisone and deflazacort (Emflaza). These glucocorticoids have similar safety and efficacy profiles and requiring step through prednisone and generic deflazacort is both clinically appropriate and cost-effective.

Investigational or Not Medically Necessary Uses

I. Dysferlinopathies: including Miyoshi Myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B)
   A. Deflazacort as an ineffective therapy in dysferlinopathies was shown in a double-blinded, placebo-controlled trial. Further evaluation is needed to support use of deflazacort (Emflaza) in this setting.

II. Vamorolone (Agamree) has not been FDA-approved, or sufficiently studied for safety and efficacy for Ulcerative Colitis
   A. There is a withdrawn phase I/II study evaluating the use of vamorolone in pediatric ulcerative colitis.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added step therapy requirement through generic deflazacort for brand vamorolone (Agamree) and brand deflazacort (Emflaza) and updated supporting evidence to reflect required step therapy.	02/2024
Realigned QL table and placed dosage form next to quantity limit. Added vamorolone to QL table Updated initial evaluation to include muscle biopsy and clinical features for diagnosis of DMD. Added vamorolone criteria and investigational condition. Updated supporting evidence.	11/2023
Updated initial approval duration to six months, and QLL box with weight-based dosing. Added requirement for neuromuscular specialist or neurologist. Included requirement for confirmation of diagnosis by genetic testing and addition of member weight to confirm dosing. Requires prednisone be tried and failed for six months to be deemed ineffective or have intolerance. Updated renewal criteria to include requirement for previous approval by Moda and not allowing establishing therapy with samples. Added examples of symptom improvement to renewal criteria.	05/2020
Revised to policy format, include use in pediatric patients down to two years of age.	07/2019
Update to criteria	01/2017
Criteria creation	05/2017

Policy Type: PA Pharmacy Coverage Policy: UMP165

Description

Test strips and meters are used to measure the concentration of glucose in the blood through a small blood draw sample from piercing the skin (typically on the finger).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Test Strips and Glucometers	Test Strips	Type 1 and type 2 diabetes mellitus	300 test strips/30 days
	Glucometers		One meter/365 days

Test Strips

Initial Evaluation

FreeStyle, FreeStyle Lite, FreeStyle InsuLinx, FreeStyle Precision Neo, Precision Xtra, Contour, and Contour Next are the preferred diabetic test strips.

- There is no prior authorization required on these preferred agents, unless requesting over the allowed quantity limits noted above.

I. **Non-preferred test strips** may be considered medically necessary when the following criteria below are met:
   A. Member is using one of the following quantity limits**:**
      1. 300 test strips per 30-day supply; **OR**
      2. Above 300 test strips per 30-day supply and there is documentation of medical necessity submitted for a quantity above 300 test strips per 30-day supply; **AND**
   B. Use of ALL of the following preferred test strips have been ineffective:
      1. FreeStyle
      2. FreeStyle Lite
      3. FreeStyle InsuLinx
      4. FreeStyle Precision Neo
      5. Precision Xtra
      6. Contour
      7. Contour Next; **OR**

C. Member uses test strips with a glucometer built into, or communicates with, an insulin pump and preferred products cannot be utilized; **OR**
D. Member uses a voice meter due to vision impairment

Glucometers

Initial Evaluation

FreeStyle Lite, FreeStyle Freedom Lite, Contour Next Gen, Contour Next EZ, and Contour Next One are covered at zero cost share to the member only through the manufacturer Free Meter Program. Members can access their free meter by using any of the options below:

- **By Pharmacy:**
  - Ascensia:
    - BIN: 018844
    - PCN: 3F
    - Group: MGDCARE
    - ID: CNMC7246982
  - Abbott:
    - BIN: 610020
    - PCN: PDMI
    - Group: 99992432
    - ID: ERXNAVITUS
- **By Telephone:**
  - Ascensia: 1-800-401-8440, use offer code BDC-MOD
  - Abbott: 1-866-224-8892, use offer code KYDCW4DQ
- **By Web:**
  - Ascensia:
    - Contour Next Gen Meter: www.ascensiadiabetes.com/meters-and-strips-savings/free-contour-next-gen-meter/
    - Contour Next EZ Meter: www.ascensiadiabetes.com/meters-and-strips-savings/free-contour-next-ez-meter/
    - Contour Next One Meter: www.ascensiadiabetes.com/meters-and-strips-savings/free-contour-next-one-meter/
  - Abbott: www.choosefreestyle.com , use offer code KYDCW4DQ

I. **All other meters** may be considered medically necessary when the following criteria below are met:
   A. Documentation that use with FreeStyle Lite, FreeStyle Freedom Lite, Contour Next Gen, Contour Next EZ, and Contour Next One is contraindicated; **OR**
   B. Member uses an insulin pump that cannot communicate with any of the following meters: FreeStyle Lite, FreeStyle Freedom Lite, Contour Next Gen, Contour Next EZ, and Contour Next One; **OR**
   C. Member requires the use of a voice meter due to vision impairment

Renewal

I. Same as initial criteria

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to include new meter program information from Ascensia; Updated "Contour Next" name to "Contour Next Gen";	01/2023
Rearranged questions to better capture intent and clarify path to coverage. Updated Glucometer table to more accurate billing information and website information	02/2022
Separated out non-preferred glucometers and test strips criteria. Added in box regarding billing preferred glucometers. Updated Renewal language to run through initial each time.	01/2021
Updated requirements language to be more consistent with plan's standard language. Adjusted order of requirements to enhance clarity.	12/2020
Criteria transitioned into policy with medically not necessary and renewal evaluation sections added.	01/2020
Criteria created	01/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP121

Description

Dichlorphenamide (Keveyis) is a carbonic anhydrase inhibitor; however, the mechanism by which it exerts its therapeutic effects in periodic paralysis is unknown.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
dichlorphenamide (Keveyis)	Primary periodic paralysis	50 mg tablets	120 tablets/30 days
Generic dichlorphenamide			

Initial Evaluation

I. **Dichlorphenamide (Keveyis)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neurologist or provider with experience in primary periodic paralysis (e.g., physiatrist); **AND**
   B. Member is 18 years of age or older; **AND**
   C. If request is for brand dichlorphenamide (Keveyis), treatment with generic dichlorphenamide has been ineffective, contraindicated, or not tolerated; **AND**
   D. A diagnosis of **primary hypokalemic or hyperkalemic periodic paralysis** when the following are met:
      1. Provider attestation that lifestyle modifications to reduce attack frequency and severity (e.g., dietary changes, exercise adjustments) have been maximized and have been ineffective or insufficient alone; **AND**
      2. Documentation of baseline attack frequency and average duration (required for renewal evaluation); **AND**
      3. Treatment with acetazolamide has been ineffective, or not tolerated; **AND**
         i. For hypokalemic periodic paralysis: treatment with a potassium-sparing diuretic (e.g., spironolactone, triamterene, eplerenone) in combination with acetazolamide has been ineffective, contraindicated, or not tolerated (Note: if acetazolamide is not tolerated, monotherapy with a potassium-sparing diuretic is required); **OR**
         ii. For hyperkalemic periodic paralysis: treatment with hydrochlorothiazide has been ineffective, contraindicated, or not tolerated.

II. Dichlorphenamide (Keveyis) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Glaucoma

III. Dichlorphenamide (Keveyis) is considered investigational when used for all other conditions, including but not limited to:
   A. Periodic paralysis not characterized as hyperkalemic or hypokalemic
   B. Pediatric periodic paralysis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation that lifestyle modifications to reduce attack frequency and severity (e.g., dietary changes, exercise adjustments) continue to be practiced; **AND**
IV. Documentation showing reduction in attack frequency, duration, or severity compared to baseline; **AND**
V. If request is for brand dichlorphenamide (Keveyis), treatment with generic dichlorphenamide has been ineffective, contraindicated, or not tolerated

Supporting Evidence

I. Periodic paralysis (PP) is a rare neuromuscular disorder due to a defect in muscle ion channels, and is characterized by attacks of painless muscle paralysis and generalized weakness. The majority of PP cases are hereditary and not a result of hypo or hyperkalemia. Two types of PP include hypokalemic and hyperkalemic, pertaining to the serum level of potassium at the time of attack. Attacks may last minutes, hours, or days causing increased morbidity and impaired quality-of-life. Nonpharmacologic interventions may reduce frequency or severity of attacks. For hypokalemic PP, effective strategies may include a low sodium and low carbohydrate diet, supplementation with potassium, limiting vigorous exercise, minimizing stress, limiting alcohol intake, and avoidance of fasting. For hyperkalemic PP, effective strategies may include avoidance of potassium-rich foods, avoidance of fasting, minimizing exposure to cold, minimizing stress, and limiting vigorous exercise. When lifestyle modifications are ineffective or insufficient for preventing attacks, medication therapy may be considered (e.g., diuretics, thiazides, carbonic anhydrase inhibitors).
II. Given the difficulty with diagnosing PP and specialized management and treatment of the condition, prescribing by, or in consultation with, a specialist is required.
III. Dichlorphenamide (Keveyis) is indicated for the treatment of primary hypokalemic and hyperkalemic PP and related variants; however, it has only been evaluated in hypokalemic and hyperkalemic PP.

IV. Dichlorphenamide (Keveyis) has been evaluated in Phase 3 clinical trials of adults with hypokalemic and hyperkalemic PP patients. Overall, trials showed that therapy may help reduce 2-4 attacks per week compared to placebo; however, the studies has several limitations: patients transitioning from acetazolamide to dichlorphenamide did not have a washout period before entering the study, hypokalemic patients could supplement with potassium as required for acute attacks, and adverse effects (e.g., dysgeusia, cognitive issues, and paresthesia) were more common in the dichlorphenamide group – which may have led to unblinding the trial. Given these considerations, therapeutic effects may not be fully attributable to dichlorphenamide (Keveyis).

V. Other treatment strategies:
- Dichlorphenamide (Keveyis) may have an advantage in the level of trials available (Phase 3); however, given trial shortcomings listed above as well as the cost of treatment, trial of acetazolamide and one additional therapy (see below) are required. Empiric treatment with acetazolamide is standard of care, and is significantly less costly ($2-8 per day vs. $330-1300 per day). Acetazolamide and dichlorphenamide are in the same medication class and are expected to have similar tolerance. Contraindications to acetazolamide are the same as those to dichlorphenamide (Keveyis). Additionally, it has not been proven that dichlorphenamide (Keveyis) is superior to acetazolamide in safety or efficacy, as there are no comparative studies.
- For hypokalemic PP prophylaxis, potassium-sparing diuretics (e.g., spironolactone, triamterene, eplerenone) may be effective pharmacotherapy. These may be used in conjunction with carbonic anhydrase inhibitors or as monotherapy in patients that did not tolerate or experienced efficacy with carbonic anhydrase inhibitors. It has not been proven that dichlorphenamide (Keveyis) is superior to potassium-sparing diuretics in safety and efficacy as there are no comparative studies. Additionally, dichlorphenamide (Keveyis) is more costly; thus, trial of a potassium-sparing diuretic is required before coverage consideration of dichlorphenamide (Keveyis). Use in addition to, or as second-line treatment after, acetazolamide may maximize efficacy of these therapies and is required prior to coverage consideration of dichlorphenamide (Keveyis).
- For hyperkalemic PP, hydrochlorothiazide may be effective pharmacotherapy. It has not been proven that dichlorphenamide (Keveyis) is superior to hydrochlorothiazide in safety or efficacy as there are no comparative studies. Additionally, dichlorphenamide (Keveyis) is more costly; thus, trial of hydrochlorothiazide is required before coverage consideration of dichlorphenamide (Keveyis).

VI. Efficacy, if realized, should occur by two months of therapy. The prescribing information indicates that response should be evaluated after two months. Given variability of patient response, risk of therapy exacerbating the condition symptoms, and cost, documentation of improvement of attack frequency, severity or duration is required prior continuation of treatment. Of note, withdrawal from the study due to acute and severe worsening of symptoms occurred in two patients in clinical trials for dichlorphenamide (Keveyis). Without reduction in attack frequency, severity, or duration, therapy should not be continued. Three months is allowed for initial approval to allow time for assessment of response and continuity of care.

Investigational or Not Medically Necessary Uses

I. Dichlorphenamide (Keveyis) is not FDA-approved, or has not been sufficiently studied for safety and efficacy for the following conditions:
   A. Glaucoma: dichlorphenamide (Daranide) was FDA-approved for glaucoma in 1958, and it was subsequently thought to be effective, off-label, for periodic paralysis. Dichlorphenamide (Daranide) was discontinued in 2002, given lack of use for glaucoma and availability of many effective therapies for glaucoma. Therapy is now available from an alternative manufacturer, as brand Keveyis. Although dichlorphenamide has been utilized in glaucoma historically, at this time it is unproven if dichlorphenamide (Keveyis) is more likely to produce similar therapeutic results or is superior to other agents that could be utilized for glaucoma (i.e., ophthalmic carbonic anhydrase inhibitors). Additionally, it is not generally recognized as an appropriate treatment for this condition. Furthermore, dichlorphenamide (Keveyis) is significantly more costly that other therapies that could be utilized. Given these factors dichlorphenamide (Keveyis) is not medically necessary for treatment of gluacoma.
   B. PP not characterized as hypokalemic or hyperkalemic (i.e., Thyrotoxic PP, Andersen syndrome, etc.): dichlorphenamide (Keveyis) is indicated for the treatment of primary hyperkalemic PP, primary hypokalemic PP, and related variants; however, has only been evaluated in hypokalemic and hyperkalemic PP. Use for other variations of PP is considered experimental and investigational.
   C. Pediatric/adolescent PP: Dichlorphenamide (Keveyis) has not been sufficiently evaluated and is not FDA-approved in pediatric or adolescent patients. To date, one study has attempted to evaluate safety and efficacy of dichlorphenamide (Keveyis) in adolescent patients. The study included six adolescents that were exposed to therapy, five of which were evaluable for efficacy. Although median decrease from baseline in weekly attack frequency was numerically greater compared to placebo, the trial had multiple shortcomings. It was not powered to statistically evaluate changes in attack frequency for the adolescent subgroup, the trial duration was only nine weeks long, few patients were evaluated, and the dose varied between patients. Safety concerns included skin rash, dizziness, numbness, lightheadedness, slow thinking, nausea, weakness, and weight loss among adolescent patients. This trial did not sufficiently determine consequences of therapy in adolescents, and safety and efficacy in this population remains unknown; thus, is considered experimental and investigational. Lifestyle modifications and alternative therapies may be considered.

References

1. Keveyis [Prescribing Information]. Hawthorne, NY: Taro Pharmaceuticals; November 2019.
2. Statland JM, Fontaine B, Hanna MG, et al. Review of the Diagnosis and Treatment of Periodic Paralysis. Muscle Nerve. 2018;57(4):522-530.
3. Ciafaloni E, Cohen F, Griggs R. Efficacy and safety of dichlorphenamide for primary periodic paralysis in adolescents compared with adults. *Pediatr Neurol*. 2019;101:43-46.
4. Sansone VA, Burge J, McDermott MP, et al. Randomized, placebo-controlled trials of dichlorphenamide in periodic paralysis. Neurology. 2016;86(15):1408-1416.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added generic dichlorphenamide to QL table; added requirement to t/f generic dichlorphenamide prior to us of branded Keveyis	01/2023
Criteria updated: Changed initial approval from two to three months, addition of age requirement, addition of requirement regarding lifestyle modifications, distinction between hyperkalemic and hypokalemic PP with additional associated medication trial. Updated renewal criteria to standard format and to allow only in the event of improvement in the condition. Update to latest policy format, addition of NMN and E/I indications.	07/2022
Prior authorization criteria transitioned to policy format. Updated initial and renewal durations as response should be seen within two months of therapy. Addition of specialist requirements. Addition of renewal criteria.	12/2019
Policy created	09/2015

Policy Type: PA/SP Pharmacy Coverage Policy: UMP104

Description

Dornase alfa (Pulmozyme®) inhalation solution is highly purified solution of recombinant human deoxyribonuclease I (rhDNase), an enzyme which selectively cleaves DNA. In vitro, dornase alfa (Pulmozyme) hydrolyzes the DNA in sputum of cystic fibrosis (CF) patients and reduces sputum viscoelasticity.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
dornase alfa (Pulmozyme)	2.5 mg/2.5 mL single-use ampule	Cystic fibrosis	30 single-use ampule/ 30 days

Initial Evaluation

I. Dornase alfa (Pulmozyme) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by or in consultation with a pulmonologist; **AND**
   B. A diagnosis of **cystic fibrosis (CF); AND**
   C. Medication will be used in conjunction with standard CF therapy [e.g. tobramycin (Bethkis®; Kitabis Pak®; Tobi®; Tobi Podhaler®), azithromycin (Zithromax®), aztreonam (Cayston®), ivacaftor (Kalydeco®), lumacaftor/ivacaftor (Orkambi®), inhaled or oral N-acetylcysteine (Acetadote®, Acys-5®, Mucomyst®, Cetylev®)]

II. Dornase alfa (Pulmozyme) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent; **AND**
II. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

I. Dornase alfa (Pulmozyme) has been evaluated in a randomized, placebo-controlled trial of clinically stable CF patients, five years of age and older and receiving standard therapies for CF. Patients were treated with placebo, 2.5 mg of dornase alfa (Pulmozyme) once a day, or 2.5 mg of dornase alfa (Pulmozyme) twice a day for six months.

II. Administration of dornase alfa (Pulmozyme) reduced the risk of all exacerbations of respiratory symptoms requiring parenteral antibiotic therapy and developing any respiratory tract infection by 27% and 29% for the 2.5 mg daily dose and the 2.5 mg twice daily dose. Data suggests that the effects on respiratory tract infections in older patients (> 21 years) may be lower than in younger patients, and that twice daily dosing may be required in the older patients.

III. While clinical trial data is limited in pediatric patients younger than five years of age, the use of dornase alfa (Pulmozyme) should be considered for pediatric CF patients who may experience potential benefit in pulmonary function or who may be at risk of respiratory tract infection.

IV. Dornase alfa (Pulmozyme) is used in treatment of CF; however, due to the complexity of the disease it should be prescribed by, or in consultation with, a pulmonologist experienced in the treatment of CF.

V. Several methods of newborn screening may be implemented to detect potential CF, such as the immunoreactivity trypsinogen test (IRT), double IRT testing, and pancreatitis-associated protein testing. A positive or equivocal screening test should be followed by CFTR genetic testing and the sweat chloride test.

VI. Dornase alfa (Pulmozyme) is indicated as an adjunct to standard CF therapies [e.g. tobramycin (Bethkis; Kitabis Pak; Tobi; Tobi Podhaler), azithromycin (Zithromax), aztreonam (Cayston), ivacaftor (Kalydeco), lumacaftor/ivacaftor (Orkambi), inhaled or oral N-acetylcysteine (Acetadote, Acys-5, Mucomyst, Cetylev), ipratropium Bromide (Atrovent HFA)].

VII. The recommended dosage is one 2.5 mg single-use ampule inhaled once daily using a recommended nebulizer. Some patients may benefit from twice daily administration. Maximum dose upon clinical review is 60 single-use ampule per 30 days.

Investigational or Not Medically Necessary Uses

There is limited or no evidence to support the use of dornase alfa (Pulmozyme) in conditions other than CF.

References

1. Pulmozyme [package insert]. Genetech, Inc. South San Francisco, CA. December 2014.
2. DeSimone, E. (2018, May 18). Cystic Fibrosis: Update on Treatment Guidelines and New Recommendations. Retrieved from https://www.uspharmacist.com/article/cystic-fibrosis-update-on-treatment-guidelines-and-new-recommendations
3. Fuchs, H. J., Borowitz, D. S., Christiansen, D. H., Morris, E. M., Nash, M. L., Ramsey, B. W., Wohl, M. E. (1994). Effect of Aerosolized Recombinant Human DNase on Exacerbations of Respiratory Symptoms and on Pulmonary Function in Patients with Cystic Fibrosis. New England Journal of Medicine, 331(10), 637–642. doi: 0.1056/nejm199409083311003
4. Mccoy, K., Hamilton, S., & Johnson, C. (1996). Effects of 12-Week Administration of Dornase Alfa in Patients with Advanced Cystic Fibrosis Lung Disease. Chest, 110(4), 889–895. doi: 10.1378/chest.110.4.889

Policy Implementation/Update:

Date Created	10/6/2017
Date Effective	10/6/2017
Last Updated	11/15/2019
Last Reviewed	11/15/2019

Action and Summary of Changes	Date
Updated criteria to policy format	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP122

Description

Droxidopa (Northera®) is an orally administered synthetic amino acid analog that is metabolized to a norepinephrine by the enzyme aromatic L-amino acid decarboxylase (dopa-decarboxylase). Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
droxidopa (Northera)	100 mg capsules	neurogenic orthostatic hypotension (nOH)	90 capsules /30 days
	200 mg capsules		180 capsules /30 days
	300 mg capsules		180 capsules/30 days

Initial Evaluation

Generic droxidopa is the preferred agent.

- There is no prior authorization required for generic droxidopa, unless requesting above the quantity limit noted above.

I. Brand droxidopa (Northera) may be considered medically necessary when the following criteria below are met:

A. Member is 18 years of age or older; **AND**

B. Medication is prescribed by, or in consultation with, a neurologist or cardiologist; **AND**

C. A diagnosis of **neurogenic orthostatic hypotension (nOH)** when the following are met:

1. Member is experiencing one of the following symptoms:
   i. orthostatic dizziness
   ii. light-headedness
   iii. syncope; **AND**
2. Member has an additional diagnosis of:
   i. Primary autonomic failure (Parkinson disease, multiple system atrophy, or pure autonomic failure); **OR**
   ii. Dopamine beta-hydroxylase deficiency; **OR**
   iii. Non-diabetic autonomic neuropathy; **AND**
3. Member has attempted at least one non-pharmacologic intervention (e.g., use of compression stockings/abdominal binder, increasing salt and fluid intake, regular exercise, or discontinuation or reduction of antihypertensive medications); **AND**

4. Treatment with at least one standard therapy (e.g., dihydroergotamine, ephedrine, fludrocortisone, midodrine) for symptomatic nOH has been ineffective, contraindicated, or not tolerated; **AND**
5. Documentation of contraindication or intolerance to generic droxidopa oral capsule (e.g., allergy to an excipient).

II. Droxidopa (Northera) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g. orthostatic dizziness, light-headedness, or syncope).

Supporting Evidence

I. There is a lack of scientific evidence from clinical trials to show safety and efficacy for the use of droxidopa (Northera) in pediatric patients.
II. Neurogenic orthostatic hypotension (nOH) is a fall in blood pressure upon standing as a result of reduced norepinephrine release from sympathetic nerve terminals. nOH is a feature of several neurological disorders that affect the autonomic nervous system, most notably in Parkinson's disease (PD), multiple system atrophy, pure autonomic failure, and other autonomic neuropathies. Droxidopa (Northera) is a prodrug, which is converted to norepinephrine, increases BP, and improves symptoms of nOH. Due to the complexity and association with progressive neurodegenerative disorders, droxidopa (Northera) needs to be prescribed by, or in consultation with, a neurologist or cardiologist.
III. Orthostatic hypotension (OH), a fall in blood pressure (BP) upon standing not due to reduced norepinephrine release, is a very common problem, particularly in the frail elderly. It is the result of a variety of medical conditions, such as intravascular volume depletion, severe anemia, use of antihypertensive therapies, and physical deconditioning. It usually resolves after the underlying cause is treated. nOH, in contrast, is a much less common and chronic condition. nOH is the result of a failure to increase sympathetic vasomotor nerve outflow and an inability to raise peripheral vascular resistance on standing. nOH is a feature of several neurological disorders that affect autonomic neurons. These include neurodegenerative diseases associated with the abnormal deposition of the protein α-synuclein (i.e., synucleinopathies such as Parkinson disease), other peripheral neuropathies, high spinal cord injury, and a handful of rare genetic diseases.
IV. Droxidopa (Northera) is indicated for the treatment of orthostatic dizziness, lightheadedness, or syncope in adult patients with symptomatic nOH caused by primary autonomic failure

(Parkinson's disease [PD], multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.

V. Consensus guidelines for the treatment of nOH are lacking, although there are expert reviews, there are currently no long-term studies showing the impact of treatment on survival, falls, or quality of life. Up to 70% patients with nOH also have supine hypertension, which poses a therapeutic challenge as increasing BP in the upright position can worsen hypertension when supine. Therefore, treatment of nOH requires careful consideration of the potential risks and benefits. The goal of treatment is to reduce symptom burden, prolong standing time, and improve physical capabilities. The steps in management include removing aggravating factors (drug-induced hypotension, anemia, dehydration, prolonged bed rest and physical deconditioning), implementing non-pharmacological measures (physical counter maneuvers, life-style changes, volume expansion, acute drinking of water, sleep with the head of the bed raised, compression stockings, small frequent meals), and pharmacological approaches; while the other methods are effective, many patients with nOH still require pharmacological treatment to raise BP. This is achieved with two strategies: Expanding intravascular volume and increasing peripheral vascular resistance. Medications used for the treatment of nOH consist of the following: dihydroergotamine, ephedrine, fludrocortisone, midodrine, erythropoietin, atomoxetine, pyridostigmine, and droxidopa (Northera).

VI. No sufficient evidence was found to show superiority of one agent over the other.

VII. Classic symptoms of nOH include lightheadedness, dizziness or feeling close to fainting, and when the fall in BP is severe enough: loss of consciousness. In contrast to vasovagal (neurally-mediated) syncope, syncope in nOH occurs without signs of autonomic activation such as sweating, tachycardia, nausea or abdominal discomfort. After syncope, patients with nOH recover quickly and may be unaware of the event. Patients report that symptom severity varies day-to-day and fluctuates throughout the day. Mornings tend to be most difficult as symptoms are aggravated by intravascular volume loss overnight. Meals, particularly carbohydrate-rich, produce splanchnic vasodilatation and post-prandial hypotension (i.e., fall in BP within 2 hours of eating). Physical inactivity and cardiovascular deconditioning are common in patients with nOH, and, as a result, worsens the symptom severity creating a vicious cycle.

Investigational or Not Medically Necessary Uses

There is limited or no evidence to support the use of droxidopa (Northera) in conditions other than nOH.

References

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3. Horacio Kaufmann, MD, Lucy Norcliffe-Kaufmann, PhD, and Jose-Alberto Palma, MD PhD (2015). Droxidopa in neurogenic orthostatic hypotension. Expert Review of Cardiovascular Therapy, 13(8), 875–891. Doi: 10.1586/14779072.2015.1057504. PMID: 26092297 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4509799/

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated initial and renewal criteria to direct to generic	04/2021
Updated criteria to policy format; Added age limit, added attempted at least one non-pharmacologic intervention criteria	11/2019
Policy created	11/2014

Policy Type: PA/SP Pharmacy Coverage Policy: UMP019

Description

Dupilumab (Dupixent) is a subcutaneously administered monoclonal antibody (IgG4 Kappa) that antagonizes interleukin-4 (IL-4) and interleukin-13 (IL-13).

Length of Authorization

- Initial:
  - i. Prurigo nodularis: 6 months
  - ii. All other diagnoses: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
dupilumab (Dupixent)	Asthma (moderate to severe)	200 mg/1.14mL pen injector or prefilled syringe	**Adult:** **First Month**: 4 (200mg OR 300mg) syringes/pens (4.56mL OR 8ml)/42 days **Maintenance:** 2 (200mg OR 300mg) syringes/pens (2.28mL OR 4ml)/28 days
			Pediatric (6-11 years of age): **No Loading Dose** **Maintenance:** • **15 to less than 30 kg:** 1 (200mg/1.14mL) syringes (2.28mL)/28 days; **OR** 1 (300mg/2mL) syringes/pens (2mL)/28days • **30 kg or more:** 2 (200mg/1.14mL) syringes/pens (2.28mL)/28 days
	Atopic Dermatitis (moderate to severe); Atopic Dermatitis (moderate to severe) and comorbid Asthma (Moderate to severe)	300 mg/2mL pen injector or prefilled syringe	**Adult:** **First Month:** 4 (300mg) syringes/pens (8 mL)/28 days **Maintenance:** 2 (300mg) syringes/pens (4 mL)/28 days
			Pediatric (6 – 17 years of age): **First Month:** • **15 to less than 30 kg:** 2 (300mg) syringes/pens (4 mL)/28 days • **30 to less than 60 kg:** 4 (200mg) syringes/pens (4.56 mL)/28 days • **60 kg or more:** 4 (300mg) syringes/pens (8 mL)/28 days **Maintenance:**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

			• **15 to less than 30 kg:** 1 (300mg) syringes/pens (2 mL)/28 days • **30 to less than 60 kg:** 2 (200mg) syringes/pens (2.28 mL)/28 days • **60 kg or more:** 2 (300mg) syringes/pens (4 mL)/28 days
			Pediatric (6 months – 5 years of age): **No Loading Dose** **Maintenance:** • **5 to less than 15kg:** 2 (200mg) syringe/pen (2.28mL)/56 days • **15 to less than 30kg:** 2 (300mg) syringes/pens (4mL)/56 days
	Chronic rhinosinusitis with nasal polyposis	300 mg/2mL pen injector or prefilled syringe	2 (300mg) syringes/pens (4 mL)/28 days
	Prurigo Nodularis	300 mg/2mL pen injector or prefilled syringe	**First month:** 4 (300mg) syringes/pens (8 mL)/28 days **Maintenance:** 2 (300mg) syringes/pens (4 mL)/28 days
	Eosinophilic esophagitis	200 mg/1.14mL pen injector or prefilled syringe 300 mg/2mL pen injector or prefilled syringe	• **15 to less than 30kg:** 2 (200mg) syringes/pens (2.28 mL)/28 days • **30 to less than 40kg:** 2 (300mg) syringes/pens (4 mL)/28 days • **40kg and more**: 4 (300mg) syringes/pens (8mL)/28 days

Initial Evaluation

I. **Dupilumab (Dupixent)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, gastroenterology, immunology, or ENT (ear, nose, throat); **AND**
   B. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, mepolizumab, omalizumab, reslizumab, etc.); **AND**
   C. A diagnosis of one of the following:
      1. **Atopic dermatitis (moderate to severe); AND**
         i. Member is six months of age or older; **AND**
            a. Body surface area (BSA) involvement of at least 10%; **OR**

i. Involves areas of the face, ears, hands, feet, or genitalia; **AND**

ii. Treatment with at least <u>two</u> of the following groups has been ineffective or not tolerated, unless ALL are contraindicated:
   a. Group 1: Topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
   b. Group 2: Topical calcineurin inhibitors (e.g. pimecrolimus cream, tacrolimus ointment)
   c. Group 3: Topical PDE-4 inhibitors (e.g. crisaborole [Eucrisa]); **OR**

2. **Asthma (moderate to severe)**; **AND**
   i. Member is 6 years of age or older; **AND**
   ii. Member has **MODERATE** asthma as defined by <u>one</u> of the following:
      a. Daily symptoms
      b. Nighttime awakenings > 1x/week but not nightly
      c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs daily
      d. Some limitation to normal activities
      e. Lung function (percent predicted FEV1) >60%, but <80%
      f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to mild asthma; **OR**
   iii. Member has **SEVERE** asthma as defined by <u>one</u> of the following:
      a. Symptoms throughout the day
      b. Nighttime awakenings, often 7x/week
      c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs several times per day
      d. Extremely limited normal activities
      e. Lung function (percent predicted FEV1) <60%
      f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**
   iv. Member must have asthma with an eosinophilic phenotype defined as blood eosinophils ≥150 cells/µL within the last 12 months; **AND**
      a. Member must have two or more exacerbations in the previous year requiring daily oral corticosteroids for at least 3 days (in addition to the regular maintenance therapy defined below); **OR**
   v. Member is dependent on oral corticosteroids for asthma control; **AND**
   vi. Member is currently being treated with:
      a. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
         i. One additional asthma controller medication (e.g., long-acting beta-2 agonist [LABA] {e.g., Serevent Diskus}, long-acting muscarinic antagonist [LAMA] {e.g., Spiriva Respimat}, leukotriene receptor antagonist [e.g., Singular], or theophylline); **OR**

b. A maximally tolerated ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **AND**

vii. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of Dupixent, unless contraindicated; **OR**

3. **Chronic rhinosinusitis with nasal polyposis (CRSwNP); AND**
   i. Member is 18 years of age or older; **AND**
   ii. Provider attests that the member has ALL of the following:
      a. Diagnosis of bilateral sinonasal polyposis as evidenced by an endoscopy or computed tomography (CT); **AND**
      b. Member has impaired Health-Related Quality of Life due to ongoing nasal congestion, blockage, or obstruction with moderate to severe symptom severity; **AND**
      c. Member has at least <u>one</u> of the following symptoms:
         i. Nasal discharge
         ii. Facial pain or pressure
         iii. Reduction or loss of smell; **AND**
   iii. Documentation of current persistent symptomatic nasal polyps despite maximal treatment with ALL of the following, unless ineffective, not tolerated, or contraindicated:
      a. Intranasal corticosteroid; **AND**
      b. Oral systemic corticosteroid therapy within the last 12 months; **AND**
   iv. Background intranasal corticosteroid (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of Dupixent, unless contraindicated; **OR**

4. **Eosinophilic Esophagitis (EoE); AND**
   i. Member is one year of age or older; **AND**
   ii. Member weighs at least 40kg (88 lbs); **AND**
   iii. Provider attests that the member has ALL of the following:
      a. Symptoms consistent with eosinophilic esophagitis (e.g., dysphagia, food impaction, vomiting, central chest and upper abdominal pain, etc.); **AND**
      b. Eosinophil-predominant inflammation, consisting of a peak value of ≥15 eos/hpf or ~60 eosinophils/mm^2, as confirmed by endoscopic biopsy; **AND**
      c. Underlying cause of the member's condition is NOT considered to be any other allergic condition(s) or other form(s) of esophageal eosinophilia; **AND**
   iv. Member has experienced persistent EoE symptoms during or following an adequate trial of dietary restriction (e.g., empiric elimination diet); **AND**
   v. Treatment with at least one agent in each of the following classes has been ineffective, contraindicated, or not tolerated:
      a. Proton pump inhibitors (PPIs) for at least eight weeks; **AND**

b. Swallowed topical corticosteroids (e.g., fluticasone, budesonide); **OR**

5. **Prurigo nodularis (moderate to severe)**
   i. Member is 18 years of age or older; **AND**
   ii. Member has a confirmed diagnosis of moderate to severe prurigo nodularis based on all of the following:
      a. Presence of nodules for at least 3 months; **AND**
      b. Pruritis is moderate to severe in severity (e.g., Worst-Itch Numeric Rating Scale (WI-NRS) score of at least 7); **AND**
      c. Provider attests underlying cause of prurigo nodularis is not considered to be drug-induced or caused by other medical conditions, such as dermatillomania; **AND**
   iii. Treatment with at least one medium to very high potency topical corticosteroid (*see appendix*) has been ineffective, not tolerated, or contraindicated; **AND**
   i. Treatment with at least one of the following has been ineffective or not tolerated, unless ALL are contraindicated:
      a. Topical calcineurin inhibitors (e.g. pimecrolimus cream, tacrolimus ointment)
      b. Topical vitamin D analogue (e.g., calcipotriene)
      c. Phototherapy (UVA or PUVB)
      d. Systemic immunosuppressants (e.g. methotrexate or cyclosporine)

II. Dupilumab (Dupixent) is considered investigational when used for all other conditions, including but not limited to:
   A. Chronic obstructive pulmonary disease (COPD)
   B. Food and environmental allergies
   C. Other forms of esophagitis
   D. Gastrointestinal reflux disorder (GERD)
   E. Non-EoE eosinophilic gastrointestinal disorders
   F. Chronic spontaneous urticaria (CSU)
   G. Bullous pemphigoid/prurigo and related conditions (e.g., pemphigoid nodularis, actinic purigo, lichen planus, multiple keratoacanthomas, epidermolysis bullosa pruriginosa, etc.)
   H. Emergency treatment of allergic reactions, including anaphylaxis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, mepolizumab, omalizumab, reslizumab, etc.); **AND**
IV. A diagnosis of one of the following:

- **Atopic dermatitis (moderate to severe); AND**
    i. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, BSA involvement, pruritis symptoms); **OR**
- **Asthma (moderate to severe); AND**
    i. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **AND**
    ii. Background controller medications (e.g., ICS/LABA product listed above) will be continued with the use of dupilumab (Dupixent), unless contraindicated; **OR**
- **Chronic rhinosinusitis with nasal polyposis (CRSwNP); AND**
    i. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in nasal congestion/obstruction severity, reduction in nasal polyps); **AND**
    ii. Background intranasal corticosteroid (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of dupilumab (Dupixent), unless contraindicated; **OR**
- **Eosinophilic esophagitis; AND**
    i. Member has exhibited improvement or stability of disease (e.g., improvement in dysphagia/vomiting/abdominal pain, reduction in eosinophils); **OR**
- **Prurigo nodularis; AND**
    i. Member has exhibited improvement or stability of disease symptoms (e.g., reduced itching/pruritis, improved skin appearance, reduction in number of nodules, etc.)

Supporting Evidence

I. Dupilumab (Dupixent) is FDA approved as an add-on maintenance treatment for patients 12 years and older with moderate to severe asthma with eosinophilic phenotype or with oral corticosteroid dependent asthma, moderate to severe atopic dermatitis for patients 6 months and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, as an add-on maintenance treatment for adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP), and for the treatment of adult patients with prurigo nodularis (PN).

II. Dupilumab trials excluded concomitant biologic therapy; moreover, there is lack of evidence supporting treatment with dual use of biologic therapies and a potential for increased risk of side effects.

III. **Moderate to severe atopic dermatitis**

- For patients aged 12 years or older, dupilumab (Dupixent) was studied in four randomized, double-blind, placebo-controlled trials. In all four trials, investigators enrolled patients who had previous inadequate responses to a topical medication with a PGA score of at least

three (scale of zero to four) and a minimum BSA involvement of ≥10%. In all four trials, patients in the dupilumab (Dupixent) arm achieved statistically significant improvement when compared to the placebo arm. See table below for details.

	Trial 1		Trial 2		Trial 3		Trial 4	
	DUPIXENT 300 mg Q2W N=224	PBO N=224	DUPIXENT 300 mg Q2W N=233	PBO N=236	DUPIXENT 300 mg Q2W + TCS N=106	PBO + TCS N=315	DUPIXENT 200 mg (<60 kg) or 300 mg (>60 kg) Q2W N=82	PBO N=85
% of patients with IGA 0 or 1	38%	10%	36%	9%	39%	12%	24%	2%
% of patients with EASI-75	51%	15%	44%	12%	69%	23%	42%	8%

- For patients aged 6 to 11 years, dupilumab (Dupixent) approval was based on the results from a 16-week, phase III, double-blind, placebo-controlled trial. Investigators enrolled pediatric patients who have had a previous inadequate response to a topical medication with a PGA score of four (scale of zero to four) and a minimum BSA involvement of ≥15%. Patients in both dupilumab arms achieved statistically significant improvements when compared to the placebo arm, see table below for details.

	<30 kg			≥30 kg		
	PBO + TCS n=61	Q4W + TCS n=61	Q2W + TCS n=63	PBO + TCS n=62	Q4W + TCS n=61	Q2W + TCS n=59
% of patients with IGA 0 or 1	13.1%	29.5% p<0.05	20.6%	9.7%	36.1% p<0.001	39% p<0.001
% of patients with EASI-75	27.9%	75.4% p<0.0001	60.3% p<0.001	25.8%	63.9% p<0.0001	74.6% p<0.0001

- For patients aged 6 months to 5 years, dupilumab (Dupixent) approval was based on the safety results from a 16-week trial consisting of 161 patients with a diagnosis of moderate-to-severe atopic dermatitis who were using dupilumab (Dupixent) in combination with a topical corticosteroid (AD-1539). Additionally, long-term safety of dupilumab (Dupixent) with or without a concomitant topical corticosteroid was evaluated in a 52-week open-label extension study consisting of 180 pediatric patients with atopic dermatitis (AD-1434); the majority of patients received dupilumab (Dupixent) dosed at 300mg every 4 weeks. The safety profile of dupilumab (Dupixent) with or without concurrent topical corticosteroid was similar between these two studies and consistent with the known safety profile of this medication in the adult and pediatric 6–17-years-old population. Notably, hand-foot-and-mouth disease and skin papilloma were reported in 9 (5%) and 4 (2%) of subjects, respectively. However, none of these cases led to study drug discontinuation during the trial.
- Treatments for mild-to-moderate atopic dermatitis include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and/or crisaborole (Eucrisa) – a PDE4 inhibitor, and phototherapy. Symptomatic treatments include oral and topical antihistamines and sleep aids for nighttime pruritus. Treatment choice between these products is dependent on severity, location, and other patient specific factors (e.g., allergies, age). According to AAD guidelines, TCIs may be preferable to TCS in patients with recalcitrance to steroids,

sensitive areas involved, steroid-induced atrophy, and long-term uninterrupted topical steroid use.

- Treatment for moderate to severe disease includes the same topical classes noted above and, for those not amenable to topical, systemic immunosuppressants (e.g., corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), JAK inhibitors (e.g., abrocitinib, upadacitinib), and dupilumab (Dupixent), a biologic IgG4 that is FDA-approved for pediatrics and adults as a biologic option for moderate-to-severe atopic dermatitis. Currently, there are no head to head trials evaluating safety and/or efficacy differences or superiority between biologic therapies in atopic dermatitis. Dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis and is approved down to six years of age. Upadacitinib (Rinvoq) has been evaluated and is FDA approved in patients down to 12 years of age. Abrocitinib (Cibinqo) is FDA approved in adult patients only.
- There may be patient specific scenarios in which the use of additional topical agents following failure of one class of topical agents would be impractical. Insight from dermatology specialists indicate that patients who have at least 15% BSA involvement, or involvement in sensitive areas (e.g., eyelids, axilla, genitals, gluteal cleft), and have severe disease are potential candidates for systemic biologic therapy. Severe disease, as defined by NICE guidelines, includes widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation), and severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep; severe disease can also be classified as physician's global assessment (PGA) score of 4.0. Additionally, administration of topical agents may become impractical for patients with high disease burden (BSA ≥ 20%), considering twice daily administration is necessary for non-steroid topical agents for optimal efficacy.

IV. **Moderate to severe asthma**

- Dupilumab (Dupixent) was studied in three randomized, double-blind, placebo-controlled, multicenter trials. These trials did not require a minimum baseline blood eosinophilic count; mean baseline blood eosinophilic count for all trials were 353 cells/mcL. Trials 2 and 3 excluded patients with a screening blood eosinophil level of >1500 cells/mcL. Trials 1 and 2 required patients to have a history of at least one asthma exacerbation that required systemic corticosteroid treatment, or an emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry; patients continued background asthma treatment throughout the study. Trial 3 required dependence on daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus an additional controller(s).
    i. Trial 1: Patients enrolled were at least 18 years of age with moderate to severe asthma on a medium or high-dose ICS and a LABA. Patients were randomized to receive either dupilumab (Dupixent) 200 mg or 300 mg every other week (Q2W) or every 4 weeks following an initial dose of 400 mg, 600 mg, or placebo. The primary endpoint was mean change from baseline to Week 12 in FEV1 in patients with baseline blood eosinophil ≥300 cells/mcL receiving 200 mg, 300mg, or placebo, which were 25.9%, 25.8%, and 10.2%,

respectively. Mean difference compared to placebo for the 200 mg and 300 mg were 0.26 (95% CI 0.11, 0.4) and 0.21 (95% CI 0.06, 0.36), respectively.

ii. Trial 2: Patients enrolled were at least 12 years of age with moderate to severe asthma on a medium to high-dose ICS and a minimum of one and up to two additional controller medications. Patients were randomized to receive either dupilumab (Dupixent) 200 mg or 300 mg every 2 weeks following initial dose of 400 mg, 600 mg, or placebo. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo-controlled period receiving 200 mg vs placebo or 300 mg vs placebo, which were RR 0.52 (95% CI 0.41, 0.66) and RR 0.54 (95% CI 0.43, 0.68), respectively, and change from baseline in FEV1 at Week 12 receiving 200 mg vs placebo or 300mg vs placebo, which were 29% vs 15.9% and 32.5% vs 14.4%. Mean difference compared to placebo for the 200 mg and 300 mg were 0.21 (95% CI 0.13, 0.29) and 0.24 (95% CI 0.16, 0.32), respectively.

iii. Trial 3: Patients enrolled were at least 12 years of age with asthma who required daily OCS in addition to regular use of high-dose ICS plus an additional controller. Patients were randomized to receive either dupilumab (Dupixent) 300 mg or placebo every 2 weeks for 24 weeks following an initial dose of 600 mg or placebo. Patients continued existing asthma therapy during the trial; OCS dose was reduced every 4 weeks during the OCS reduction phase (Weeks 4 to 20) as long as asthma control was maintained. The primary endpoint was the percent of reduction from baseline of the final oral corticosteroid dose at week 24 while maintaining asthma control in those receiving either 300 mg or placebo, which was 90% (95% CI 60%, 80%) vs 42% (95% CI 33%, 51%), respectively.

- The Global Initiative for Asthma (GINA) 2020 update recommends the addition of respiratory biologics, with respect to their allergic biologics, after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 (medium dose ICS-LABA) or Step 5 (high dose ICS-LABA) therapy. Other controller options for Step 4 include high dose ICS-LABA or add-on tiotropium, or add-on LTRA. Other controller options for Step 5 include add-on anti-IL5, or add-on low dose OCS, though guidelines note to consider side effects.

V. **Chronic rhinosinusitis with nasal polyposis (CRSwNP)**

- Dupilumab (Dupixent) approval was based on the results from two phase 3 pivotal trials SINUS-24 and SINUS-52. SINUS-24 was a 24-week study, while SINUS-52 was a 52-week study. Both trials evaluated dupilumab (Dupixent) 300mg administered every two weeks combined with standard-of-care mometasone fuorate nasal spray (MFNS) and compared to placebo injection plus MFNS. In both trials, there were two co-primary endpoints, improvement in nasal congestion/obstruction severity and reduction in nasal polyps. At 24 weeks, patients in the dupilumab (Dupixent) arm achieved statistically significant improvements when compared to the placebo arm.

  i. Fifty-seven percent and 51% improvement in their nasal congestion/obstruction severity compared to a 19% and 15% improvement with placebo in SINUS-24 and SINUS-52, respectively.

ii. Thirty-three percent and 27% reduction in their nasal polyps score compared to a 7% and 4% increase with placebo in SINUS-24 and SINUS-52, respectively.

- The American Academy of Allergy, Asthma, and Immunology (AAAAI), American College of Allergy, Asthma, and Immunology (ACAAI), and Joint Council of Allergy, Asthma, and Immunology (JCAAI) 2014 guidelines recommend short-term treatment with oral steroids in patients with CRSwNP "because it decreases nasal polyp size and symptoms". Additionally, guidelines recommend both intranasal corticosteroids and omalizumab for treatment of CRSwNP.

VI. **Eosinophilic esophagitis (EoE)**

- Dupilumab (Dupixent) was approved for the treatment of eosinophilic esophagitis (EoE) in patients aged 12 years and older weighing at least 40kg based on data from a single Phase 3, randomized, double-blind, placebo-controlled (Liberty EoE TREET) trial consisting of three parts (A, B, and C).
- Results from Parts A and B 24-week treatment periods of the Liberty EoE TREET trial were evaluated for the FDA approval of the EoE indication, as Part C is still ongoing. In both parts, there were two co-primary endpoints: the proportion of subjects achieving histological remission defined as peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 24 and the absolute change in the subject reported DSQ score from baseline to Week 24. Dupilumab (Dupixent) met the co-primary endpoint in both Parts A and B for the 300mg weekly dose only. The dupilumab (Dupixent) 300mg every two-week dosing failed to meet statistical significance for the absolute change in subject reported DSQ score. Notably, the FDA has chosen to only approve the 300mg weekly dose for treatment of EoE.

	Part A		Part B		
	Dupixent 300mg QW N = 42	**Placebo N = 39**	**Dupixent 300mg QW N = 80**	**Dupixent 300mg Q2W N = 81**	**Placebo N = 79**
Co-primary Endpoints					
Proportion of subjects achieving histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf), n (%)	25* (59.5)	2 (5.1)	47* (58.5)	49* (60.5)	5 (6.3)
Absolute change from baseline in DSQ score, LS mean (SE)	-21.9* (2.5)	-9.6 (2.8)	-23.8* (1.9)	-14.4 (1.86)	-13.9 (1.9)
*denotes statistically significant difference compared to placebo					

- No new safety concerns emerged during the Liberty EoE TREET trials. Overall, approximately 85% of patients treated with dupilumab (Dupixent) during the clinical trial experienced an adverse event, although most of the treatment emergent adverse events were considered to be mild or moderate. The most common adverse events experienced by patients included injection-site reaction, including erythema, pain and swelling, headache and diarrhea.
- EoE is a chronic, immune/antigen-mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. Diagnosis of EoE is made when all of the following are present: symptoms related to esophageal dysfunction (e.g., dysphagia,

food impaction, abdominal pain), eosinophil-predominant inflammation on esophageal biopsy, characteristically consisting of a peak value of ≥15 eosinophils per high power field (HPF) (or 60 eosinophils per mm2), and exclusion of other conditions that may be responsible for or contributing to symptoms of esophageal eosinophilia (e.g., eosinophilic gastritis, GERD, hyper-eosinophilic syndrome, Crohn's disease, etc.). Because EoE has a strong association with allergies, patients are recommended to undergo an evaluation by an allergist to rule out allergy-related conditions. Additionally, due to overlap of symptoms with GERD and alimentary tract involvement, evaluation by a gastroenterologist may also be appropriate.

- Dietary restriction is used as a first-line strategy to combat EoE symptoms, including dysphagia and abdominal pain. The most commonly used dietary therapy is an empiric elimination diet based on the concept of avoiding the six foods/food groups that most commonly cause the majority of IgE-mediated food reactions (e..g, milk, egg, soy, wheat, peantus/tree nuts, fish/shellfish). Other dietary therapies including testing-directed elimination diets, which utilize antigen or allergy testing to eliminate foods that trigger a positive test result, and elemental diet, which utilizes amino acid based (elemental) formula. However, these other methods are less commonly used to due to expense and difficulty to follow.
- Dupilumab (Dupixent) is the first medication to gain FDA approval for the EoE indication, and there are limited pharmacological treatment options used off-label for this indication. AGA guidelines strongly recommend treatment with swallowed topical steroids. Supported therapies in this class include fluticasone and budesonide. Fluticasone is administered as a metered-dose inhaler that is sprayed into the mouth and swallowed, while budesonide is administered as a slurry (nebulizer ampules mixed with sucralose) over the course of five to ten minutes. Guidelines also conditionally recommend the use of proton pump inhibitors (PPIs); however, PPIs have been considered standard of care for EoE and subjects in the LIBERTY EoE TREET trial were required to have failed an 8-week treatment with a high-dose PPI (i.e., twice daily dosing) prior to inclusion in the study population. Therefore, although there is limited guideline support for use of PPIs in EoE, requiring prior treatment with PPIs is appropriate as efficacy and safety of dupilumab (Dupixent) in patients with EoE and no prior use of PPIs remains unknown.

VII. **Prurigo nodularis (PN)**

- Prurigo nodularis (PN) is distinct from other pruritic disorders as its core symptoms include presence of multiple firm, nodular lesions distributed symmetrically on the trunk, arms, and/or legs with chronic pruritis lasting greater than 6 weeks in duration. A history of a persistent scratch-itch cycle is accompanied by burning, stinging, pain, and scarring, significantly impacting quality of life. Complete resolution of lesions may not occur even if there is remission in pruritic symptoms.
- Literature suggests up to 60% of patients with PN have a history of atopic conditions (atopic dermatitis, allergic rhinitis, asthma, etc.), but drug induced PN (e.g., opioids, ACE inhibitors, etc.) or PN due to other medical conditions such as neuropathy or psychiatric disease (i.e. dermatillomania, obsessive compulsive disorder, etc.) should be considered and ruled out.

- Treatment approaches: Dupilumab (Dupixent) is the first FDA-approved treatment for adults with PN. Efficacy for PN therapies are based on case reports or small observation studies, and all treatments are currently used off-label. Clinical experience and expert consensus guidelines recommend the use of the following treatment modalities with goals to reduce pruritis and reduce/heal PN nodules, often used in combination:
    i. Similar to atopic dermatitis management, moderate to very high potency topical corticosteroids (TCS) are often used as first line therapy based on clinical experience and expert consensus guideline recommendations for PN. Treatment with intralesional corticosteroids injection(s) (e.g., triamcinolone 5 – 20mg/mL) may also be an option for thick PN nodules to reduce pruritis and flatten large PN lesions. Trials of calcineurin inhibitors, capsaicin, may be used in recalcitrant disease or when TCS are not appropriate, although their use is based on small observational studies. The efficacy of topical therapies for PN has not been adequately evaluated in randomized trials.
    ii. Narrowband ultraviolet B (UVB) phototherapy is occasionally used as an adjunct therapy for patients who have not responded to topical pharmacotherapy, based on evidence from small observational studies and one randomized study. In one study, ten patients treated with UVB therapy 2-3 times weekly in combination with TSC reported significant improvement in skin lesions after 16 weekly treatments; however, accessing therapy may prove to be a barrier for many patients.
    iii. Systemic therapies: oral immunosuppressants, such as low dose methotrexate and cyclosporine, have been used off-label with success in reducing the number and severity of skin lesions. Although safety and efficacy of oral systemic therapies for PN have not been evaluated in randomized trials, expert consensus guidelines conditionally recommend systemic immunologic treatments as reasonable therapy options. Use of systemic therapies with antipruritic activity, including, but not limited to gabapentin, pregabalin, amitriptyline, thalidomide, or naltrexone, have been used in clinical practice; however, data in PN is limited and efficacy cannot be determined.
- Prurigo nodularis rarely occurs in pediatric patients and the safety and efficacy of dupilumab (Dupixent) for the treatment of PN in patients younger than 18 years of age has not been established.
- The duration of initial approval at six months is derived from the evidence reported in the dupilumab (Dupixent) trials for PN, whose results were reported at 12 and 24 weeks.
- Safety and efficacy of dupilumab (Dupixent) for adults with PN was evaluated in two Phase III, randomized, double blind, placebo-controlled trials (LIBERTY-PN-PRIME and PRIME2). The trials evaluated a total of 311 participants ages 18 to 80 years of age with a clinical diagnosis of uncontrolled PN for at least 3 months in duration, average worst itch score (WI-NRS) of ≥7, minimum of 20 PN lesions, and a history of failing a 2-week course of medium to very high potency TCS or ineligible for TCS

therapy. Background therapy include*ng low to medium potency TCS or topical calcineurin inhibitors were allowed to be used throughout the trial. The trials excluded patients with PN secondary to medications, other medical conditions, or uncontrolled thyroid disease. At baseline, the mean WI-NRS was 8.5 (severe pruritis), 66% of participants had 20 - 100 nodules (moderate), and 34% had greater than 100 nodules (severe). Less than half of the participants (43%) had a history of atopy (medical history of AD, allergic rhinitis, asthma, or food allergy). The primary endpoint assessed improvement in WI-NRS score ≥4 from baseline at 12-weeks (PRIME2) and 24-weeks (PRIME2). Key secondary outcomes assessed pruritic improvement and reduction in PN lesions (clear skin) as measured by the Investigator's Global Assessment PN-Stage [IGA PN-S] 0-4 scale. Both primary and key secondary endpoints were met as patients on dupilumab (Dupixent) experienced an improvement in itch reduction and skin clearing compared to placebo. No new safety signals were discovered, and adverse effects were consistent with the established safety profile of dupilumab (Dupixent).

	PRIME		PRIME2	
	Dupilumab (n=75)	Placebo (n=76)	Dupilumab (n=78)	Placebo (n=82)
% patients with improvement (reduction) in WI-NRS* by ≥4 points from baseline at week 12	44%	16%	37%	22%
% patients with improvement (reduction) in WI-NRS* by ≥4 points from baseline at week 24	60%	18%	58%	20%
% patients with IGA PN-S† 0 or 1 at week 24	48%	18%	45%	16%
**Worst itch score (WI-NRS) is a patient-reported outcome comprised of a single item rated on a scale from 0 ("No itch") to 10 ("Worst imaginable itch")*				
†The Investigator's Global Assessment PN-Stage (IGA PN) is a clinician-reported outcome assess the activity of PN (IGA PN-A) using a 5-point scale from 0 (clear) to 4 (severe)				

Investigational or Not Medically Necessary Uses

I. Dupilumab (Dupixent) is and has been studied in a variety of other conditions, there is currently insufficient evidence to support the use of dupilumab (Dupixent) outside of the FDA approved indications.

Appendix

I. Table 1: Topical Corticosteroid Potency Chart[12]

Potency Group	Corticosteroid	Vehicle type/form	Brand names	Available strength(s), percent (except as noted)
Super-high potency (Group 1)	Betamethasone dipropionate, augmented	Gel, lotion, ointment (optimized)	Diprolene	0.05
	Clobetasol propionate	Cream, gel, ointment, solution (scalp)	Temovate	0.05
		Cream, emollient base	Temovate E	0.05

		Lotion, shampoo, spray aerosol	Clobex	0.05
		Foam aerosol	Olux-E, Tovet	0.05
		Solution (scalp)	Cormax	0.05
	Fluocinonide	Cream	Vanos	0.1
	Flurandrenolide	Tape (roll)	Cordran	4 mcg/cm2
	Halobetasol propionate	Cream, lotion, ointment	Ultravate	0.05
High potency (Group 2)	Amcinonide	Ointment	Cyclocort¶, Amcort¶	0.1
	Betamethasone dipropionate	Ointment	Diprosone¶	0.05
		Cream, augmented formulation (AF)	Diprolene AF	0.05
	Clobetasol propionate	Cream	Impoyz	0.025
	Desoximetasone	Cream, ointment, spray	Topicort	0.25
		Gel	Topicort	0.05
	Diflorasone diacetate	Ointment	ApexiCon¶, Florone¶	0.05
		Cream, emollient	ApexiCon E	0.05
	Fluocinonide	Cream, gel, ointment, solution	Lidex¶	0.05
	Halcinonide	Cream, ointment, solution	Halog	0.1
	Halobetasol propionate	Lotion	Bryhali	0.01
High potency (Group 3)	Amcinonide	Cream	Cyclocort¶, Amcort¶	0.1
		Lotion	Amcort¶	0.1
	Betamethasone dipropionate	Cream, hydrophilic emollient	Diprosone¶	0.05
	Betamethasone valerate	Ointment	Valisone¶	0.1
		Foam	Luxiq	0.12
	Desoximetasone	Cream	Topicort LP¶	0.05
	Diflorasone diacetate	Cream	Florone¶	0.05
	Diflucortolone valerate (not available in United States)	Cream, oily cream, ointment	Nerisone (Canada, United Kingdom, others)	0.1
	Fluocinonide	Cream aqueous emollient	Lidex-E¶	0.05
	Fluticasone propionate	Ointment	Cutivate	0.005
	Mometasone furoate	Ointment	Elocon	0.1
	Triamcinolone acetonide	Cream, ointment	Aristocort HP¶, Kenalog¶, Triderm	0.5
Medium potency (Group 4)	Betamethasone dipropionate	Spray	Sernivo	0.05
	Clocortolone pivalate	Cream	Cloderm	0.1
	Fluocinolone acetonide	Ointment	Synalar¶	0.025
	Flurandrenolide	Ointment	Cordran	0.05

	Hydrocortisone valerate	Ointment	Westcort	0.2
	Mometasone furoate	Cream, lotion, ointment, solution	Elocon¶	0.1
	Triamcinolone acetonide	Cream	Kenalog¶, Triderm	0.1
		Ointment	Kenalog¶	0.1
		Ointment	Trianex	0.05
		Aerosol spray	Kenalog	0.2 mg per 2 second spray
		Dental paste	Oralone	0.1
Lower-mid potency (Group 5)	Betamethasone dipropionate	Lotion	Diprosone¶	0.05
	Betamethasone valerate	Cream	Beta-Val, Valisone¶	0.1
	Desonide	Ointment	DesOwen, Tridesilon¶	0.05
		Gel	Desonate	0.05
	Fluocinolone acetonide	Cream	Synalar¶	0.025
	Flurandrenolide	Cream, lotion	Cordran	0.05
	Fluticasone propionate	Cream, lotion	Cutivate	0.05
	Hydrocortisone butyrate	Cream, lotion, ointment, solution	Locoid, Locoid Lipocream	0.1
	Hydrocortisone probutate	Cream	Pandel	0.1
	Hydrocortisone valerate	Cream	Westcort¶	0.2
	Prednicarbate	Cream (emollient), ointment	Dermatop	0.1
	Triamcinolone acetonide	Lotion	Kenalog¶	0.1
		Ointment	Kenalog¶	0.025
Low potency (Group 6)	Alclometasone dipropionate	Cream, ointment	Aclovate	0.05
	Betamethasone valerate	Lotion	Beta-Val¶, Valisone¶	0.1
	Desonide	Cream	DesOwen, Tridesilon¶	0.05
		Lotion	DesOwen, LoKara	0.05
		Foam	Verdeso	0.05
	Fluocinolone acetonide	Cream, solution	Synalar¶	0.01
		Shampoo	Capex	0.01
		Oil (48% refined peanut oil)	Derma-Smoothe/FS Body, Derma-Smoothe/FS Scalp	0.01
	Triamcinolone acetonide	Cream, lotion	Kenalog¶, Aristocort¶	0.025
Least potent (Group 7)	Hydrocortisone (base, ≥2%)	Cream, ointment	Hytone, Nutracort¶	2.5
		Lotion	Hytone, Ala Scalp, Scalacort	2
		Solution	Texacort	2.5
	Hydrocortisone (base, <2%)	Ointment	Cortaid, Cortizone 10, Hytone, Nutracort	1

		Cream	Cortaid¶, Cortizone 10, Hytone, Synacort	1
		Gel	Cortizone 10	1
		Lotion	Aquanil HC, Sarnol-HC, Cortizone 10	1
		Spray	Cortaid	1
		Solution	Cortaid, Noble, Scalp Relief	1
		Cream, ointment	Cortaid	0.5
	Hydrocortisone acetate	Cream	MiCort-HC	2.5
		Lotion	Nucort	2

¶ Inactive United States brand name for specific product; brand may be available outside United States

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
omalizumab (Xolair)	Allergic asthma
	Chronic rhinosinusitis with nasal polyposis (CRSwNP)
Systemic Janus Associated Kinase (JAK) Inhibitors in Chronic Inflammatory Disease	Atopic dermatitis
ruxolitinib (Jakafi, Opzelura)	Atopic dermatitis
tralokinumab (Adbry)	Atopic dermatitis

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated age criteria in eosinophilic esophagitis for the newly FDA approved indication in those one year and older. Updated supporting evidence and references.	02/2024
Review conducted. Update to supporting evidence.	02/2023
Updated policy to prefer Dupixent as of 01/01/2023	12/2022
Added new indication and supporting evidence for Dupixent in the setting of prurigo nodularis. Added related pruritic conditions (urticaria, bullous pemphigoid/prurigo, etc.) to E/I. Updated references. Added related policies section.	10/2022
Added criteria and supporting evidence for new FDA-approved indication for eosinophilic esophagitis; Updated age criteria in atopic dermatitis to reflect FDA-approved age expansion from age 6 years to age 6 months and older	08/2022
Updated age criteria in asthma to reflect FDA extended indication from age 12 now to age 6 and older; updated QL table to include dosing for Atopic Dermatitis and comorbid Atopic Dermatitis and Severe to Moderate Asthma	11/2021

Added 200 mg/1.14mL pen injector; Updated to allow 12-month approval for initial therapy	07/2021
Updated Policy. Atopic dermatitis: combined pediatric and adolescent/adult criteria; updated BSA criterion and Group 1 corticosteroids. Asthma: updated criteria defining moderate or severe asthma; updated eosinophilic phenotype criterion; defined exacerbation criterion; revised maintenance treatment requirements; removed environmental trigger criterion. CRSwNP: revised diagnosis criteria to include provider attestation; updated treatment history to one intranasal corticosteroid and one OCS therapy. Renewal criteria: added standard renewal criteria documenting patient establishing treatment; added criterion excluding concomitant MCA use.	04/2021
Updated QL table to include pediatric dosing in AD	01/2021
Criteria update: updated age criteria to reflect newly FDA approved extended indication for atopic dermatitis use from 12 years of age to expanded use in pediatrics aged six to 11 years of age. Removal of PGA score as a requirement option with BSA in atopic dermatitis.	10/2020
Criteria was transitioned to policy format with the addition of supporting evidence and a section for investigation/not medically necessary usage. Addition of newly FDA approved age expansion for atopic dermatitis from 18 years of age to 12 years of age. Also, addition of newly FDA approved indication for chronic rhinosinusitis with nasal polyposis along with criteria for approval based on guidelines and clinical trials review. Lastly, the duration of initial approval has been increased form 3 months to 6 months based on evidence from ICER reports and the study design of the most recent FDA approved indication for chronic rhinosinusitis with nasal polyposis.	08/2019
Criteria update: Incorporated new diagnosis of moderate to severe asthma and appropriate criteria	12/2018
Updated format and added the renewal approval duration	01/2018
Criteria update: excluded samples and updated renewal language to general improvement	04/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP222

Split Fill Management*

Description

Duvelisib (Copiktra) is an orally administered inhibitor of phosphoinositide 3-kinase (PI3K) with inhibitory activity predominantly against PI3K-δ and PI3K-γ isoforms expressed in normal and malignant B-cells.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
duvelisib (Copiktra)	15 mg capsules	Relapsed/refractory chronic lymphocytic leukemia (CLL); Relapsed/refractory small lymphocytic lymphoma (SLL);	56 capsules/28 days
	25 mg capsules		

Initial Evaluation

I. Duvelisib (Copiktra) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
   C. Member does not have a history of histological transformation (HT); **AND**
   D. Not used in combination with any other oncology therapy; **AND**
   E. Member has not progressed while on therapy with another PI3K inhibitor [e.g. copanlisib (Aliqopa), idelalisib (Zydelig)]; **AND**
   F. A diagnosis of **relapsed/refractory chronic lymphocytic leukemia (CLL) OR relapsed/refractory small lymphocytic lymphoma (SLL)** when the following are met:
      i. Treatment with one of the following has been ineffective or not tolerated or BOTH have been contraindicated:
         a. Bruton tyrosine kinase (BTK) inhibitor [e.g. ibrutinib (Imbruvica), acalabrutinib (Calquence)] **OR**
         b. BCL2 inhibitor [e.g. venetoclax (Venclexta)]; **AND**
      ii. Treatment with at least **ONE** of the following additional therapies has been ineffective, not tolerated, or ALL are contraindicated:
         a. fludarabine/cyclophosphamide/rituximab (FCR)
         b. alkylating agent (e.g., chlorambucil, bendamustine, cyclophosphamide)

c. monoclonal antibody (e.g., ofatumumab, rituximab, obinutuzumab)
d. purine analog (e.g., fludarabine, pentostatin, cladribine)

II. Duvelisib (Copiktra) is considered investigational when used for all other conditions, including but not limited to:
A. Relapsed/refractory follicular lymphoma (FL)
B. Head and Neck Cancer
C. Stage IIB-IVB Mycosis Fungoides and Sezary Syndrome
D. Moderate to Severe Rheumatoid Arthritis
E. Coronavirus Infection (COVID-19)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by stabilization of disease or improvement in disease or disease symptoms.

Supporting Evidence

I. The safety and efficacy of duvelisib (Copiktra) for the treatment of relapsed and refractory CLL/SLL has been studied in a global, multicenter, randomized, open-label, Phase 3, superiority trial in 319 adult patients.
- The two treatment arms included the duvelisib (Copiktra) and ofatumumab arm. Treatment groups were balanced, had a median number of prior therapies of two with approximately one-third having received three or more prior lines of therapy. Most patients had previously received an alkylating agent (chlorambucil, bendamustine, cyclophosphamide) 93% in the duvelisib (Copiktra) and 95% in the ofatumumab group, a monoclonal antibody (ofatumumab, rituximab, obinutuzumab) 78% in the duvelisib (Copiktra) and 83% in the ofatumumab group, and purine analog (60% duvelisib (Copiktra); 71% ofatumumab).
- The primary endpoint of Progression-free Survival (PFS) was significantly longer for the duvelisib (Copiktra) arm compared with the ofatumumab arm (13.3 months vs 9.9 months, HR = 0.52, P < 0.0001).
- The key secondary endpoint of Overall Response Rate (ORR) was also significantly higher compared with ofatumumab (73.8% vs 45.3%; P < 0.0001), but the OS was not statistically different and the median overall survival (OS) was not reached on either treatment arm with a 12-month probability of survival of 86% (HR = 0.99; 95% CI, 0.65-

1.50) for both treatments. This could be due to the availability of multiple CLL therapies to rescue patients on either arm following disease progression, including administration of duvelisib in a separate, optional extension study to 89 patients who had confirmed progressive disease on ofatumumab in the DUO study.

- Almost all patients in the study experienced an AE, 124 duvelisib (Copiktra)-treated patients had discontinued treatment, with the most common reasons being AEs (35%), disease progression (22%), subject withdrawal (8%), and death (8%).
- Fatal adverse reactions within 30 days of the last dose occurred in 36 patients (8%) treated with duvelisib (Copiktra) 25 mg twice daily. Serious adverse reactions were reported in 289 patients (65%). The most frequent serious adverse reactions that occurred were infection (31%), diarrhea or colitis (18%), pneumonia (17%), rash (5%), and pneumonitis (5%). Adverse reactions resulted in treatment discontinuation in 156 patients (35%), most often due to diarrhea or colitis, infection, and rash. Duvelisib (Copiktra) was dose reduced in 104 patients (24%) due to adverse reactions, most often due to diarrhea or colitis and transaminase elevation. The median time to first dose modification or discontinuation was 4 months (range: 0.1 to 27), with 75% of patients having their first dose modification or discontinuation within 7 months.

II. Histological transformation (HT) refers to the evolution of a clinically indolent disease (e.g. FL) to a clinically aggressive disease [e.g. diffuse large B-cell lymphoma (DLBCL)] defined as those lymphomas in which survival of the untreated patient is measured in months. The HT that occurs in patients with CLL/SLL has been termed Richter's transformation. When histological transformation is present, these patients are generally treated differently than their primary diagnosis. The goal of therapy for most patients is to eliminate the aggressive component of the disease (i.e. the histologically transformed cells) while minimizing toxicity. The most common treatment regimens for patients with HT include conventional chemotherapy with immunotherapy and high dose therapy followed by hematopoietic cell transplantation. There is no clinical trial data to support the use of duvelisib (Copiktra) in patients with HT.

III. Per the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, CLL/SLL, recognizes duvelisib (Copiktra) as a preferred regimen for r/r CLL/SLL (Category 2A recommendation). Ibrutinib (Imbruvica), acalabrutinib (Calquence), venetoclax (Venclexta) plus rituximab are Category 1 recommendation, based on the results of the Phase 3 randomized studies (ASCEND, RESONATE and MURANO, respectively). Idelalisib (Zydelig) plus rituximab and duvelisib (Copiktra) are also preferred regimens in these populations with a category 2A recommendation due to their toxicity profile (colitis, diarrhea, and increased risk of infections).

Investigational or Not Medically Necessary Uses

I. Duvelisib (Copiktra) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Relapsed/refractory follicular lymphoma (FL)
      i. The safety and efficacy of duvelisib (Copiktra) for the treatment of relapsed and refractory FL has been studied in a single-arm, Phase 2, open-label study in 129 patients.

- Duvelisib (Copiktra) 25 mg twice daily was administered in patients with FL (N = 83) who were refractory to rituximab and to either chemotherapy or radioimmunotherapy. Patients were refractory to rituximab either alone or in combination (127 patients [98%]), 119 patients (92%) had disease refractory to an alkylating agent or purine analog, and 117 patients (91%) had disease refractory to combination therapy with rituximab and an alkylating agent.
- Patients had a median of three prior lines of therapy (range: 1 to 10), and 40% receiving four or more prior regiments, with 94% being refractory to their last therapy and 81% being refractory to 2 or more prior lines of therapy.
- The primary endpoint was met with Overall Response Rate (ORR) being 47% (95% CI, 38% to 56%). The key secondary endpoint of duration of response (DOR was 10 months (95% CI, 6.5 to 10.5 months)
- Due to treatment emergent adverse events (TEAE), forty patients (31%) discontinued duvelisib (Copiktra). In 85 (66%) of patients TEAEs were managed with dose interruption or reduction.
- The most frequent grade 3 or greater TEAEs were neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), and thrombocytopenia (11.6%). Seventeen deaths (13.2%) occurred on treatment

ii. Almost all patients in the study assessing the safety and efficacy of duvelisib (Copiktra) were refractory to rituximab (98.4%), alkylating agent/purine analog (92.2%) and alkylating agent (90.7%).

iii. The NCCN B-cell Lymphomas guideline set duvelisib (Copiktra) as a second-line therapy for FL that is relapsed or refractory to at least two prior therapies, a category 2A recommendation. Anti–CD20 antibody–based chemoimmunotherapy [e.g., obinutuzumab (Gazyva), ofatumumab (Arzerra)] is the standard initial treatment for newly diagnosed and relapsed/refractory FL. Options for treatment at first relapse include alternate non–cross-resistant chemoimmunotherapy regimens or combination lenalidomide + rituximab. Rituximab monotherapy may be appropriate for patients with late relapse as well, particularly if disease burden is low.

iv. Patients with Grade 3b FL were excluded from the clinical trial. Grade 3b FL is often referred to as follicular large cell lymphoma and patients commonly present with a more clinically aggressive course. It is commonly treated with regimens used for clinically aggressive lymphomas, such as a Diffuse Large B-Cell Lymphoma (DLBCL).

v. Although, the primary outcome of ORR was met, the quality of evidence is low considering the single arm, Phase 2, open-label trial design. Furthermore, patients included in this trial experienced significant TEAEs and limited efficacy. Given these considerations treatment with duvelisib (Copiktra) in the setting of relapsed/refractory follicular lymphoma (FL) is considered experimental/investigational.

B. Head and Neck Cancer

i. A Phase 1b/2, open label, non-randomized, single group study of duvelisib (Copiktra) in combination with pembrolizumab in subjects with recurrent or metastatic head and neck squamous cell cancer is still recruiting.

C. Stage IIB-IVB Mycosis Fungoides and Sezary Syndrome
   i. A Phase 1 open label, non-randomized, single group study with an expansion cohort of duvelisib (Copiktra) and nivolumab in Mycosis Fungoides (MF) and Sezary Syndrome (SS) is not yet recruiting.

D. Moderate to Severe Rheumatoid Arthritis
   i. A Phase 2, double blind, placebo-controlled, randomized study to evaluate multiple dose levels of duvelisib (Copiktra) with background methotrexate in subjects with active rheumatoid arthritis and an inadequate response to methotrexate alone was completed in 2018 but no results have been published.

E. Coronavirus Infection (COVID-19)
   ii. A Phase 2, double blind, placebo-controlled, randomized study to evaluate whether a two-week exposure to duvelisib (Copiktra), reduces inflammation in the lungs in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 who do not require mechanical ventilation at study initiation. The study is not yet recruiting.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria: age requirement, requirement of monotherapy, requirement of non-progression on a different PI3K inhibitor, requirement of one or more prior therapy if diagnosed with CLL/SLL Removed criteria: requirement for pneumocystis jirovecii pneumonia (PCP) prophylaxis and no history of allogenic stem cell transplant Moved the follicular lymphoma indication to investigational uses Criteria updated to policy format	2/2021
Policy created	11/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP263

Description

Edaravone (Radicava ORS) is an orally administered free radical scavenger.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
edaravone (Radicava ORS)	Amyotrophic Lateral Sclerosis (ALS)	105mg/ 5mL starter kit	70mL/28 days
		105mg/ 5mL suspension	50mL/28 days

Initial Evaluation

I. **Edaravone (Radicava ORS)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. A diagnosis of **Amyotrophic Lateral Sclerosis (ALS)** when the following are met:
      1. Provider attestation that the member has a diagnosis of ALS (e.g., clinically definite, probable ALS, bulbar ALS, etc.); **AND**
      2. Member has a disease duration of 2 years or less since diagnosis; **AND**
      3. Provider attestation that the member does NOT have advanced disease [note: advanced disease may include loss of multiple physical functionalities such as ability to swallow, walk, speak, dress/groom, etc.]; **AND**
      4. Member does not require permanent mechanical ventilation by intubation or tracheostomy; **AND**
      5. Edaravone (Radicava ORS) will be used in combination with riluzole (Rilutek); **OR**
         i. Treatment with riluzole (Rilutek) has been ineffective, not tolerated, or is contraindicated

II. Edaravone (Radicava) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute Ischemic Stroke

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **OR**
II. Member is changing from edaravone (Radicava) IV therapy to edaravone (Radicava ORS); **AND**
III. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
IV. Member does not require permanent mechanical ventilation by intubation or tracheostomy plan; **AND**
V. Provider attestation that edaravone (Radicava ORS) continues to slow or stabilize the progression of disease and treatment provides clinical benefit to the member

Supporting Evidence

I. Edaravone (Radicava) was only studied in clinical trials in adult patients and efficacy and safety of this drug for the pediatric population is not known. Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease and does not show up in younger patients, with the average age of onset being 55 years.
II. ALS is a difficult and complex disease to diagnose and treatment for this disease is specialized and individualized; thus, a specialist provider, or consultation with a specialist (e.g., neurologist), is required.
III. Edaravone (Radicava) was initially approved for IV administration for the treatment of ALS, in a six-month, randomized, placebo-controlled, double-blind study (study 19) of 137 Japanese patients with ALS, who lived independently and had the following baseline criteria: definite or probable ALS diagnosis based on El Escorial revised criteria; disease diagnosed less than 2 years before; normal respiratory function (defined as %FVC >80%); functionality retained in most activities of daily living (defined as scores of 2 points or better on each item of the ALS function rating scale- revised [ALSFRS-R]) with a specific requirement of a score of 4 on dyspnea, orthopnea, and respiratory insufficiency. The primary endpoint was the change in the treatment arms in the ALSFRS-R total scores at baseline and week 24. Majority (≥ 90%) of patients enrolled in each arm were also taking riluzole (Rilutek).
IV. The ALSFRS-R is a 12-item questionnaire assessing functional disease progression across four domains including bulbar, fine motor, gross motor, and respiratory. Each item is scored on a five-point ordinal scale from 0 (loss or significant impairment) up to 4 (normal function) with a possible cumulative score of 48. A score of 2 or better on each item would be a minimum ALSFRS-R score of 24. The ALSFRS-R score correlates to preserved function with a higher score meaning function closer to a normal individual without ALS. Patients with a lower total score are those with advanced disease who have lost function over several of these domains (e.g. lost ability to swallow, walk, speak, dress themselves, grip/hold items); these patients are also associated with worst disease outcomes.
V. The primary efficacy outcome for Study 19 was the change in ALSFRS-R score from baseline to week 24. The change from baseline and at week 24 of the ALSFRS-R score was reported as least-squares mean (LSM) change ± standard error [95 % confidence interval (CI)]. Edaravone

(Radicava) had a change of -5.01 ± 0.64 versus -7.50 ± 0.66 for placebo. This correlated with a treatment difference of 2.49 (SE 0.76, 0.99-3.98, 95% CI; *p* 0.0013) in favor of edaravone (Radicava).

VI. Oral edaravone (Radicava ORS) suspension was approved in 2022 in a global, open-label, phase 3 safety study of 185 patients receiving 105mg of edaravone (Radicava) on the same IV dosing schedule. While patients were included in the study with a baseline FVC of 70 or greater, and a disease diagnosis within 3 years, this study did not evaluate efficacy in these parameters and only assessed safety data. Once again in the ORS study, 87% of patients were also using riluzole (Rilutek). The 105mg oral dose was found in the pharmacokinetic phase 1 trial to provide the same drug exposure as the 60mg-IV formulation.

VII. The IV-edaravone (Radicava) is generally well tolerated with abnormal gait (13%) and bruising (15%) being the most common adverse events, followed by headache (10%), dermatitis/eczema (8/7%), and respiratory concerns (dyspnea, hypoxia, failure 6%). Additionally, Radicava ORS has an incidence of fatigue (7.6%).

VIII. The American Academy of Neurology (AAN) does not provide specific guidance on the use of edaravone (Radicava) in ALS patients. As of November 2022, the guidelines recommend starting riluzole as a first-line therapy upon diagnosis to slow disease progression, and the majority of the guideline centers around palliative care and support. Available clinical data surrounding the efficacy of edaravone (Radicava) is based on the proposed benefit of slowing the progression of disease symptoms but did not exhibit a clear survival benefit.

IX. In an outreach to a key opinion leader (KOL), a neurologist, who has experience in treating ALS patients, the expert noted that there is no formal guidance on the use of edaravone (Radicava) outside of how the medication was studied (i.e. over 80% FVC predicted and ALSFRS-R total starting score of 24, etc.) The expert did note that the FDA has expanded approval to all patients with ALS; however, insurers have mainly adopted criteria to match the clinical trials. The reviewer did note in 2021 there was a recommendation to relax this criterion, but it has not been formally accepted by either the AAN or the American Associated of Neuromuscular and Electrodiagnostic Medicine. Additionally, there was no specific part of the ALSFRS-R score, which may be valued as more of an indicator for disease progression besides those with a bulbar dysfunction (often evidenced in swallowing or speech problems) and that once a diagnosis of ALS has been reached, the offer to use edaravone (Radicava) is presented to all patients.

X. A recent long-term edaravone (Radicava) efficacy in ALS post-hoc analysis of study 19 was published showing edaravone (Radicava) maintained benefits in patients up to one year post the clinical trial versus placebo, as measured by changes (reduction) in the ALSFRS-R scores. However, true long-term benefits of edaravone (Radicava) are still unknown and there is no way to tell if the drug is working individually. In our KOL outreach, the expert noted that once a patient has begun therapy, it is difficult to establish a stopping point. However, it would be rational to stop therapy once the disease has progressed too far along for a benefit, such as the patient being on permanent machinal ventilation.

XI. Proposed therapy pathway and benefits of edaravone are supported by a review from the American Journal of Managed Care, where specialists in ALS supported both an attestation from a neurologist of continued benefit from the drug as a criterion for continuation of edaravone and stopping therapy once invasive ventilation was required. Additionally, during the confirmatory trial for IV-edaravone, therapy was discontinued if the subject required a

tracheotomy or all-day respiratory support. The open-label extension trial after study 19 utilized the criterion of discontinuing therapy when the %FVC was < 50% and the P_aCO_2 (blood gas) was ≥ 45mm of Hg. Thus, current clinical data does not support continued benefits of edaravone therapy in patients, who progress to advanced disease and require respiratory interventions.

XII. Edaravone (IV or oral) formulations are expected to serve as an adjunct therapy to first line riluzole and may be utilized by the majority of patients with an initial diagnosis of ALS. Due to the convenience and advantage of oral administration, patients established on IV edaravone may convert to oral edaravone (Radicava ORS) to a higher degree. Additionally, Radicava ORS may also be considered as an initial formulation of choice. For members converting to the oral formulation (Radicava ORS) from the IV- edaravone (Radicava), loading dose is not required (1:1 change based on bioequivalence data).

Investigational or Not Medically Necessary Uses

I. Edaravone (Radicava) is considered investigational for the use of Acute Ischemic Stroke, including when used in combination with dexborneol. At this time, the clinical data is inconclusive and edaravone (Radicava) remains not FDA approved for this indication.

References

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6. Barrington CJ, Burruano M, Carney C; et al. Addressing the role of edaravone in the management of amyotrophic lateral sclerosis and gaps in care and access: expert panel recommendations. Am J Manag Care. 2021 Aug;27(12 Suppl):S231-S237. doi: 10.37765/ajmc.2021.88732. PMID: 34382759.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
riluzole (Rilutek®, Tiglutik®, Exervan®)	Amyotrophic Lateral sclerosis (ALS)

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP275

Description

Elacestrant (Orserdu) is an orally administered estrogen receptor antagonist indicated for ER-positive, HER2-negative, ESR1-mutated advanced or metastatic breast cancer.

Length of Authorization

- Initial: 6 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
Elacestrant (Orserdu)	Breast cancer, HER2-negative, HR-positive, ESR1-positive advanced or metastatic	345 mg tablet	30 tablets/30 days
		86 mg tablet	90 tablets/30 days*

**Quantity Limit Exceptions are not allowed*

Initial Evaluation

I. **Elacestrant (Orserdu)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an oncologist; **AND**
   C. Medication will not be used in combination with any other oncolytic therapy; **AND**
   D. The member is a postmenopausal female, premenopausal or perimenopausal female receiving ovarian suppression/ablation (e.g., surgical ablation, suppression with GnRH therapy [e.g., leuprolide], etc.); **OR**
      1. The member is hormone suppressed male (e.g., GnRH therapy [e.g., leuprolide] used concomitantly); **AND**
   E. A diagnosis of **advanced or metastatic breast cancer** when the following are met:
      1. The breast cancer is HR-positive, and HER2-negative; **AND**
      2. Documentation that the member has ESR1 mutation as confirmed by an FDA approved test (e.g., Guardant360 CDx assay); **AND**
      3. The member had disease progression on, or after treatment with a CDK4/6 inhibitor (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.); **AND**
      4. The member has had disease progression on at least one prior endocrine therapy for advanced or metastatic breast cancer (e.g., fulvestrant, letrozole, anastrozole, exemestane, tamoxifen)

II. Elacestrant (Orserdu) is considered investigational when used for all other conditions, including but not limited to:

A. Elacestrant (Orserdu) used in combination with another oncolytic therapy
B. Breast cancer that is not HR+, HER2-, ESR1 mutated
C. Neoadjuvant or adjuvant therapy for early-stage non-metastatic breast cancer (i.e., not advanced or metastatic)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication will not be used in combination with any other oncolytic therapy; **AND**
IV. Member has exhibited response to the treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

I. Elacestrant (Orserdu) is the first medication FDA-approved specifically targeting ESR1 mutation. It joins many other agents for the treatment of ER/PR-positive, HER2-negative, advanced, or metastatic breast cancer. Elacestrant (Orserdu) is FDA-approved for the treatment of patients 18 years of age and older. Safety and efficacy of elacestrant (Orserdu) has not been studied in the pediatric population. Additionally, the current clinical data only supports the use of elacestrant (Orserdu) as a monotherapy.
II. The recommended dosage of elacestrant (Orserdu) is 345 mg taken orally with food once daily until disease progression or unacceptable toxicity occurs. Elacestrant (Orserdu) is also available as an 86 mg formulation, which is only utilized when dose reductions are necessary due to drug toxicity.
III. Given the complexities involved with the diagnosis and treatment of breast cancer, systemic therapy for advanced or metastatic breast cancer must be initiated and supervised by an oncologist.
IV. Endocrine therapy (ET), specifically an aromatase inhibitor (AI; e.g., anastrozole, letrozole, or exemestane) or fulvestrant in combination with a cyclin-dependent kinase (CDK) 4/6 inhibitor (e.g., ribociclib, abemaciclib) is the preferred first-line treatment for ER-positive, HER2-negative, metastatic breast cancer. After disease progression, options depend on the type of previous therapy received. These include endocrine monotherapy with fulvestrant, an AI, or tamoxifen, everolimus plus ET, alpelisib in combination with fulvestrant (PIK3CA mutated only), and chemotherapy. Sequential ET is preferred over chemotherapy due to toxicity. Presence of an ESR1 mutation limits sequential ET options as these tumors are typically resistant to both AIs and tamoxifen. However, certain tumors with ESR1 mutation may retain sensitivity to fulvestrant.
V. The expected place in therapy for elacestrant (Orserdu) is in the second- or third-line setting, after progression on or after endocrine therapy (first or second line), including one line containing a CDK4/6 inhibitor in patients with ESR1 mutation. National Comprehensive Cancer Network guidelines for the treatment of breast cancer have been updated to include elacestrant

(Orserdu) in other recommended regimens as the subsequent-line therapy for ESR1 mutated recurrent, advanced, or metastatic (stage IV) disease (Category 2A recommendation).

VI. Elacestrant (Orserdu) was studied in a Phase III, randomized, open-label, multicenter trial (EMERALD) against standard of care (SOC) ET, which included fulvestrant or AIs. The clinical trial participants (N= 478) included postmenopausal women and men with ER-positive, HER2-negative advanced or metastatic breast cancer. The median age was 63 years, 228 patients (47.8%) had ESR1 mutation (all female), all had prior CDK4/6 inhibitor therapy (100%), 207 (43.4%) received two prior lines of ET, and 106 (22.2%) received one prior chemotherapy. The primary and secondary outcomes were evaluated in all patients and in those with ESR1 mutation and included progression-free survival (PFS) and overall survival (OS), respectively.

VII. Elacestrant (Orserdu) reported a statistically significant improvement in PFS compared to SOC in patients with ESR1 mutation (median PFS 3.8 months vs 1.9 months, p=0.0005). Although median OS did not reach statistical significance in the ESR1 mutated subpopulation, OS numerically favored the elacestrant (Orserdu) arm (24.2 months vs 23.5 months). The PFS endpoint was also met in the intention to treat population, however, the US FDA considered these results to be driven by the 48% of patients in the ESR1 mutated subpopulation. In an exploratory analysis of ESR1 non-mutated population, the median PFS was 1.9 months for elacestrant (Orserdu) and 2.0 months for SOC (HR 0.86, 95% CI: 0.63-1.19).

V. The safety profile of elacestrant (Orserdu) is similar or slightly less favorable when compared to SOC endocrine therapy. Most common adverse events (AE) for elacestrant (Orserdu) versus SOC, respectively, were musculoskeletal pain (41% vs 39%) nausea (35% vs 18.8%), fatigue (19.0% vs 18.8%), vomiting (19.0% vs 8.3%), decreased appetite (14.8% vs 9.2%), arthralgia (14.3% vs 16.2), cholesterol increase (30% vs 17%), and triglycerides increase (27% vs 15%). Treatment-related grade 3/4 AEs and events leading to discontinuation for elacestrant (Orserdu) versus standard of care therapies were 7.2% versus 3.0% and 3.4% versus 0.9%, respectively. The most common grade 3/4 adverse events for elacestrant (Orserdu) were musculoskeletal pain (7%) and nausea (2.5%).

VI. NCCN panel recommends that patients with HR-positive disease should have adequate ovarian suppression/ablation and that these patients be treated in the same way as post-menopausal patients. Within the EMERALD trial, patients receiving ovarian ablation were included, but patients receiving ongoing hormone suppression were excluded. However, current practice consensus and historical clinical data in advanced breast cancer therapy supports the use of systemic therapies in all female patients, including premenopausal or perimenopausal females, provided these patients achieve a hormone-induced (GnRH analog such as leuprolide (Lupron)) or surgery-induced menopause. It is expected that the response to oncolytic therapies in these patient populations may be clinically comparable to that in naturally postmenopausal patients.

Investigational or Not Medically Necessary Uses

I. Elacestrant (Orserdu) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Elacestrant (Orserdu) used in combination with another oncolytic therapy
   B. Breast cancer that is not HR+, HER2-, ESR1 mutated
   C. Neoadjuvant or adjuvant therapy for early-stage non-metastatic breast cancer (i.e., not advanced or metastatic)

References

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Related Policies:

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2023

Policy Type: PA Pharmacy Coverage Policy: UMP179

Description

Eluxadoline (Viberzi) is an orally administered mu-opioid receptor agonist that interacts with receptors in the stomach.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
eluxadoline (Viberzi)	75 mg tablets	Irritable bowel syndrome with diarrhea (IBS-D)	60 tablets/30 days
	100 mg tablets		

Initial Evaluation

I. Eluxadoline (Viberzi) may be considered medically necessary when the following criteria are met:
   A. A diagnosis of **Irritable Bowel Syndrome with Diarrhea (IBS-D)**; **AND**
      1. The member is 18 year of age or older; **AND**
      2. Prescribed by, or in consultation with, a gastroenterologist; **AND**
      3. Treatment with at least three therapies from three different groups have been ineffective, not tolerated, or **ALL** are contraindicated (please note, if one or more groups is contraindicated, a trial of three agents from the remaining groups will be required):
         a. Group 1: antidiarrheal (e.g. loperamide, bismuth subsalicylate, diphenoxylate/atropine, or paregoric)
         b. Group 2: bile acid sequestrant (e.g. cholestyramine and colestipol)
         c. Group 3: antispasmodic (e.g. dicyclomine and hyoscyamine)
         d. Group 4: Tricyclic serotonergic agent: (e.g. amitriptyline, nortriptyline, imipramine, or desipramine)

II. Eluxadoline (Viberzi) is considered investigational when used for all other conditions, including but not limited to:
   A. Diabetic diarrhea
   B. Diarrhea associated with fecal incontinence
   C. Pediatric IBS-D
   D. Mixed IBS or IBS with constipation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
IV. The member has demonstrated a beneficial response to therapy [e.g., symptomatic improvement, improvement in pain associated with IBS-D, a decrease in score for the Bristol Stool Scale (BSS) for stool consistency]

Supporting Evidence

I. The efficacy and safety of eluxadoline (Viberzi) for IBS-D was evaluated in two randomized, double-blind, placebo-controlled trials. Treatment arms were 75 mg, 100 mg or placebo, all administered twice daily. Patients were 18-80 years of age, and all met ROME III criteria for IBS-D. Patients, on average, had a pain score of 3 (0-10) in abdominal pain due to IBS-D, an average daily stool consistency of 5.5 or greater, and at least five days with a BSS score of 5 or greater (1-7). The BSS for stool consistency is rated on a scale of 1-7, with 1 being hard to pass or lumpy stool, and 7 being entirely liquid stool. Efficacy was assessed via a responder composite endpoint of simultaneous improvement in the daily worse abdominal pain score by 30% or greater compared to baseline AND a reduction in BSS to less than 5 for at least half of the days within a 12-week timeframe.
    - Study 1: A 26-week study of 1281 patients, with an additional 26 weeks for safety evaluation. Eluxadoline (Viberzi) showed a 23-29% response rate compared to 17% for placebo. Composite response rates were statistically significant at 12 weeks for both strengths, and the 26-week endpoint was statistically significant for the 100 mg.
    - Study 2: A 26-week study of 1145 patients. This study also included a 4-week withdrawal period upon completion of the 26-week phase. During the withdrawal period, patients were permitted to take rescue loperamide therapy for uncontrolled diarrhea. Eluxadoline (Viberzi) showed a 29-33% response rate compared to 16-20% for placebo. Composite response rates were statistically significant for both strengths at week 12 and 26.
II. Conventional treatment options for IBS-D include antidiarrheals, antibiotics, antispasmodics, antidepressants, and bile acid sequestrants; all of which, the American College of Gastroenterology gave moderate or weak recommendations because of poor quality of evidence and applicability to patient groups. However, due to insufficient comparative evidence for efficacy, conventional treatment options still provide a better value over eluxadoline (Viberzi). Notably, Of the antidepressants, tricyclic agents have been shown to slow intestinal transit; however, SSRI/SNRI agents have less published data and the data available is inconsistent in showing benefit in IBS.

Investigational or Not Medically Necessary Uses

I. Eluxadoline (Viberzi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Diabetic diarrhea
   B. Diarrhea associated with fecal incontinence
   C. Pediatric IBS-D
   D. Mixed IBS or IBS with constipation

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Update to three conventional therapies required prior to coverage. Update to require specialist prescriber.	04/2020
Policy Created	02/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP016

Description
Emicizumab-kxwh (Hemlibra) is a monoclonal antibody used for routine prophylaxis to prevent or decrease the frequency of bleeding episodes for patients with hemophilia A with or without inhibitors.

Length of Authorization
- Initial: 6 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*‡
Hemlibra, emicizumab-kxwh	30 mg	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A with or without factor VIII inhibitors	Up to 690 mg every 28 days
	60 mg		
	105 mg		
	150 mg		
	300mg		

* Max dose based on 115kg person
‡ Members must be dosed at a frequency that will produce the least wastage per dose based on available vial sizes

Initial Evaluation

I. **Emicizumab-kxwh (Hemlibra)** may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **hemophilia A *with* inhibitors** and the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Clinical documentation confirming of a history of inhibitors [i.e. high anti-FVIII titer (≥ 5 Bethesda units)]; **AND**
      3. Emicizumab-kxwh (Hemlibra) will be used as routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
      4. Emicizumab-kxwh (Hemlibra) will not be used in combination with Immune Tolerance Induction (ITI); **AND**
      5. At least one of the following is met:
         i. Member has at least two documented episodes of spontaneous bleeding into joints; **OR**
         ii. Member has had an inadequate response to ITI; **OR**
         iii. Member is currently on, or has had an inadequate response to routine prophylaxis with a bypassing agent (e.g. NovoSeven, FEIBA); **OR**
   B. Member has a confirmed diagnosis of **hemophilia A *without* inhibitors** and the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

2. Clinical documentation confirming that the member does not have a history of inhibitors [i.e. high anti-FVIII titer (≥ 5 Bethesda units); **AND**
3. Emicizumab-kxwh (Hemlibra) will be used as routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
    i. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
    ii. Member has had more than one documented episode of spontaneous bleeding; **AND**
4. Clinical documentation that prior prophylaxis with factor VIII was ineffective for the prevention of bleeding episodes

II. Emicizumab-kxwh (Hemlibra) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline

Supporting Evidence

I. Hemophilia A (factor VIII deficiency) is an X-linked inherited coagulation factor deficiency that results in lifelong bleeding disorders. The availability of factor replacement products has dramatically improved care for those with hemophilia A. Emicizumab-kxwh (Hemlibra) represents a new mechanism of action for the management of hemophilia A with and without inhibitors.

II. There are varying severities of hemophilia A depending on the level of factor produced by the patient. Hemophilia A is divided into the following categories based on severity:
    i. **Severe**: <1% factor activity (<0.01 IU/mL)
    ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
    iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL

III. There are three general approaches to bleeding management in those with hemophilia A:
- Episodic ("on demand") treatment that is given at the time of clinically evident bleeding
- Perioperative management of bleeding for those undergoing elective surgery/procedures
- Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia A is to replace the deficient coagulation factor either through episodic ("on demand") treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor VIII products are the treatment of choice for hemophilia A as recommended by The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia A. Therapy should be initiated early with the goal of keeping the trough factor VIII level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. People with hemophilia A can develop antibodies to the factor replacement product that can interfere with the ability to treat bleeding and achieve adequate homeostasis. These antibodies, called inhibitors, develop in about 23-30% of people with Hemophilia A. Inhibitors often develop during childhood, especially during the first 50 exposure days to factor, with the greatest risk occurring between the first ten to 20 treatments.

VI. Treatment options for people who develop inhibitors are limited. Immune tolerance induction (ITI) is the main method for inhibitor eradication. It involves the administration of repeated doses of factor to tolerize the individual's immune system to the factor and reduce antibody production.

VII. Other options to treat bleeding in patients with inhibitors include bypassing products [e.g. recombinant activated factor VII (NovoSeven®), factor eight inhibitor bypassing agent (FEIBA®)], plasmapheresis, and high-dose factor infusion. Emicizumab-kxwh (Hemlibra) is indicated for prophylaxis in patients with hemophilia A and inhibitors. Choice of therapy is individualized and dependent on many factors.

VIII. The safety and efficacy of emicizumab-kxwh (Hemlibra) in adult and pediatric patients with inhibitors was established in two Phase 3 trials (HAVEN 1 and HAVEN 2). Patients treated with emicizumab-kxwh (Hemlibra) experienced significantly fewer bleeds compared to patients who received no prophylaxis.

IX. The safety and efficacy of emicizumab-kxwh (Hemlibra) in patients without inhibitors was established in two Phase 3 trials (HAVEN 3 and HAVEN 4). Prophylaxis with emicizumab-kxwh (Hemlibra) resulted in a reduction in bleeding compared to those who received no prophylaxis.

X. Emicizumab-kxwh (Hemlibra) prophylaxis has not been compared to any other treatment option (e.g. bypassing agent, factor VIII replacement); therefore, the comparative safety and efficacy is unknown.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of emicizumab-kxwh (Hemlibra) in any other condition.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added new 300mg/2mL strength to policy QL table	01/2024
New policy created for emicizumab-kxwh (Hemlibra)	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP188

Description

Emtricitabine/tenofovir alafenamide (Descovy®) is a two-drug combination of emtricitabine (FTC) 200 mg and tenofovir alafenamide (TAF) 25 mg indicated for the treatment of HIV-1 infection and pre-exposure prophylaxis of HIV infection from sexual acquisition.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
emtricitabine/tenofovir alafenamide (Descovy)	200-25 mg tablets	Pre-Exposure Prophylaxis (PrEP); Treatment of HIV-1	30 tablets/30 days
	120-15 mg tablets	Treatment of HIV-1	

Initial Evaluation

I. **Emtricitabine/tenofovir alafenamide (Descovy)** may be considered medically necessary when the following criteria are met:
   A. A diagnosis of the following:
      1. A diagnosis of **HIV-1** and the following is met:
         i. Medication is prescribed by, or in consultation with, an infectious disease or HIV specialist; **AND**
         ii. Member's bodyweight is 14-16kg; **OR**
         iii. Member's bodyweight is 17kg (37.5lbs) or greater; **AND**
            a. Documentation that the member is not a candidate for a generic tenofovir disoproxil fumarate-based regimen due to contraindication or intolerance defined by any one of the following**:**
               i. Requires renal hemodialysis; **OR**
               ii. Stabilized creatinine clearance (CrCl) less than 60mL/min within the prior 3 months; **OR**
               iii. Stabilized creatinine clearance (CrCl) between 60-89 mL/min; **AND**
                  1. Member has hypertension; **AND**
                  2. Member has one of the following:
                     a. Diabetes
                     b. Hepatitis C

c. Vascular kidney disease (e.g., renal artery stenosis)
d. Structural abnormalities (e.g., polycystic kidney, dysplastic kidney, renal mass)
e. Member is African American with a family history of kidney disease; **OR**

iv. Member is high risk for bone complications as determined by a history of one of the following:
1. Vertebral compression factor
2. Arm or hip fracture with minimal trauma
3. Member has chronic kidney disease with proteinuria, low phosphate or is grade 3 or worse
4. T score, less than, or equal to, -2.0 (DXA) at the femoral neck or spine
5. Chronic, high dose glucocorticoid-therapy defined as more than 5 mg/day of prednisone, or equivalent, daily; **AND**
a. Member has ongoing use of glucocorticoid therapy
b. Documentation of the member's current glucocorticoid regimen
c. The expected duration of glucocorticoid therapy is greater than 2 months**; OR**

b. Request is for emtricitabine/tenofovir alafenamide (Descovy) and member's bodyweight is 14-16 kg; **OR**

2. Medication will be used in the setting of **Pre-Exposure Prophylaxis (PrEP)** when the following are met:
i. Member is at high risk for acquiring HIV-1 infection from sexual acquisition (e.g., engaging in sexual activity with a HIV-1 infected partner, multiple diagnoses of sexually transmitted infections); **AND**
ii. Member has a negative HIV-1 test no more than seven days prior to initiating treatment; **AND**
iii. Member's body weight is greater than, or equal to, 35 kg (77lbs); **AND**
iv. Documentation that the member is not a candidate for generic emtricitabine/tenofovir disoproxil fumarate due to contraindication or intolerance defined as any one of the following:
a. Requires renal hemodialysis
b. Stabilized creatinine clearance (CrCl) less than 60 mL/min but greater than, or equal to, 30 mL/min within the prior 3 months
c. Member has experienced significant adverse effects to emtricitabine/tenofovir disoproxil fumarate; **AND**
i. Documentation that adverse effects significantly impact adherence or quality of life; **AND**

ii. Documentation that adverse effects resolved upon drug discontinuation

II. Emtricitabine/tenofovir alafenamide (Descovy) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Prevention of HIV in adults and adolescents not at risk of HIV-1 infection from sexual acquisition

III. Emtricitabine/tenofovir alafenamide (Descovy) is considered investigational when used for all other conditions, including but not limited to:
   A. Prevention of HIV in adults and adolescents not at risk of HIV-1 infection from sexual acquisition
   B. Use for prevention of other sexually transmitted diseases (STI's)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of one of the following:
   A. **HIV-1**; **AND**
      1. Member's condition has not worsened, while on therapy as evidenced by one of the following:
         i. A viral load less than 200 copies/mL; **OR**
         ii. An increasing CD4 cell count; **OR**
   B. Medication will be used in the setting of **Pre-Exposure Prophylaxis (PrEP); AND**
      a. Member is at high risk for acquiring HIV-1 infection from sexual acquisition (e.g., engaging in sexual activity with a HIV-1 infected partner, multiple diagnoses of sexually transmitted infections); **AND**
      b. Member has had a negative HIV-1 test within the last 3 months; AND
      c. Documentation that the member is not a candidate for generic emtricitabine/tenofovir disoproxil fumarate due to any one of the following:
         i. Requires renal hemodialysis; **OR**
         ii. Stabilized creatinine clearance (CrCl) less than 60 mL/min within the prior 3 months; **OR**
         iii. Member has experienced significant adverse effects to emtricitabine/tenofovir disoproxil fumarate; **AND**
            1. Documentation that adverse effects significantly impact adherence or quality of life; **AND**
            2. Documentation that adverse effects resolved upon drug discontinuation

Supporting Evidence

HIV-1

I. Due to the ongoing and complex nature of treating those that are HIV-1 positive, it is important this medication is only prescribed by those that are trained in infectious diseases or specializes in HIV treatment.

II. Safety and efficacy of emtricitabine/tenofovir alafenamide (Descovy) has been established in seven clinical trials in patients with a diagnosis of HIV-1.
   - From those seven clinical trials two were randomized, double-blind, active-controlled, Phase 3 studies in HIV-1 infected treatment naïve adults (Study 104 and Study 111) where patients received E/C/F/TAF or E/C/F/TDF or placebo.
     - The primary endpoint was percentage of participants with HIV-1 RNA < 50 Copies/mL. E/C/F/TAF was non-inferior to E/C/F/TDF for the combined primary outcome (800 patients [92%] vs 784 patients [90%], adjusted difference 2.0%, 95% CI −0.7% to 4.7%).
     - Secondary endpoint of mean increases from baseline in CD4 cell counts was higher for the E/C/F/TAF through week 48 (E/C/F/TAF 230 (SD 177.3) cells/mL; E/C/F/TDF 211 (170.7) cells/mL) with a difference in LSM 19 cells/mL, 95% CI: 3-36 cells/mL; p=0.024.
   - Study 109 was a randomized, open-label, active-controlled, noninferiority study in HIV-1 infected virologically suppressed adults who received FTC+TAF with elvitegravir, cobicistat, emtricitabine, and TAF - E/C/F/TAF (TAF group) or emtricitabine, TDF, atazanavir, and cobicistat (COBI) or ritonavir or FTC+TDF with elvitegravir +COBI (TDF group).
     - The primary endpoint was percentage of participants with HIV-1 RNA < 50 copies/mL. Of patients previously on elvitegravir, cobicistat, emtricitabine, and TDF before randomization, 98% of those who switched to TAF maintained virological control, compared to the 97% who continued their regimen (percentage difference 1.0%; 95% CI −1.9 to 3.9).
     - Secondary endpoint: Mean Bone Mineral Density (BMD) at the hip and spine increased in the TAF group while remaining stable or decreasing in the TDF group (p<0.0001). Hip and spine BMD improved in patients assigned to the TAF group compared with the TDF group, irrespective of previous treatment.
     - T-score BMD for both hip and spine increased in patients assigned to the TAF group, while remaining stable in those who continued their initial TDF based regimen. A greater number of patients in the TAF group than in the TDF group recovered from osteopenia or osteoporosis at either the hip or the spine during the 48 weeks (p<0.0001).
     - Additional secondary endpoint was change from baseline in serum creatinine in those assigned to the TDF group compared with the TAF group (2.9 µmol/L [SD 9.29] vs −0.4 µmol/L [10.14] in the TAF group; difference in least squares mean for TAF group vs TDF group was −3.33 µmol/L [95% CI −4.57 to −2.10 µmol/L] (p<0·0001).
   - Study 112 was an open-label trial that looked at HIV-1 infected virologically suppressed adults with renal impairment (estimated creatinine clearance between 30 and 69 mL/min. The study included 242 adults on 150 mg elvitegravir, 150 mg cobicistat, 200 mg FTC, and 10 mg TAF (E/C/F/TAF).

- The primary outcomes were change from baseline in the estimated glomerular filtration rate (eGFR). Through the 48 weeks there was no clinically appreciable change from baseline in estimated creatinine clearance observed, with direction and magnitude varying by filtration marker and equation. Results were similar for patients whether baseline eGFR was <50 or ≥50 mL/min or whether they switched from a TDF-based regimen.
- The prevalence of significant proteinuria (UPCR > 200 mg/g) and albuminuria (UACR ≥ 30 mg/g) decreased from 42% to 11% and from 49% to 21%, respectively.
- BMD significantly increased after switch to E/C/F/TAF for patients on a TDF-containing regimen pre-switch and remained stable after switch to E/C/F/TAF for patients on non-TDF-containing regimen pre-switch. Mean percent changes from baseline to week 48 in hip and spine BMDs significantly increased (+1.47% and +2.29%, respectively), and more patients had significant (≥3%) gains in hip or spine BMD than those who had significant loss.

III. Emtricitabine/tenofovir alafenamide (Descovy) is not recommended in patients with estimated creatinine clearance below 15 to below 30 mL/min, or in individuals with estimated creatinine clearance below 15 mL/min who are not receiving chronic hemodialysis.

IV. Stage two CKD is defined by a GFR between 60-89 mL/min for three months or longer along with kidney damage.

V. Emtricitabine/tenofovir alafenamide (Descovy) is not approved in the treatment of chronic HBV infection as the safety and efficacy has not yet been established in patients who are coinfected with HIV-1 and HBV. As severe acute exacerbations of hepatitis B (e.g., liver decompensation and liver failure) have been reported in patients who are coinfected with HIV-1 and HBV who have discontinued products containing FTC and/or TDF and may occur when emtricitabine/tenofovir alafenamide (Descovy) is discontinued. Due to this, patients who are coinfected with HIV-1 and HBV who have discontinued emtricitabine/tenofovir alafenamide (Descovy) should be closely monitored with both clinical and laboratory follow-up.

VI. No dosage adjustment of emtricitabine/tenofovir alafenamide (Descovy) is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment as emtricitabine/tenofovir alafenamide (Descovy) has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

VII. Estimated creatinine clearance, urine glucose, and urine protein should be assessed before initiating emtricitabine/tenofovir alafenamide (Descovy) therapy and should be monitored during therapy in all patients. Serum phosphorus should be monitored in patients with chronic kidney disease as these patients are at higher risk of developing Fanconi syndrome on tenofovir prodrugs. Emtricitabine/tenofovir alafenamide (Descovy) should be discontinued in patients who develop clinically significant decreases in renal function or evidence of Fanconi syndrome.

VIII. No safety or efficacy data is available in patients with renal impairment who received emtricitabine/tenofovir disoproxil fumarate (Truvada) using these dosing guidelines, so the potential benefit of emtricitabine/tenofovir disoproxil fumarate (Truvada) therapy should be assessed against the potential risk of renal toxicity. Emtricitabine/tenofovir disoproxil fumarate (Truvada) is not recommended in patients with estimated creatinine clearance below 30 mL/min or patients requiring hemodialysis.

IX. In clinical trials in HIV-1 infected treatment-naïve adults a significant decline in BMD was observed in 15% of subjects treated with FTC+TAF with EVG+COBI. However, as the long-term clinical significance of these changes has not been established, assessment of BMD should be considered for adults and pediatric patients treated with emtricitabine/tenofovir alafenamide (Descovy) who have a history of pathologic bone fracture or other risk factors for osteoporosis or bone loss. Calcium and vitamin D supplementation may be beneficial for all patients and should be considered. Cases of osteomalacia associated with proximal renal tubulopathy, manifested as bone pain or pain in extremities and which may contribute to fractures, have been reported in association with the use of TDF-containing products. Hypophosphatemia and osteomalacia secondary to PRT have occurred in patients who are at risk of renal dysfunction who present with persistent or worsening bone or muscle symptoms while receiving products containing TDF. However, as this was not studied in clinical studies of emtricitabine/tenofovir alafenamide (Descovy), the risk of osteomalacia with emtricitabine/tenofovir alafenamide (Descovy) is not known.

X. The efficacy and safety of emtricitabine/tenofovir alafenamide (Descovy), used in combination with other antiretroviral agents for the treatment of HIV-1 infection, was established in pediatric patients 12 years of age and older who had a body weight greater than, or equal to, 35 kg. Use of emtricitabine/tenofovir alafenamide (Descovy) in this age group is supported by adequate and well controlled studies of FTC+TAF with EVG+COBI in adults and by a 24-week open label trial of 23 antiretroviral treatment-naïve HIV-1 infected pediatric subjects, aged 12-18 years old, weighing at least 35 kg, and who were treated with FTC+TAF with EVG+COBI. The safety and efficacy of FTC+TAF with EVG+COBI was similar to that of antiretroviral treatment-naïve HIV-1 infected adults on this same regimen.

XI. Use of emtricitabine/tenofovir alafenamide (Descovy) in pediatric patients aged two to less than six years of age and weighing at least 14 to less than 25kg is supported by an open-label trial of FTC+TAF with bictegravir (N=22; cohort 3) in virologically suppressed pediatric patients and studies of FTC+TAF with EVG+COBI in adults. The safety and efficacy of FTC+TAF in these pediatric patients were similar to that observed in adults who received FTC+TAF with bictegravir. Emtricitabine/tenofovir disoproxil fumarate (Truvada) has been studied in pediatric patients weighing ≥17kg only. Patients weighing 14kg to less than 17kg are not candidates for emtricitabine/tenofovir disoproxil fumarate (Truvada) as efficacy and safety of emtricitabine/tenofovir disoproxil fumarate (Truvada) has not been established in this population.

XII. In clinical trials, 80 of the 97 subjects enrolled were 65 years and over and received FTC+TAF and EVG+COBI, with no differences in safety or efficacy being observed between elderly subjects and those between 12 and 65 years of age.

PrEP

I. The efficacy and safety of emtricitabine/tenofovir alafenamide (Descovy) to reduce the risk of acquiring HIV-1 infection were studied in a randomized, double-blind, active-controlled multinational trial (DISCOVER) in HIV-seronegative men (N=5,262) or transgender women (N=73) who have sex with men and are at risk for HIV-1 infection. Subjects were included in the trial if they met criteria for high-risk behavior defined as one of the following: two or more unique condom less anal sex partners in the past 12 weeks or a diagnosis of rectal gonorrhea/chlamydia or syphilis in the past 24 weeks. Clinical trial compared the incidence of

documented HIV-1 infection per 100 person-years in participants randomized to once daily emtricitabine/tenofovir alafenamide (Descovy) and emtricitabine/tenofovir disoproxil fumarate (Truvada) and found that study drug was non-inferior to comparator at reducing the risk of acquiring HIV-infection with rate ratio of 0.468 [95% CI, 0.19, 1.15].

II. The FDA HIV-1 PrEP indication for emtricitabine/tenofovir alafenamide (Descovy) does not include individuals at risk of HIV-1 from receptive vaginal sex, however, there are preliminary pharmacokinetic data in healthy, non-pregnant, HIV negative, premenopausal (aged 18-50) cis-gender women evaluated in a Phase 1 clinical trial (NCT02904369). Results demonstrate that participants had higher tenofovir-diphosphate (TVF-DP) levels in peripheral blood mononuclear cells (PBMCs) with tenofovir alafenamide (TAF) than with tenofovir disoproxil fumarate (TDF), suggesting emtricitabine/tenofovir alafenamide (Descovy) should be just as effective in preventing HIV-infections in this population. No new safety concerns were reported with the TAF formulation. Thus, emtricitabine/tenofovir alafenamide (Descovy) is expected to produce similar results as emtricitabine/tenofovir disoproxil fumarate (Truvada) in this population. Use of emtricitabine/tenofovir disoproxil fumarate (Truvada) in cis-gender women is supported by a randomized, double-blind, placebo-controlled Partners PrEP study.

III. Per Center for Disease Control (CDC) guidelines, while on PrEP, a person is advised to also get periodic HIV and STD testing. CDC recommends documenting a negative HIV test result within the week before initiating (or reinitiating) PrEP medications, ideally with an antigen/antibody test conducted by a laboratory. For patient safety, HIV testing should be repeated at least every three months after oral PrEP initiation. If the person acquires HIV while taking PrEP, they must immediately be provided a full antiretroviral therapy (ART) regimen to prevent drug resistance.

IV. The safety and efficacy of emtricitabine/tenofovir alafenamide (Descovy) for prevention of HIV-1 infection has not been evaluated in patients weighing <35kg (77lbs). At this time, emtricitabine/tenofovir alafenamide (Descovy) is only indicated in at-risk adults and adolescents weighing at least 35kg for PrEP.

V. Emtricitabine/tenofovir disoproxil fumarate is FDA approved for PrEP in healthy adults and adolescents at risk for acquiring HIV-1 infection and continues to be the most commonly prescribed oral medication for those meeting criteria for PrEP use. There are no clinically meaningful efficacy or safety differences between emtricitabine/tenofovir disoproxil fumarate and emtricitabine/tenofovir alafenamide (Descovy). At this time, generic emtricitabine/tenofovir disoproxil fumarate remains the most cost-effective agent and in the absence of contraindications is required to be trialed first. Contraindications to the use of emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP include individuals with estimated creatinine clearance below 60mL/min or those requiring hemodialysis. Relative contraindications additionally include those previously treated with emtricitabine/tenofovir disoproxil fumarate and experiencing adverse reactions related to the drug such that adverse reactions impacted adherence and/or quality of life and led to drug discontinuation.

VI. For those established on emtricitabine/tenofovir alafenamide (Descovy) through a previous health plan, medical necessity requirements for use of brand Descovy over use of generic of emtricitabine/tenofovir disoproxil fumarate remains required.

VII. Clinically significant bone mineral density (BMD) changes have not been observed in clinical trials studying emtricitabine/tenofovir disoproxil fumarate for HIV-1 PrEP. A 3%-4% decline in BMD was seen in HIV-infected persons treated with combination antiretroviral therapy;

however, it is unclear whether a similar decline would be seen in HIV-uninfected persons taking fewer antiretroviral medications for PrEP. At this time, clinical guidelines do not recommend DEXA scans or other assessments of bone health before initiation of PrEP or for monitoring of persons while taking PrEP. Therefore, decreased bone mineral density is not considered a contraindication to treatment with emtricitabine/tenofovir disoproxil fumarate at this time.

Investigational or Not Medically Necessary Uses

I. Emtricitabine/tenofovir alafenamide (Descovy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Prevention of HIV in adults and adolescents not at risk of HIV-1 infection from sexual acquisition
   B. Use as a cure for those HIV-1 positive
   C. Use as a preventive measure against other STI's

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Removed specialist requirement in the setting of PrEP.	06/2023
Effective 01/01/2023 - Removal of PA requirement for Biktarvy, therefore removed from policy.	12/2022
Updated renewal criteria to allow a path to coverage for those established through a previous health plan. Updated PrEP renewal criteria to require use of generic Truvada. Updated supporting evidence section. Updated references.	08/2022
Included new Descovy strength (120-15mg tablets); updated HIV-1 initial criteria to expand use in pediatric patients weighing between 14 and 16kg; updated HIV-1 indication weight criterion from 25kg to 17kg to align with Truvada's label, added/defined additional contraindications to generic Truvada in the setting of PrEP, removed criteria requiring use in adults at risk from receptive vaginal sex from PrEP, defined HIV-1 testing requirement frequency in the renewal section for PrEP, updated supporting evidence sections, updated references.	05/2022
Added 30/120/15mg Biktarvy tablet to policy and requirement of weight minimum.	12/2021
Edits to wording of criteria C.2. for requirement of HBV screening prior to therapy initiation with Biktarvy; added supporting information to the supporting evidence section	01/2021
Instead of tenofovir disoproxil fumarate (Truvada) requiring step through generic tenofovir disoproxil fumarate	12/2020
Policy created	07/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP091

Description

Encorafenib (Braftovi) is a kinase inhibitor of in-vitro growth of tumor cell lines expressing BRAF V600 E, D, and K mutations. Binimetinib (Mektovi) is a reversible kinase inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activity. These agents are FDA-approved for combination use.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
encorafenib (Braftovi)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy; Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy	50 mg capsule	180 capsules/30 days
		75 mg capsule	180 capsules/30 days
binimetinib (Mektovi)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy	15 mg tablet	180 tablets/30 days

Initial Evaluation

I. Encorafenib (Braftovi) and binimetinib (Mektovi) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medications are prescribed by, or in consultation with, an oncologist, dermatologist, or gastroenterologist; **AND**
   C. Encorafenib (Braftovi) and binimetinib (Mektovi) will **not** be used in combination with any other oncolytic agent unless specified below (e.g. encorafenib (Braftovi) and cetuximab (Erbitux) for the treatment of colorectal cancer); **AND**
   D. The member has **not** progressed on prior BRAF-inhibitor therapy (e.g., dabrafeinib, vemurafenib); **AND**
   E. A diagnosis of one of the following:
      1. **Advanced (stage III) or metastatic (stage IV) cutaneous melanoma**; **AND**
         i. Encorafenib (Braftovi) and binimetinib (Mektovi) will be used in combination; **AND**
         ii. Mutation status of BRAF V600E or V600K; **OR**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

2. **Metastatic (stage IV) colorectal cancer (CRC)**; **AND**
    i. The request is for encorafenib (Braftovi) in combination with cetuximab (Erbitux); **AND**
    ii. Mutation status of BRAF V600E mutation; **AND**
    iii. The member has previously tried and failed at least one systemic therapy (e.g. FOLFIRI, irinotecan, oxaliplatin)

II. Encorafenib (Braftovi) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Colorectal cancer in combination with binimetinib (Mektovi) and cetuximab (Erbitux)

III. Encorafenib (Braftovi) and binimetinib (Mektovi) are considered investigational when used for all other conditions, including but not limited to:
    A. KRAS-mutated cancer
    B. Adolescents with BRAF-mutant melanoma
    C. Thyroid cancer
    D. Lung cancer (e.g., non-small cell lung cancer, non-squamous carcinoma of the lung)
    E. CNS cancers (e.g., glioma, neurofibromas)
    F. Gastrointestinal cancer (e.g., GIST)
    G. Pancreatic cancer
    H. Colorectal cancer in combination with panitumumab (Vectibix)

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
    A. For treatment of melanoma: encorafenib (Braftovi) and binimetinib (Mektovi) will be used in combination; **OR**
    B. For treatment of colorectal cancer: encorafenib (Braftovi) and cetuximab (Erbitux) will be used in combination

Supporting Evidence

I. Advanced or Metastatic Melanoma
    - BRAF/MEK inhibitors have been studied in advanced and metastatic melanoma. Surgical resection remains the mainstay of therapy prior to stage III and have favorable outcomes for most patients. Patients at stage II have a high risk of progressing to advanced disease and have a high risk of recurrence; however, there is currently no evidence to support safety and efficacy in this population for any BRAF/MEK therapy combination.

- There is limited evidence regarding the safety and efficacy of BRAF/MEK inhibitor therapy in those that have progressed on a previous or alternative BRAF/MEK therapy combination. Results from a phase I/II study showed that those that had previous BRAF therapy, further treatment with dabrafenib (Tafinlar)/trametinib (Mekinist), had poor response rates, progression free survival (PFS), and overall survival (OS) compared to those that had not been previously treated with these specific mechanisms of action. Most notably, a subset analysis showed that patients who had rapidly progressed on BRAF therapy (less than six months to progression) derived no clinical benefit from second line/subsequent treatment.
- BRAF V600E and V600K mutations are the most common mutation of BRAF driver mutations; however, several other BRAF mutations exist. NCCN supports the use of BRAF/MEK inhibitors for any V600 mutation; however, there is currently no evidence for safety or efficacy to support the use of encorafenib (Braftovi) and binimetinib (Mektovi) in settings outside of V600E or V600K.
- Encorafenib (Braftovi), in combination with binimetinib (Mektovi), was evaluated in a randomized, active-controlled, open-label multicenter trial (n=577). Subjects had a BRAF V600E or K mutation-positive, unresectable or metastatic melanoma, and were permitted to have prior immunotherapy for advanced or metastatic disease. Prior use of BRAF therapy was not allowed.
    i. Subjects were randomized to receive encorafenib (Braftovi) in combination with binimetinib (Mektovi), encorafenib (Braftovi) monotherapy, or vemurafenib (Zelboraf) monotherapy. The primary outcome was PFS. Secondary outcomes included OS, objective response rate (ORR), and duration of response (DoR).
    ii. The combination of Braftovi and Mektovi showed a statistically significant improvement in PFS compared to vemurafenib (Zelboraf) (14.9 months vs 7.3 months, $p<0.0001$). There were statistically significant improvements in ORR and DoR. Overall survival data was published in 2018, with OS duration of 33.6 months for combination therapy compared to 16.9 months with vemurafenib monotherapy ($p<0.0001$).
    iii. The safety and efficacy of combination therapy with Braftovi and Mektovi was evaluated, compared to encorafenib (Braftovi) alone, and results were more favorable for combination therapy. The current FDA-approval is for dual therapy.

II. Metastatic Colorectal Cancer

- Encorafenib (Braftovi), in combination with cetuximab (Erbitux), was studied in one ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 trial with 645 patients with BRAF V600E mutation-positive metastatic CRC. The primary efficacy endpoint was OS. The median OS was 9 months for encorafenib (Braftovi)/binimetinib/(Mektovi)/cetuximab (Erbitux) and 8.4 months for encorafenib (Braftovi)/cetuximab (Erbitux) compared to 5.4 months for irinotecan (Camptosar)/cetuximab (Erbitux) with a HR of 0.52 (95% CI 0.39, 0.70) and 0.60 (95% CI 0.45, 0.79), respectively. The median PFS was 4.3 months for encorafenib (Braftovi)/binimetinib/(Mektovi)/cetuximab (Erbitux) and 4.2 months for encorafenib (Braftovi)/cetuximab (Erbitux) compared to 1.5 months for irinotecan (Camptosar)/cetuximab (Erbitux) with a HR of 0.38 (95% CI 0.29, 0.49) and 0.40 (95% CI 0.31, 0.52), respectively. The estimated six-month survival was 71% in the

triple therapy group and 65% in the dual therapy group with a HR of 0.79 (95% CI 0.59, 1.06).

- NCCN guidelines note that triple therapy with encorafenib (Braftovi)/binimetinib (Mektovi)/cetuximab (Erbitux) has evidence for use in metastatic colorectal cancer; however, when listing recommended therapy options, they only note encorafenib (Braftovi) in combination with cetuximab (Erbitux) or panitumumab (Vectibix). The recommendation for encorafenib (Braftovi) in combination with cetuximab (Erbitux) or panitumumab (Vectibix) is Category 2A. Although both cetuximab (Erbitux) and panitumumab (Vectibix) are listed as combination options within NCCN, clinical data available is limited to encorafenib (Braftovi) in combination with cetuximab (Erbitux).

Investigational or Not Medically Necessary Uses

I. Encorafenib (Braftovi) and binimetinib (Mektovi) have not been sufficiently studied for safety and/or efficacy in the following settings:
   A. KRAS-mutation cancer
   B. Adolescents with BRAF-mutant melanoma
   C. Thyroid cancer
   D. Lung cancer (e.g., non-small cell lung cancer, non-squamous carcinoma of the lung)
   E. CNS cancers (e.g., glioma, neurofibromas)
   F. Gastrointestinal cancer (e.g., GIST)
   G. Pancreatic cancer
   H. Colorectal cancer in combination with panitumumab (Vectibix)
      i. There have been no large, well-designed studies of encorafenib (Braftovi) or binimetinib (Mektovi) in combination with panitumumab (Vectibix).
   I. Encorafenib (Braftovi) in combination with binimetinib (Mektovi) and cetuximab (Erbitux) for colorectal cancer
      i. Encorafenib (Braftovi), in combination with binimetinib (Mektovi), and cetuximab (Erbitux) was studied in one ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 trial with 645 patients with BRAF V600E mutation-positive metastatic colorectal cancer. The efficacy of triple therapy was not significantly superior to dual therapy.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updates to supportive evidence addressing lack of clinical data available for encorafenib (Braftovi) in combination with panitumumab (Vectibix).	11/2022
Updated with new indication for Braftovi for metastatic colorectal cancer in combination with cetuximab. Updated language to state not for combination use besides agents listed in the criteria. Removed exclusions for colorectal cancer and V600-mutated cancer besides melanoma.	06/2020
Prior authorization criteria transitioned to policy, updated criteria with the following: age edit, allowance of dermatologist prescribing, specialist requirement on renewal.	11/2019
Criteria created	07/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP082

Description

Entrectinib (Rozlytrek) is an orally administered selective kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
entrectinib (Rozlyrek)	Neurotrophic receptor tyrosine kinase gene fusion positive solid tumors Non-small cell lung cancer, metastatic, ROS1-positive	50 mg pellets	**Pediatric:** Dosing per body surface area* to the nearest full-size package
		100 mg capsules	30 capsules/30 days
		200 mg capsules	90 capsules/30 days

**See appendix for body surface area dosing for pediatric patients with NTRK positive solid tumors*

Initial Evaluation

I. **Entrectinib (Rozlytrek)** may be considered medically necessary when the following criteria below are met:
   A. Prescribed by or in consultation with an oncologist; **AND**
   B. Medication will not be used in combination with any other oncolytic medication; **AND**
   C. A diagnosis of one of the following:
      1. **Solid tumor with a confirmed NTRK gene fusion**; **AND**
         i. Member is one month of age or older; **AND**
         ii. If member is under the age of 18, the member's body surface area (BSA) is submitted; **AND**
         iii. Member has metastatic disease; **OR**
            a. Surgical resection is likely to result in severe morbidity (i.e., tumor is unresectable); **AND**
         iv. Member does not have an acquired resistance mutation; **AND**
         v. Attestation that all alternative therapies for diagnosis and stage of cancer have been exhausted as defined by:
            a. Progression following all appropriate treatments; **OR**
            b. Nonresponse to all available therapies; **OR**
            c. All available therapies are contraindicated or not tolerated; **OR**

d. No standard or satisfactory treatments exist; **OR**

2. **ROS1-positive non-small cell lung cancer as detected by an FDA-approved test**; **AND**
    i. Member is 18 years of age or older; **AND**
    ii. Member has not progressed on any previous ROS1 targeted therapy [e.g., crizotinib (Xalkori), ceritinib (Zykadia), lorlatinib (Lorbrena), etc.]

II. Entrectinib (Rozlytrek) is considered investigational when used for all other conditions, including but not limited to:
    A. Non-small cell lung cancer without NTRK fusion or ROS1-positive gene rearrangements (e.g., ALK-positive NSCLC)
    B. Solid tumors that do not harbor NTRK gene fusions

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication will not be used in combination with any other oncolytic medication; **AND**
IV. Response to therapy as indicated by stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

I. Entrectinib (Rozlytrek) is currently FDA approved for adult patients with a *ROS1*-positive metastatic non-small cell lung cancer (NSCLC) and received an accelerated approval in 2019 for adult and pediatric patients ages 12 and older for neurotrophic tyrosine receptor kinase (NTRK) positive solid tumors, metastatic or where surgical resection is likely to cause severe morbidity. In October 2023, this accelerated approval in NTRK solid tumors was expanded to include age one month and older.
II. Due to the complexity of treatment and diagnosis, of either indication, it is recommended that patients are seen by, or in consultation with an oncologist.
III. Neither therapy is approved to be used in combination with another oncolytic medication; therefore, entrectinib (Rozlytrek) should be used as monotherapy.
IV. Safety and efficacy data for entrectinib (Rozlytrek) is available through the following clinical trials: Phase 2 STARTRK-2, Phase 1 STARTRK-2, Phase 1 ALKA-372-001, and Phase 1/2 STARTRK-NG and TAPISTRY. The last two supporting approval in pediatric subjects.
    - STARTRK2: Basket study of entrectinib (Rozlytrek) for the treatment of patients with solid tumors harboring NTRK1/2/3, ROS1 or ALK gene rearrangements (fusions). This pivotal trial was non-randomized, open-label and analyzed 206 subjects for safety. For efficacy, data was captured for 51 NTRK fusion-positive and 37 ROS1-positive subjects.
    - STARTRK1: A Phase I, single-arm, open-label study evaluated the same population parameters as STARTRK2, and included 76 subjects for the safety evaluation. Two

subjects with NTRK fusion-positive and 7 subjects with ROS1-positive disease were evaluated for efficacy.

- ALKA-372-001: A Phase I, single-arm, open-label study evaluated the same population in STARTRK1 and 2. Safety data was gathered from 57 subjects. One subject had NTRK fusion-positive and 9 subjects had ROS1-positive disease were evaluated for efficacy.
- STARTRK-NG: A Phase I/IIb, single-arm, open-label study evaluated dose escalation and expansion in children and adolescents with recurrent or refractory solid tumors with or without TRK, ROS1, or ALK fusions. No subjects were included that had NTRK fusion-positive or ROS1-positive NSCLC. Twenty-nine subjects were evaluated. In 2023, this was expanded to include NTRK and ROS1 gene fusions; 15 subjects with NTRK 1/2/3 and eight with ROS1 were included in the primary outcomes.
- TAPISTRY: Phase 2, open-label, multi-cohort study in patients with locally advanced, unresectable, or metastatic solid tumors. This trial tests multiple different treatment arms and mutation types. For entrectinib (Rozlytrek), recruitment of 50 subjects for ROS1 arm and 200 patients for the NTRK arm is being projected. The trial does not conclude until 2032.

NTRK Positive Solid Tumors

V. Data for NTRK fusion-positive solid tumor FDA-approval for adult patients included a pooled group of 54 subjects across the trials listed above. Patients were mainly white, female with a median age of 58, and 96% of patients had metastatic disease, including 22% with CNS metastases, and 4% had locally advanced, unresectable disease. All patients had received prior treatment for their cancer including surgery (n = 43), radiotherapy (n = 36), or systemic therapy (n = 48). Forty patients (74%) received prior systemic therapy for metastatic disease with one prior systemic regimen and 17% (n = 9) received 3 or more prior systemic regimens. The primary outcome was an objective response rate (ORR) of: 59% (43-71), with 46% achieving partial response (PR) and 13% achieving complete response (CR).

VI. Data for NTRK fusion positive solid tumor in pediatric patients included 33 patients from the last two trials listed above. Patients were on average four years of age, white with locally advanced disease (71%) or metastatic disease (29%) with 85% of patients having prior therapy for their cancer including surgery (n=20), radiotherapy (n=7) and/or systemic therapy (n=22). The primary endpoint was ORR which was 70% (51-84) with 27% having a partial response (PR) and 42% having a complete response (CR).

ROS1-positive NSCLC

VII. Data for ROS1-positive NSCLC FDA-approved included a pooled 92 subjects across the trials listed above with the primary outcome of ORR: 74% (64-83), 59% with PR and 15% CR.

VIII. NTRK fusions are found in a wide variety of cancers and are generally mutually exclusive from other targetable oncogenic drivers. There is a lack of standard of care and these patients are generally treated according to the histological tumor type and do not have targeted therapy. There is only one other agent, larotrectinib (Vitrakvi), for a similar setting to entrectinib (Rozlytrek). It was FDA-approved less than one year before entrectinib (Rozlytrek) in November 2018. The medication was evaluated in those that had progressed following treatment or had no satisfactory treatment alternative(s). Additionally, subjects that had metastatic disease or surgical resection were likely to result in severe morbidity.

IX. ROS1-positive NSCLC is a rare subtype of NSCLC, accounting for only 1-2% of all cases. ROS1-positive NSCLC is a progressive disease with the most common site of metastases being the CNS. Currently, the NCCN 1.2024 NSCLC guidelines recommend entrectinib, crizotinib, repotrectinib or ceritinib as preferred therapy for ROS1- positive NSCLC. Crizotinib (Xalkori) is FDA-approved, but has limited data for safety and efficacy and has not been shown to target CNS metastases. Ceritinib (Zykadia) has been used in some instances, which may have more CNS activity; however, safety and efficacy data is very limited and it is not FDA-approved for ROS1-positive NSCLC. Repotrectinib (Augtyro) did allow those with CNS activity in the study as long as stable, responses were shown in seven of the eight patients. Entrectinib (Rozlytrek) has shown some CNS activity, and in clinical trials five of seven subjects with CNS metastases showed CNS response.

X. In clinical trials dose interruption occurred in 46% of subjects, and dose reduction was required in 28%. Grade 3-4 adverse drug events occurred in 60% of subjects in the trial.

XI. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Investigational or Not Medically Necessary Uses

I. Entrectinib (Rozlytrek) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Non-small cell lung cancer without NTRK fusion or ROS1-positive gene rearrangements (e.g., ALK-positive NSCLC)
      i. Due to the mechanism of action, investigation in ALK-positive NSCLC is underway; however, safety and efficacy have not been defined.
   B. Solid tumors that do not harbor NTRK gene fusions
      i. Efficacy and safety of entrectinib (Rozlytrek) in solid tumors without NTRK fusions has not been sufficiently evaluated.

Appendix

I. Table 1: Pediatric dosing for NTRK gene fusion positive solid tumors

Body Surface Area (BSA)	Recommended Dosage, Orally, once daily
≤0.5 m^2	300 mg/m^2
0.51 to 0.80 m^2	200 mg
0.81 to 1.10 m^2	300 mg
1.11 to 1.50 m^2	400 mg
≥1.51 m^2	600 mg

- In general, the average BSA for a newborn child is 0.25m^2; a two- year-old is 0.5m^2; a five-year-old child is 0.77m^2; a ten-year-old child is 1.14m^2.

References

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2. Farago AF, Le LP, Zheng Z, et al. Durable Clinical Response to Entrectinib in NTRK1-Rearranged Non-Small Cell Lung Cancer. J Thorac Oncol. 2015;10(12):1670-4.
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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
larotrectinib (VITRAKVI®)	NTRK Gene Fusion Positive Solid Tumors
ALK+ Inhibitors	Non-Small Cell Lung Cancer

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated initial approval duration from three months to six months. Updated new age expansion for NTRK positive solid tumors in patients one month and older. Removal of specialist requirement upon renewal, removal of toxicity assessment upon renewal, and addition of standard sample renewal language. Updated supporting evidence across all indications. Updated references and added related policy table.	02/2024
Removed split fill requirement	10/31/22
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Previous Reviews	09/2019 11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP023

Split Fill Management* (applies to dacomitinib [Vizimpro] and erlotinib [Tarceva] only)

Description

Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), and gefitinib (Iressa) are orally administered epidermal growth factor receptor (EGFR) and tyrosine kinase inhibitors (TKIs).

Length of Authorization

- Initial: Three months; split fill applies to dacomitinib (Vizimpro) and erlotinib (Tarceva) only
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
osimertinib (Tagrisso)	40 mg tablets	NSCLC	30 tablets/30 days
	80 mg tablets		
dacomitinib (Vizimpro)	15 mg tablets	NSCLC	30 tablets/30 days
	30 mg tablets		
	45 mg tablets		
generic erlotinib	25 mg tablets	NSCLC; Pancreatic cancer	90 tablets/30 days
	100 mg tablets		30 tablets/30 days
	150 mg tablets	NSCLC	30 tablets/30 days
erlotinib (Tarceva)	25 mg tablets	NSCLC; Pancreatic cancer	90 tablets/30 days
	100 mg tablets		30 tablets/30 days
	150 mg tablets	NSCLC	30 tablets/30 days
afatinib (Gilotrif)	20 mg tablets	NSCLC	30 tablets/30 days
	30 mg tablets		
	40 mg tablets		
gefitinib (Iressa)	250 mg tablets	NSCLC	30 tablets/30 days
gefitinib (generic Iressa)	250 mg tablets	NSCLC	30 tablets/30 days

Initial Evaluation

I. **Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), gefitinib (generic Iressa), and gefitinib (Iressa)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist; **AND**

C. The medication will not be used in combination with any other agent listed in this policy, or another medication for the condition being treated unless outlined specifically below; **AND**
D. Criteria below are met for the specific agent requested;
    1. **For osimertinib (Tagrisso)**
        i. Non-small cell lung cancer, early stage IB-IIIA; **AND**
            a. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated; **AND**
            b. The member has <u>not</u> had disease progression on prior EGFR TKI therapy (no previous use of any other agent listed in this policy); **AND**
            c. Osimertinib (Tagrisso) will be used as adjuvant therapy after the member has undergone complete surgical resection of the tumor; **AND**
            d. The member has been previously treated with, or is ineligible to receive, platinum-based chemotherapy (e.g., cisplatin); **OR**
        ii. Locally advanced unresectable or metastatic (stage IV) non-small cell lung cancer being treated for <u>ONE</u> of the following (a or b):
            a. First-line treatment in the metastatic setting that has NOT progressed while using another EGFR TKI; **AND**
                i. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated; **OR**
            b. After disease progression on another EGFR TKI; **AND**
                i. The tumor is documented to be EGFR T790 mutation-positive
    2. **For dacomitinib (Vizimpro)**
        i. Metastatic (stage IV) non-small cell lung cancer; **AND**
        ii. The member has <u>not</u> had disease progression on prior EGFR TKI therapy (no previous use of any other agent listed in this policy); **AND**
        iii. The treatment will be used for first-line treatment in the metastatic setting (i.e., the member has not received ANY other therapy in the metastatic setting, including, but not limited to, chemotherapy); **AND**
        iv. The member does **NOT** have brain metastases; **AND**
        v. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated
    3. For erlotinib (Tarceva)
        i. Generic erlotinib is prescribed; **OR**
            a. the member has tried and failed, has a contraindication to, or intolerance to generic erlotinib; **AND**
        ii. Use is for one of the following (a or b):
            a. Locally advanced or metastatic (stage IV) non-small cell lung cancer; **AND**
                i. The member has <u>not</u> had disease progression on prior EGFR TKI therapy (no previous use of any other agent listed in this policy); **AND**

ii. The treatment will be used for first-line, maintenance, second-line, or greater-line treatment, and may have progressed after previous chemotherapy; **AND**
iii. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated; **OR**

b. A diagnosis of locally advanced, unresectable or metastatic (stage IV), pancreatic cancer; **AND**
i. The treatment will be used for first-line treatment in the locally advanced or metastatic setting; **AND**
ii. The medication will be used in combination with gemcitabine

4. For afatinib (Gilotrif)

i. Metastatic (stage IV) non-small cell lung cancer; **AND**
a. The member has <u>not</u> had disease progression on prior EGFR TKI therapy (no previous use of any other agent listed in this policy); **AND**
b. The treatment will be used for first-line treatment in metastatic setting; **AND**
c. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated, or has L861Q, G719X, or S7681 mutation; **OR**

ii. Metastatic, squamous non-small cell lung cancer that has progressed on or after treatment with platinum-based chemotherapy (e.g., cisplatin, carboplatin, etc.)

5. For gefitinib (generic Iressa) or BRAND gefitinib (Iressa)

i. Metastatic (stage IV) non-small cell lung cancer; **AND**
ii. The member has <u>not</u> had disease progression on prior EGFR TKI therapy (no previous use of any other agent listed in this policy); **AND**
iii. The treatment will be used for first-line treatment in the locally advanced or metastatic setting; **AND**
iv. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated
v. Request is for generic gefitinib (generic Iressa); **OR**
vi. Request is for branded gefitinib (Iressa); **AND**
Documentation of intolerance or contraindication to generic gefitinib (generic Iressa)

II. Dacomitinib (Vizimpro) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
A. The treatment of NSCLC in the second line setting

III. Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), and gefitinib (Iressa) are considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:

A. When used in combination with any other treatment including chemotherapy or targeted agent
B. Early stage EGFR NSCLC with agents other than osimertinib (Tagrisso), pancreatic cancer, squamous NCCLC
C. Head and neck cancer
D. Renal cell carcinoma
E. Bone cancer including, but not limited to, chordoma
F. Central nervous system cancers without primary tumor source of NSCLC
G. Hepatobiliary cancers

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication will not be used in combination with any other agent listed in this policy, or another medication for the oncolytic condition being treated; **OR**
    A. The request is for erlotinib (Tarceva) in combination with gemcitabine for the treatment of pancreatic cancer; **AND**
IV. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
V. If the request is for brand erlotinib (Tarceva), generic erlotinib has not been tolerated or is contraindicated; **OR**
VI. If the request is for brand gefitinib (Iressa), generic gefitinib not been tolerated or is contraindicated

Supporting Evidence

I. Osimertinib (Tagrisso) is FDA-approved in the first and second line setting for metastatic NSCLC depending on mutation characteristics. The FLAURA trial included 556 treatment naïve participants with EGFR NSCLC and was compared to gefitinib or erlotinib. Osimertinib (Tagrisso) demonstrated improvement in progression free survival (PFS). Although a surrogate outcome, overall survival (OS) is still being collected and the safety profile was favorable compared to other EGFR TKIs. Osimertinib (Tagrisso) showed greater intracranial efficacy and tolerability.
II. Tumors that progress on TKIs are found to have a substitution of methionine for threonine at position 790 (T790M) mutation, the only treatment with evidence in this setting is osimertinib (Tagrisso). Currently, there is no evidence for safety or efficacy in the second line setting for osimertinib (Tagrisso) in absence of this mutation and the medication shall not be used.
III. Osimertinib (Tagrisso) was subsequently FDA-approved for early stage (IB-IIIA), EGFR exon 19 deletion or 21 L858R mutated NSCLC as an adjuvant therapy to surgical tumor resection. In the Phase 3 (ADAURA) trial osimertinib (Tagrisso) demonstrated disease free survival for patients with stage IB-IIIA disease. At the time of reporting, the OS and quality of life data were immature. Patients were excluded from the trial if they had received any prior EGFR-TKI therapy. Safety of osimertinib (Tagrisso) in this population is unknown, and efficacy would not be expected in this setting after progression on another agent within the same class. All patients

had the EGFR exon 19 or exon 21 L858R mutation, and all patients had undergone complete (negative margins) surgical resection of NSCLC tumors. The majority of patients (76%) with stage II-IIIA disease had received previous adjuvant platinum-based chemotherapy, as well as 25% of those with stage IB disease (53% had received prior platinum therapy overall). Use of previous platinum-based chemotherapy is not required by the FDA-approved indication; however, platinum-based chemotherapy has been an established treatment for this stage of disease and is recommended over oral therapy in treatment guidelines and has a more established safety and efficacy profile (e.g., data are available to indicate OS with this therapy). Therefore, use of platinum-based chemotherapy is often the more appropriate and established treatment option, unless it has not been tolerated, patients are ineligible, or are contraindicated.

IV. Dacomitinib (Vizimpro) is FDA-approved for the treatment of adult with metastatic non-small cell lung cancer with EGFR exon 19 or 21 deletion mutation.

V. The efficacy and safety of dacomitinib (Vizimpro) was demonstrated in an open-label trial that assessed dacomitinib (Vizimpro) in the first-line, metastatic disease, treatment naïve, monotherapy setting. Patients were excluded if they had previous use of another EGFR TKI and/or presence of brain metastases. Dacomitinib (Vizimpro) was compared against gefitinib (Iressa), and showed an improvement in PFS; however, this has unknown correlation to overall survival or quality of life parameters in NSCLC at this time.

VI. Dacomitinib (Vizimpro) has been studied in the second-line setting, as well as in non-small cell lung cancer with undetermined mutational status; however, the trials showed no improvement in outcomes compared to erlotinib (Tarceva) or placebo.

VII. Erlotinib (Tarceva) was evaluated in the OPTIMAL, EURTAC, and ENSURE trials versus chemotherapy. Objective response rates (ORR) and PFS were favorable for erlotinib (Tarceva).

VIII. Erlotinib (Tarceva) was evaluated in combination with gemcitabine for pancreatic cancer. Results of phase III studies have indicated an increase in survival compared to gemcitabine alone; however, grade I and II adverse events are expected to occur at greater frequency with combination therapy.

IX. Afatinib (Gilotrif) was evaluated in the LUX clinical trials program versus chemotherapy and showed an increase in PFS as well as time to symptom progression and quality of life. Afatinib (Gilotrif) is also FDA-approved for S761I, L861Q, and G719X mutations.

X. Afatinib (Gilotrif) was evaluated in an RCT versus erlotinib (Tarceva) for previously treated, metastatic, squamous NSCLC. The results were favorable for afatinib (Gilotrif) over erlotinib (Tarceva) in PFS and OS.

XI. Gefitinib (Iressa) showed favorable PFS against chemotherapy in several RCTs.

XII. Treatment of EGFR TKI for NSCLC shall be individualized based on provider and patient preferences, and disease characteristics. There have been several trials comparing agents in this policy. Gefitinib (Iressa) has shown comparable efficacy to erlotinib (Tarceva) and afatinib (Gilotrif) and may modestly improve outcomes over gefitinib (Iressa); however, it may increase risk of serious toxicities as well.

XIII. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Investigational or Not Medically Necessary Uses

I. Dacomitinib (Vizimpro) was evaluated versus placebo and erlotinib (Tarceva) in the second-line setting; however, the trials showed no improvement in outcomes compared to erlotinib (Tarceva) or placebo.

II. The agents in this policy have not been sufficiently evaluated in the following settings. Some data may be available or may be recommended by NCCN; however, safety and efficacy have not been established:
    A. When used in combination with other treatments (e.g., chemotherapy or targeted agent)
    B. Early stage EGFR NSCLC outside of osimertinib (Tagrisso), pancreatic cancer, squamous NCCLC
    C. Head and neck cancer
    D. Renal cell carcinoma
    E. Bone cancer including, but not limited to, chordoma
    F. Central nervous system cancers without primary tumor source of NSCLC
    G. Hepatobiliary cancers

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added generic erlotinib to QL table	01/2024
Added gefitinib (generic Iressa) to the policy; required step through generic gefitinib prior to use of branded Iressa; updated to match current policy formatting	07/2023
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Policy updated to include osimertinib (Tagrisso) indication of early stage, adjuvant treatment to surgical resection in NSCLC.	01/2021
Criteria update and policy creation: All EGFR TKI agents combined into one policy, streamline quantity limits, renewal criteria, duration or approval upon initial and renewal request. Update Tagrisso criteria to allow for use in the first line setting. Addition of age requirement and prescriber requirement for all agents.	07/2019
Gilotrif criteria update: updated criteria to include L861Q, G719X, or S768I mutations and metastatic, squamous NSCLC that has progressed after treatment with platinum-based chemotherapy. Due to the statement that afatinib is not recommended as second-line therapy for squamous cell carcinoma from National Comprehensive Cancer Network (NCCN), a clinical note has been added to address the request for afatinib in members who are diagnosed with squamous NSCLC that has progressed on platinum-based chemotherapy. Tagrisso criteria update: Include clinical note regarding the Flaura trial and recent NCCN NSCLC Guidelines. Also, a route for approval if patient has a contraindication to erlotinib, afatinib and gefitinib.	03/2018
Gilotrif criteria update: updated criteria to new format, deleted renal and hepatic function questions, and deleted female contraception questions as this is properly managed by providers	01/2018
Previous reviews	12/2015, 01/2015, 09/2013, 05/2013, 11/2012, 03/2012, 03/2012, 10/2008, 04/2007
Criteria created	09/2005

Policy Type: PA/SP Pharmacy Coverage Policy: UMP031

Split Fill Management*

Description

Erdafitinib (Balversa) is an oral kinase inhibitor that inhibits enzymatic activity of FGFR 1-4.

Length of Authorization

- Initial: Three months, split fill
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*	DDID
erdafitinib (Balversa)	3 mg tablets	Advanced or metastatic urothelial carcinoma FGFR3 or FGFR2 genetic alteration, second-line after platinum therapy progression	**Maintenance**: 90 tablets/30 days	206400
	4 mg tablets		**Initial**: 28 tablets per 14-day supply for one fill **Maintenance**: 60 tablets/30 days	206401
	5 mg tablets		**Maintenance**: 30 tablets/30 days	206402

*Total daily dose should not exceed 9 mg per day. This may be achieved by 5 mg plus 4 mg, or by three 3mg tablets.

Initial Evaluation

I. Erdafitinib (Balversa) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. The medication is prescribed by or in consultation with an oncologist or urologist; **AND**
   C. Not to be used in combination with other oncolytic medications (i.e., must be used as a monotherapy for the conditions listed below); **AND**
   D. The provider attests that the member will be treated with a maximum of 8 mg per day for at least two weeks to assess for tolerability before considering a total daily dose of 9 mg per day; **AND**
   E. A diagnosis of urothelial carcinoma when the following are met:
      1. Disease is considered advanced or metastatic; **AND**
      2. Genetic alteration is FGFR**3** point mutation or fusion as detected by an FDA-approved test; **AND (one of i or ii)**
         i. The member has previously progressed during or following at least one line of prior platinum-containing chemotherapy (e.g., cisplatin, carboplatin); **OR**

ii. The member previously progressed during or following neoadjuvant or adjuvant platinum-containing chemotherapy (e.g., cisplatin, carboplatin); **AND**
    a. The platinum-containing chemotherapy was administered within the last 12 months

II. Erdafitinib (Balversa) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Urothelial carcinoma that has FGFR**2** genetic alteration (e.g., fusion or point mutation)

III. Erdafitinib (Balversa) is considered investigational when used for all other conditions, including, but not limited to:
    A. Urothelial carcinoma prior to the advanced or metastatic setting
    B. Urothelial carcinoma without FGFR mutation, or without previous treatment with platinum-based chemotherapy
    C. For urothelial carcinoma, or otherwise, treatment with a dose greater than 9 mg per day
    D. Conditions outside of urothelial carcinoma (e.g., Non-Hodgkin Lymphoma, gliomas, osteosarcoma, histiocytosis, soft tissue sarcoma, etc.)

Renewal Evaluation

I. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
II. The medication is not used in combination with other oncolytic medications (i.e., erdafitinib [Balversa] is used as monotherapy); **AND**
III. Tumor response is documented with stabilization of disease or decrease in size of tumor or tumor spread; **AND**
IV. The member has an absence of unacceptable toxicity from the drug (e.g., ophthalmic disturbances, hyperphosphatemia).

Supporting Evidence

I. Erdafitinib (Balversa) was evaluated in one, single-arm, open-label trial. Eighty-seven subjects (n=87) had advanced or metastatic urothelial carcinoma with FGFR**2** or FGFR**3** genetic alterations. Additionally, subjects must have progressed on or after at least one line of prior platinum-containing chemotherapy. This included those that had received neoadjuvant or adjuvant platinum-containing chemotherapy in the past 12 months.
II. No pediatric patients were included in the trial. Subjects assessed were between the ages of 36 and 87. Ninety-seven percent of subjects had received prior cisplatin or carboplatin, and 10% had received both. Twenty-four percent of subjects had received prior anti-PD-L1/PD-1 therapy (immunotherapy). No concomitant oncolytic medications were allowed during the trial.
III. The study assessed for objective response rate (ORR), including both partial and complete response (PR and CR), and duration of response (DoR). Thirty-two percent of subjects met the ORR (2 patients showed CR), and the median duration of response was 5.4 months.
IV. High rates of dose-reduction and dose-interruption were observed, at 53% and 68% respectively. Serious adverse events including, but not limited to, ophthalmic disturbances, hyperphosphatemia, and fatal myocardial infarction, occurred during the trial (1-20%).

Investigational or Not Medically Necessary Uses

I. The pivotal trial evaluated for the FDA-approved indication of urothelial carcinoma included six patients with a FGFR**2** fusion genetic alteration, and no patients that had FGFR**2** point mutation. None of these six patients showed an ORR on or after treatment with erdafitinib (Balversa). As of April 2019, there is no evidence that this population has responded to therapy.
II. Currently, the available outcomes data for erdafitinib (Balversa) was based on a maximum dose of 9 mg per day. No subjects were on concurrent oncolytic therapies. All subjects were verified to be with FGFR-mutation, and with advanced or metastatic urothelial carcinoma. Safety and efficacy outcomes in patients not previously progressed on or after platinum-containing chemotherapy is unknown at the time of this writing.
III. Erdafitinib (Balversa) is currently in clinical trials for a variety of other conditions (e.g, Non-Hodgkin Lymphoma, gliomas, osteosarcoma, histiocytosis, soft tissue sarcoma, etc.).

*The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

References

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Policy Implementation/Update:

Date Created	April 2019
Date Effective	August 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	**Date**

Policy Type: PA/SP Pharmacy Coverage Policy: UMP124

Description
Epoetin alfa (Retacrit, Procrit, Epogen) is a glycoprotein that stimulates red blood cell production, whereas, darbepoetin alfa (Aranesp) stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

Length of Authorization
Initial and Renewal:

Epoetin alfa (Procrit, Epogen):

- Chronic kidney disease with or without dialysis – Three months
- Cancer chemotherapy – 12 months
- Anemia due to zidovudine therapy – 12 months
- Allogeneic blood transfusion in surgery patients – 14-days

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
darbepoetin alfa (Aranesp)	25 mcg/mL vial	Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy	4 vials/syringes per 30 days
	40 mcg/mL vial		
	60 mcg/mL vial		
	100 mcg/mL vial		
	150 mcg/mL vial		
	200 mcg/0.75 mL vial		
	300 mcg/mL vial		
	10 mcg/0.4 mL syringe		
	25 mcg/0.42 mL syringe		
	40 mcg/0.4 mL syringe		
	60 mcg/0.3 mL syringe		
	100 mcg/0.5 syringe		
	150 mcg/0.3 syringe		
	200 mcg/0.4 mL syringe		
	300 mcg/0.6 mL syringe		
	500 mcg/mL syringe		
epoetin alfa (Retacrit)	2000 units/mL vial	Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy; Anemia due to zidovudine therapy; Allogeneic blood transfusion	**2,000U, 3,000U, 4,000U and 10,000U vials**: 12 vials per 30 days **20,000U and 40,000U vials:** 4 vials per 30 days
	3000 units/mL vial		
	4000 units/mL vial		
	10000 units/mL vial		
	40000 units/mL vial		
epoetin alfa (Procrit)	2000 units/mL vial	Chronic Kidney Disease With or Without Dialysis;	
	3000 units/mL vial		

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

	4000 units/mL vial	Cancer chemotherapy; Anemia due to zidovudine therapy; Allogeneic blood transfusion	**2,000U, 3,000U, 4,000U and 10,000U vials**: 12 vials per 30 days **20,000U and 40,000U vials:** 4 vials per 30 days
	10000 units/mL vial		
	20000 units/mL vial		
	20000 units/2 mL vial		
	40000 units/mL vial		
epoetin alfa (Epogen)	2000 units/mL vial	Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy; Anemia due to zidovudine therapy; Allogeneic blood transfusion	**2,000U, 3,000U, 4,000U and 10,000U vials**: 12 vials per 30 days **20,000U and 40,000U vials:** 4 vials per 30 days
	3000 units/mL vial		
	4000 units/mL vial		
	10000 units/mL vial		
	20000 units/mL vial		
	20000 units/2 mL vial		

Initial Evaluation

Epoetin alfa (Retacrit) and darbepoetin alfa (Aranesp) are both preferred erythropoiesis-stimulating agent (ESA) products.

- There is no prior authorization required for epoetin alfa (Retacrit) or darbepoetin alfa (Aranesp) unless requesting above the quantity limit noted above.

I. **Epoetin alfa (Procrit, Epogen)** may be considered medically necessary when the following criteria below are met:
   A. Lab values are obtained within 30 days of administration (unless otherwise indicated); **AND**
   B. Prior to initiation of therapy, member should have adequate iron stores as demonstrated by serum ferritin ≥ 100 ng/mL (mcg/L) and transferrin saturation (TSAT) ≥ 20%; **AND**
   C. Upon initiation of therapy Hemoglobin (Hb) is < 10 g/dL and/or Hematocrit (Hct) < 30% (unless otherwise specified); **AND**
   D. A diagnosis of one of the following when the request is for **epoetin alfa (Procrit, Epogen)**:
      1. Anemia secondary to myelodysplastic syndrome (MDS); AND
         i. Member has an endogenous serum erythropoietin level of ≤ 500 mUnits/mL; **AND**
         ii. Member has lower risk disease [i.e. defined as IPSS-R (Very Low, Low, Intermediate), IPSS (Low/Intermediate-1), WPSS (Very Low, Low, Intermediate)]; **AND**
            a. Used for treatment of symptomatic anemia, as an alternative to lenalidomide, in members with del(5q); **OR**
            b. Used for treatment of symptomatic anemia in members without del(5q); **AND**
               i. Member has ring sideroblasts < 15% and used as a single agent **OR** in combination with lenalidomide in members who have failed single agent therapy; **OR**
               ii. Member has ring sideroblasts ≥ 15% and used in combination with a granulocyte-colony stimulating factor (G-CSF); **AND**

iii. Treatment with epoetin alfa (Retacrit) or darbepoetin alfa (Aranesp) has been ineffective, not tolerated, or is contraindicated; **OR**

2. **Anemia secondary to Myeloproliferative Neoplasms (MPN) – Myelofibrosis; AND**
   i. Member has an endogenous serum erythropoietin level of < 500 mUnits/mL; **AND**
   ii. Treatment with epoetin alfa (Retacrit) or darbepoetin alfa (Aranesp) has been ineffective, not tolerated, or is contraindicated**; OR**
3. **Anemia secondary to chemotherapy treatment; AND**
   i. Member is receiving concomitant myelosuppressive chemotherapy; **AND**
   ii. Chemotherapy treatment plan is not intended to cure the disease (i.e. palliative chemotherapy); **AND**
   iii. There are a minimum of two additional months of planned chemotherapy; **AND**
   iv. Treatment with epoetin alfa (Retacrit) or darbepoetin alfa (Aranesp) has been ineffective, not tolerated, or is contraindicated; **OR**
4. **Anemia secondary to chronic kidney disease; AND**
   i. Member is at least one month of age or older; **AND**
   ii. Treatment with epoetin alfa (Retacrit) or darbepoetin alfa (Aranesp) has been ineffective, not tolerated, or is contraindicated; **OR**
5. **Anemia secondary to rheumatoid arthritis; AND**
   i. Treatment with epoetin alfa (Retacrit) has been ineffective, not tolerated, or is contraindicated; **OR**
6. **Anemia secondary to zidovudine treated, HIV-infected members; AND**
   i. Member has an endogenous serum erythropoietin level of < 500 mUnits/mL; **AND**
   ii. Member is receiving zidovudine administered at ≤ 4200 mg/week; **AND**
   iii. Treatment with epoetin alfa (Retacrit) has been ineffective, not tolerated, or is contraindicated; **OR**
7. **Reduction of allogenic blood transfusions in elective, non-cardiac, non-vascular surgery; AND**
   i. Hemoglobin (Hb) between 10 g/dL and 13 g/dL and/or Hematocrit (Hct) between 30% and 39%; **AND**
   ii. Member is at high-risk of blood-loss from surgery that is elective, non-cardiac and non-vascular; **AND**
   iii. Member is unwilling or unable to participate in an autologous blood donation program prior to surgery; **AND**
   iv. Treatment with epoetin alfa (Retacrit) has been ineffective, not tolerated, or is contraindicated

II. Darbepoetin alfa (Aranesp), epoetin alfa (Procrit, Epogen) are considered investigational when used for all other conditions.

Renewal Evaluation

I. Lab values are obtained within 30 days of the date of administration (unless otherwise indicated); **AND**

II. Adequate iron stores as demonstrated by serum ferritin ≥ 100 ng/mL (mcg/L) and transferrin saturation (TSAT) ≥ 20% measured within the previous 3 months; **AND**

III. Documentation of continued need for therapy indicated by Hemoglobin (Hb) and/or Hematocrit (Hct) as follows:

Indication	Hb and/or Hct Response
Anemia secondary to myelodysplastic syndrome (MDS)	Hemoglobin (Hb) <12 g/dL and/or Hematocrit (Hct) <36%
Anemia secondary to myeloproliferative neoplasms (MF, post-PV myelofibrosis, post-ET myelofibrosis)	Hemoglobin (Hb) <10 g/dL and/or Hematocrit (Hct) <30%
Reduction of allogeneic blood transfusions in elective, non-cardiac, non-vascular surgery	Hemoglobin(Hb) between 10 g/dL and 13 g/dL and/or Hematocrit(Hct) between 30% and 39%
Anemia secondary to chemotherapy treatment	Hemoglobin (Hb) <10 g/dL and/or Hematocrit (Hct) < 30%
Anemia secondary to zidovudine treated, HIV-infected patients	Hemoglobin (Hb)< 12 g/dL and/or Hematocrit (Hct) < 36%;
Anemia secondary to chronic kidney disease	*Pediatric patients*: Hemoglobin (Hb) < 12 g/dL and/or Hematocrit (Hct) < 36% *Adults*: Hemoglobin (Hb) < 11 g/dL and/or Hematocrit (Hct) < 33%
All other indications	Hemoglobin (Hb) < 11 g/dL and/or Hematocrit (Hct) < 33%

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added Aranesp as a preferred product not requiring prior authorization; Updated formatting to align with current process;	08/2022
Updated renewal section criteria point III to read as "Documentation of continued need for therapy indicated by Hemoglobin (Hb) and/or Hematocrit (Hct) as follows:".	04/2020
• Transitioned to policy format • Added language regarding preferred product, Retacrit and removal of PA requirement • Aligned criteria with medical benefit for consistency across benefits, which included clarifying initial requirements (e.g. labs obtained within 30 days, adequate iron stores, Hg/Hct levels) • Added coverage criteria for anemia associated with rheumatoid arthritis, anemia secondary to MDS, and anemia secondary to myelofibrosis • Added specific renewal criteria	12/2019
Previous reviews	10/2018, 11/2012, 08/2012
Policy created	06/2011

Policy Type: PA/SP Pharmacy Coverage Policy: UMP026

Description

Esketamine (Spravato) is an intranasal N-methyl-D-aspartate (NMDA) receptor antagonist. The mechanism by which esketamine (Spravato) exerts its antidepressant effect is unknown.

Length of Authorization

- Treatment resistant depression (TRD)
  - Initial: Six months
  - Renewal: 12 months
- Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior
  - Initial: Four weeks
  - Renewal: Cannot be renewed

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit*
esketamine (Spravato)	Treatment resistant depression (TRD), in conjunction with an oral antidepressant	56 mg dose kit	**Initial:** • PA #1: 24 devices per 28 days • PA #2 (maintenance dosing): 12 devices per 28 days* for the remaining five months **Renewal:** 12 devices per 28 days*
		84 mg dose kit	
	Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior, in conjunction with an oral antidepressant	56 mg dose kit	24 devices per 28 days
		84 mg dose kit	

*Allows for 56mg or 84mg at weekly or every other week dosing.

Initial Evaluation

I. **Esketamine (Spravato)** may be considered medically necessary when the following criteria below are met:
   A. Member is between 18 and 64 years of age; **AND**
   B. Medication is prescribed by, or in consultation with, a psychiatrist; **AND**
   C. Member does **not** have a current or prior Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis of:

1. Concomitant psychotic disorder; **OR**
2. Major depressive disorder (MDD) with psychosis; **OR**
3. Bipolar or related disorders (confirmed by the MINI); **OR**
4. Obsessive compulsive disorder (current episode only); **OR**
5. Intellectual disability; **OR**
6. Personality disorder; **AND**

D. The member does **not** have a contraindication to and has **not** previously failed ketamine; **AND**

E. Documentation of ongoing use of an antidepressant to be used concurrently with esketamine (Spravato); **AND**

F. A diagnosis of **Treatment Resistant Depression (TRD)** when the following are met:
   1. Diagnosis of **Major Depressive Disorder (MDD)** was made following Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria; **AND**
      i. Member is experiencing a persistent MDD episode, the duration of which must be greater than, or equal to, two years; **OR**
      ii. Member is experiencing recurrent MDD (an interval of at least two consecutive months between separate episodes during which criteria are not met for a major depressive episode); **AND**
   2. Documentation of baseline assessment [e.g. Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Rating Scale for Depression (HAM-D), Nine-Item Patient Health Questionnaire (PHQ-9), Sheehan Disability Scale (SDS)]; **AND**
   3. Treatment with **ALL** of the following has been ineffective, contraindicated, or not tolerated in the treatment of the current episode:
      i. Psychotherapy in conjunction with antidepressant treatment [e.g. cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT), problem-solving therapy (PST) etc.]; **AND**
      ii. At least four antidepressants from two or more different classes (i.e. SSRI, SNRI, TCA, MAO) at an optimized dose for at least 8 weeks; **AND**
      iii. Augmentation with an atypical antipsychotic (i.e. olanzapine, aripiprazole) or lithium; **AND**
   4. Treatment with electroconvulsive therapy (ECT) **or** repetitive transcranial magnetic stimulation (rTMS) has been ineffective, contraindicated, or not tolerated; **OR**
      i. Member has documentation of contraindication to BOTH; **OR**

G. A diagnosis of **depressive symptoms with major depressive disorder (MDD) with acute suicidal ideation or behavior** when the following are met:
   1. Member has a severe depressive episode (cannot care for self, participate in life, has persistent thoughts of hopelessness, persistent sad, anxious or "empty" mood, thoughts of suicide); **AND**
   2. Provider attests that without esketamine (Spravato), member may require an emergency department (ED) visit or an inpatient psychiatric hospitalization in the next 24-48 hours.

II. Esketamine (Spravato) is considered not medically necessary when criteria above are not met and/or when used for treatment resistant depression in members 65 years of age or older.

III. Esketamine (Spravato) is considered investigational when used for all other conditions, including but not limited to:
   A. Pain management
   B. Anesthesia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of improvement from baseline assessment (e.g., PHQ-9, Clinically Useful Depression Outcome Scale, Quick Inventory of Depressive Symptomatology-Self Report 16 Item, MADRS, HAM-D) by 50% or more, indicating clinical benefit for treatment resistant depression; **OR**
   A. Documentation attesting member is in remission (MADRS total score ≤12, HRSD or HAM-D score less than 10, PHQ-9 score less than 5 or SDS score of less than 6 at day 28,); **AND**
IV. Documentation of ongoing use of an oral antidepressant; **AND**
V. Provider attests that member is utilizing the least frequent dosing to maintain disease response and/or remission

Supporting Evidence

I. Clinical trials showing statistical significance in clinical outcomes had a population aged between 18-64 years of age. TRANSFORM-3 evaluated patients 65 years and older and outcomes were found to be not statistically significant. There are current ongoing clinical trials to further evaluate this population.
II. TRANSFORM-1 evaluated a similar population to pivotal trial TRANSFORM-2 but found a lack of statistical significance in clinical outcomes in patients aged 18-64 years.
III. Considering the severity and complexity of the disease state and the safety profile of esketamine (Spravato), this therapy needs to be prescribed by, or in consultation with, a psychiatrist.
IV. Patients with DSM-5 diagnosis of concomitant psychotic disorder, MDD with psychosis, bipolar or related disorders, obsessive compulsive disorder (OCD), and personality disorder were excluded from the esketamine (Spravato) landmark studies (NCT02418585 and NCT02493868) and are not currently being studied for treatment with esketamine (Spravato). The known adverse events include dissociative or perceptual changes (including distortion of time, space, and illusions) and derealization and depersonalization (61% to 75% of SPRAVATO-treated patients developed dissociative or perceptual changes based on the Clinician Administered Dissociative Symptoms Scale). There is no safety and efficacy clinical trial data to support the use of esketamine (Spravato) in this patient population. Considering the symptomology of the

disease states, known adverse events and unknown long-term safety profile, it is unknown how esketamine (Spravato) would affect this patient population.

V. There is no clinical trial data to show efficacy of esketamine (Spravato) in patients who have not responded to ketamine infusions that have been used in treatment of MDD off label. There is no clinical trial safety data to support the use of esketamine (Spravato) if ketamine has been contraindicated or not tolerated. Participants who have previously demonstrated nonresponse of depressive symptoms to ketamine were excluded from the clinical trial.

VI. Clinical trials were conducted as dual therapy in conjunction with oral antidepressants and esketamine (Spravato) is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults and depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior.

VII. Esketamine (Spravato) is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults. In clinical trials, TRD was defined as a DSM-5 diagnosis of major depressive disorder (MDD) [recurrent or single-episode (duration ≥2 years) without psychotic features or recurrent MDD (an interval of at least two consecutive months between separate episodes during which criteria are not met for a major depressive episode);] in patients who have not responded adequately to at least two different antidepressants of adequate dose and duration in the current depressive episode.

VIII. There are no current American Psychiatric Association (APA) guidelines specific to TRD. In the 2019 APA guidelines for treatment of depression in the general adult population, initial treatment of MDD was recommended to include a second-generation oral antidepressant and psychotherapy, either as monotherapy or in combination with each other.

- Recommended psychotherapies include:
  - Behavioral therapy
  - Cognitive-behavioral therapy (CBT) evaluates, challenges, and modifies dysfunctional thoughts that maintain depression. Behavioral strategies are also used to increase pleasant activities to treat anhedonia.
  - Interpersonal psychotherapy (IPT) is a structured and brief intervention addressing social issues that maintain depression.
  - Problem-solving therapy (PST) teaches to define personal problems, develop multiple solutions, identify the best one and implement it, then assess its effectiveness.
  - Supportive therapy
- Meta-analyses that compare the effectiveness of CBT, IPT, and PST indicate no large differences in effectiveness between these treatments.

IX. Standard practice for treatment resistant depression, supported by the American Psychiatric Association (APA), include:

- Use of monotherapy antidepressants
- Trial of more than one antidepressant
- Augmentation with additional antidepressant therapy
- Augmentation with other therapies including antipsychotics or lithium.

X. The National Institute for Health and Care Excellence (NICE) guideline for treatment of depression defines treatment resistant depression (TRD) as ‘people with major depressive

disorder who fail to respond to two different oral antidepressants'. Within the recommended treatment pathway, treatment options for TRD include:

- Oral antidepressants
- Augmentation with lithium or an antipsychotic treatment, or combined with another oral antidepressant
- Electroconvulsive therapy (ECT)

XI. Electroconvulsive therapy (ECT) has the highest rates of response and remission of any form of antidepressant treatment, with 70%–90% of those treated showing improvement. According to APA, ECT should be considered for patients with severe major depressive disorder that is not responsive to psychotherapeutic and/or pharmacological interventions, particularly those with significant functional impairment who have not responded to numerous medication trials. Contraindications to ECT according to FDA labeling includes:

- Severe and unstable cardiovascular conditions (e.g., recent myocardial infarction, unstable angina, congestive heart failure, critical aortic stenosis, uncontrolled hypertension/hypotension)
- Cerebrovascular conditions (e.g., aneurysm, arteriovenous malformation)
- Increased intracranial pressure
- Space-occupying cerebral lesions (e.g., tumors)
- Recent hemorrhagic or ischemic stroke
- Severe and unstable pulmonary conditions (e.g., chronic obstructive pulmonary disease, asthma, pneumonia)

XII. Transcranial magnetic stimulation (TMS) uses a specifically designed magnetic coil that is placed in contact with the head to generate rapidly alternating magnetic-resonance imaging-strength magnetic fields and produce electrical stimulation of superficial cortical neurons. Based on the results of a multisite randomized sham-controlled clinical trial of high-frequency TMS over the left dorsolateral prefrontal cortex, TMS was cleared by the FDA in 2008 for use in individuals with major depressive disorder who have not had a satisfactory response to at least one antidepressant trial in the current episode of illness. Clinical guidelines recommend reserving use of rTMS to patients who have failed at least three antidepressant therapies. Contraindications to rTMS according to FDA labeling includes metallic objects and implanted stimulator devices in or near the head.

XIII. Brain stimulation therapies, including ECT and rTMS, require multiple sessions per week for up to 6-12 weeks to be effective. Ability to coordinate work and childcare schedules, as well as access to care should be taken into consideration when determining if these therapies are appropriate for a patient.

XIV. For the treatment of depressive symptoms with major depressive disorder (MDD) with acute suicidal ideation or behavior, esketamine (Spravato) was studied in 456 patients in two phase III, double-blind, randomized, multicenter studies (ASPIRE I and ASPIRE II). Esketamine was compared to placebo with standard-of-care (SOC).

- The first dose of study drug was administered in an emergency department or in an inpatient psychiatric unit. Patients were to remain hospitalized for a recommended 5 days (14 days in 7 countries in European Union based on health authority request during the clinical trial approval). Shorter or longer periods of hospitalization were permitted, if clinically necessary, per local standard practice.

- The primary outcome: Change in the Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline (day 1, pre-dose) to 24 hours post–first dose
    - ASPIRE I: esketamine + SOC (mean [SD]: –16.4 [11.95]) and placebo + SOC (–12.8 [10.73]), with significantly greater improvement with esketamine (least-squares mean difference [SE]: –3.8 [1.39]; 95% CI, −6.56 to −1.09; 2-sided P = 0.006)
    - ASPIRE II: esketamine + SOC (mean [SD]: –15.7 [11.56]) and the placebo + SOC (–12.4 [10.43]), with significantly greater improvement in depressive symptoms with esketamine ([SE]: –3.9 [1.39], 95% CI: -6.60, -1.11; 2-sided p=0.006).
- The secondary: Change in the Clinical Global Impression - Severity of Suicidality - Revised (CGI-SS-R) score from baseline to 24 hours after the first dose
    - ASPIRE I and ASPIRE II: Both treatment groups demonstrated improvements in severity of suicidality scores; however, the treatment difference was not significant (P=0.379)
    - The efficacy of esketamine (Spravato) regarding suicidality has not been established in the clinical trial.

XV. Suicidal ideation is defined as thoughts of serving as the agent of one's own death and may vary in seriousness depending on the specificity of suicide plans and the degree of suicidal intent.
- Suicidal intent is the subjective expectation and desire for a self-destructive act to end in death.
- Lethality of suicidal behavior is the objective danger to life associated with a suicide method or action. Lethality is distinct from and may not always coincide with an individual's expectation of what is medically dangerous.

XVI. Symptoms for MDD, according to Anxiety and Depression Association of America (ADAA), are persistent sad, anxious or "empty" mood, feelings of hopelessness, pessimism, feelings of guilt, worthlessness, helplessness, loss of interest or pleasure in hobbies and activities, including sex, decreased energy, fatigue, feeling "slowed down", difficulty concentrating, remembering, making decisions, insomnia, early-morning awakening, or oversleeping, low appetite and weight loss or overeating and weight gain, thoughts of death or suicide, suicide attempts, restlessness, irritability, and persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders and pain for which no other cause can be diagnosed.

XVII. In ASPIRE I and ASPIRE II clinical trial the safety and efficacy of esketamine (Spravato) has been evaluated in the treatment of patients for whom acute psychiatric hospitalization (within 24 to 48 hours) is clinically warranted due to their imminent risk of suicide.

XVIII. The MADRS is a clinician-rated scale designed to measure depression severity and to detect changes due to antidepressant treatment. The scale consists of 10 items (to evaluates apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel [interest level], pessimistic thoughts, and suicidal thoughts), each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), summed for a total possible score range of 0-60. Higher scores represent a more severe condition. Negative change in score indicates improvement. MADRS measures severity of depression in individuals 18 years and older. Each item is rated on a 7-point scale. The scale is an adaptation of the Hamilton Depression Rating Scale and has a greater sensitivity to change over time. The scale can be completed in 20 to 30 minutes.

XIX. The Patient Health Questionnaire (PHQ) is a self-report measure designed to screen depressive symptoms. It takes one to five minutes to complete and roughly the same amount of time for a clinician to review the responses. The PHQ-9 is available in multiple languages. The diagnostic validity of the PHQ has recently been established in 2 studies involving 3,000 patients in 8 primary care clinics and 3,000 patients in 7 obstetrics-gynecology clinics. At 9 items, the PHQ depression scale (which we call the PHQ-9) is half the length of many other depression measures, has comparable sensitivity and specificity, and consists of the actual 9 criteria upon which the diagnosis of DSM-IV depressive disorders is based.

XX. The Hamilton Rating Scale for Depression, abbreviated HDRS, HRSD, or HAM-D, measures depression in individuals before, during, and after treatment. The scale is administered by a health care professional and contains 21 items, but is scored based on the first 17 items, which are measured either on 5-point or 3-point scales. It takes 15 to 20 minutes to complete and score. Results of a meta-analysis over a period of 49 years suggest that HRSD provides a reliable assessment of depression.

XXI. The SDS is a brief, 5-item self-report tool that assesses functional impairment in work/school, social life, and family life. Total score ranges from 0-30 (0 unimpaired, 30 highly impaired) and segments [work/school (0-10), social life (0-10), family life/home responsibilities (0-10] get scored. Scores of ≥5 on any of the 3 scales, with high scores associated with significant functional impairment, and sensitivity is 83% and specificity 69%.

XXII. Remission for MADRS is defined with a total score ≤12, HRSD or HAM-D score less than 10, PHQ-9 score less than 5 or SDS score of less than 6 at day 28.

XXIII. Data from SUSTAIN-2, a phase 3, open-label, long term (up to one year) clinical trial to evaluate long-term safety and efficacy of esketamine nasal spray plus oral antidepressant therapy, showed that reduction in dosing frequency from weekly to every-other-week regimens was achieved in 38.1% of patients. This indicates that for a considerable majority of patients, dose reduction to every-other-week regimens may not be clinically appropriate. Provider evaluation of the member's likelihood to maintain clinical stability or remission of depressive symptoms on weekly vs. every-other-week dosing can be reliably trusted with minimal risk for overutilization.

Investigational or Not Medically Necessary Uses

I. Pain management
   A. Not FDA approved. Safety and efficacy for use of esketamine (Spravato) for pain management or anesthesia has not been established.

Appendix

	QL	Dosing Schedule		Cumulative Spravato Doses/Devices
Induction Phase: Week 1 - 4	24 devices/28 days*	Week 1 (twice weekly dosing)	Day 1, dose 1	56 mg (2 devices)
			Second dose	56 mg (4 devices) or 84 mg (5 devices)
		Week 2 (twice weekly dosing)		56 mg (8 devices) or 84 mg (11 devices)
		Week 3 (twice weekly dosing)		56 mg (12 devices) or 84 mg (17 devices)
		Week 4 (twice weekly dosing)		56 mg (16 devices) or 84 mg (23 devices)
		Week 5 (once a week dosing)		56 mg (2 devices) or 84 mg (3 devices)

Maintenance Phase: Week 5 - 8	12 devices/28 days	Week 6 (once a week dosing)	56 mg (4 devices) or 84 mg (6 devices)
		Week 7 (once a week dosing)	56 mg (6 devices) or 84 mg (9 devices)
		Week 8 (once a week dosing)	56 mg (8 devices) or 84 mg (12 devices)
Maintenance: Week 9 and after	12 devices/28 days	Week 9 - ∞ (every two weeks dosing or once weekly dosing)	56 mg (4-8 devices/28) or 84 mg (6 – 12 devices/28)

*Max allowance: 24 devices/28 days: This includes the 2 devices from the 56mg dose done on day one. Although we technically expect patients to use a maximum of 23 devices, a maximum of 24 devices in the first month would allow all weeks to pay below the max dose loaded.

I. Table 1: Quantity limits on per week level for the treatment of treatment resistant depression (TRD)

II. Table 2: Antidepressant Example (*please note list below is not comprehensive*)

Selective Serotonin Reuptake Inhibitors (SSRI)	
• Paroxetine (Paxil) • Fluvoxamine (Luvox) • Escitalopram (Lexapro)	• Sertraline (Zoloft) • Fluoxetine (Prozac) • Citalopram (Celexa)
Serotonin and Norepinephrine Reuptake Inhibitors (SNRI)	
• Duloxetine (Cymbalta) • Venlafaxine (Effexor) • Desvenlafaxine (Pristiq)	• Milnacipran (Savella) • Levomilnacipran (Fetzima)
Tricyclic antidepressant (TCA)	
• Amitriptyline (Elavil) • Clomipramine (Anafranil) • Nortriptyline (Pamelor)	
Other	
• Bupropion (Wellbutrin) • Mirtazapine (Remeron)	• Vilazodone (Viibryd) • Vortioxetine (Trintellix) • Nefazodone (Serzone)

III. Table 3: Quantity limits for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Week	Cumulative Spravato Doses/Devices
Week 1 (twice weekly)	84mg (6 devices)
Week 2 (twice weekly)	56mg (4 devices) or 84mg (12 devices)
Week 3 (twice weekly)	56mg (8 devices) or 84mg (18 devices)
Week 4 (twice weekly)	56mg (10 devices) or 84mg (24 devices)

IV. Table 4: Medical billing units

Stage:	Total Units Approved:	Length of Approval:
Initial	3024	2 months
Continuation/Renewal	12096	12 months

	Quantity Limit	Dosing Schedule		Cumulative Spravato Doses/ Devices	Billing Units
			Day 1, dose 1	56 mg (2 devices)	

Induction Phase: Week 1 - 4	24 devices/28 days*	Week 1 (twice weekly dosing)	Second dose	56 mg (4 devices) or 84 mg (5 devices)	2016 units (to allow for 56mg and 84mg)
		Week 2 (twice weekly dosing)		56 mg (8 devices) or 84 mg (11 devices)	
		Week 3 (twice weekly dosing)		56 mg (12 devices) or 84 mg (17 devices)	
		Week 4 (twice weekly dosing)		56 mg (16 devices) or 84 mg (23 devices)	
Maintenance Phase: Week 5 - 8	12 devices/28 days	Week 5 (once a week dosing)		56 mg (2 devices) or 84 mg (3 devices)	1008 units (to allow for 56mg or 84mg units)
		Week 6 (once a week dosing)		56 mg (4 devices) or 84 mg (6 devices)	
		Week 7 (once a week dosing)		56 mg (6 devices) or 84 mg (9 devices)	
		Week 8 (once a week dosing)		56 mg (8 devices) or 84 mg (12 devices)	
Maintenance: Week 9 and after	12 devices/28 days	Week 9 - ∞ (every two weeks dosing or once weekly dosing)		56 mg (4-8 devices/28) or 84 mg (6 – 12 devices/28)	1008 units (to allow for 56mg or 84mg units)
Units: 1:1 conversion (1 unit = 1mg)					

For further guidance, please reference Spravato's billing guide at: https://www.spravatohcp.com/sites/www.spravatohcp-v1.com/files/spravato_access_reimbursement_guideline.pdf?v=14878

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Policy Implementation/Update:

Action and Summary of Changes	Date
Extended initial duration approval timeframe from two months to six months	08/2023
Added medical billing unit conversion	06/2023
Updated QL table/PAC instructions, appendix tables, and references	04/2023
• Removed requirement of augmentation with an additional antidepressant • Updated renewal requirement for weekly dosing to require provider attestation that member is using least frequent dosing possible to maintain symptom control/remission • Updated quantity limit to 12 devices per month to align with allowance of weekly administration; noted quantity exceptions will not be allowed in the maintenance phase • Updated supporting evidence	05/2022

• Added new indication of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior and appropriate criteria • Updated criteria for TRD to reflect that prior treatment failures must be associated with the current depressive episode and changed the number of prior antidepressants to four from two different classes	10/2020
• Added major depressive disorder (MDD) symptoms, including suicidal ideation in patients who are at imminent risk for suicide as an investigational indication • Added criteria: o Documentation of improvement from baseline assessment by 50% or more, indicating clinical benefit for treatment resistant depression or documentation attesting member is in remission (MADRS total score ≤12, HRSD or HAM-D score less than 10, PHQ-9 score less than 5 or SDS score of less than 6 at day 28,); o The member does not have a contraindication to and has not previously failed ketamine o Treatment has been ineffective, contraindicated, or not tolerated with psychotherapy in conjunction with antidepressant treatment [e.g. cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT), problem-solving therapy (PST) etc.] and ECT (Electroconvulsive therapy) or repetitive transcranial magnetic stimulation (rTMS) unless all are contraindicated has been ineffective, contraindicated, or not tolerated o Diagnoses of major depressive disorder (MDD) was made following Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria and member is experiencing a persistent MDD episode (duration greater than or equal to two years) or member is experiencing recurrent MDD (an interval of at least two consecutive months between separate episodes during which criteria are not met for a major depressive episode) o Member doesn't have a current or prior Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis of concomitant psychotic disorder or major depressive disorder (MDD) with psychosis or bipolar or related disorders (confirmed by the MINI) or obsessive-compulsive disorder (current episode only) or intellectual disability or personality disorder o Medication is prescribed by, or in consultation with a psychiatrist • Updated quantity limit to better align with dosing regimen	03/2020
Policy effective	05/2019
Policy created	03/2019

Policy Type: Step Pharmacy Coverage Policy: UMP319

Description

Estradiol and progesterone (Bijuva) is an orally administered estrogen/progestin hormone replacement combination.

Length of Authorization

- Initial/Renewal: 12 months

Coverage Criteria

I. Estradiol and progesterone (Bijuva) may be considered medically necessary when the following criteria below are met:
   A. Treatment with two of the following: Amabelz, estradiol/norrthindone acet, Fyavolv, Jinteli, Lopreeza, Mimvey, Mimivey Lo, or norethindrone ac-eth estradiol has been ineffective, contraindicated, or not tolerated.

Policy Type: PA/SP Pharmacy Coverage Policy: UMP125

Split Fill Management*

Description

Everolimus (Afinitor, Afinitor Disperz) is an orally administered mammalian target of rapamycin (mTOR) inhibitor to reduce cell proliferation, angiogenesis, and glucose uptake.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
everolimus (generic Afinitor)	2.5 mg tablet	Angiomyolipoma of the kidney, tuberous sclerosis syndrome; Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole; Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic; Renal cell carcinoma, advanced disease; Subependymal giant cell astrocytoma	28 tablets/28 days For subependymal giant cell astrocytoma: quantity associated with 4.5 mg/m^2 daily
	5 mg tablet		
	7.5 mg tablet		
	10 mg tablet		
everolimus (Afinitor)	2.5 mg tablet		
	5 mg tablet		
	7.5 mg tablet		
	10 mg tablet		
everolimus (Afinitor Disperz)	2 mg tablet	Partial seizure, adjunct, tuberous sclerosis syndrome; Subependymal giant cell astrocytoma	Quantity associated with 5 mg/m^2 daily for partial seizure, 4.5 mg/m^2 daily for subependymal giant cell astrocytoma.
	3 mg tablet		
	5 mg tablet		
everolimus (generic Afinitor Disperz)	2 mg tablet		
	3 mg tablet		
	5 mg tablet		

Initial Evaluation

I. **Everolimus (Afinitor Disperz)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an oncologist, hematologist, or neurologist; **AND**
   B. Generic everolimus (generic for Afinitor Disperz) is prescribed, unless member has a contraindication to generic product; **AND**
   C. A diagnosis of one of the following:
      1. **Subependymal giant cell astrocytoma; AND**
         i. Everolimus will not be used in combination with any other oncolytic medication; **OR**
      2. **Partial seizure, associated with tuberous sclerosis syndrome; AND**
         i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
         ii. The member is refractory to at least two other antiepileptic therapies (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine); **AND**
         iii. The member will continue therapy with at least one other antiepileptic medication (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine)

II. **Everolimus (Afinitor)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist, hematologist, or neurologist; **AND**
   C. Generic everolimus (generic for Afinitor) is prescribed, unless member has a contraindication to generic product; **AND**
   D. A diagnosis of one of the following:
      1. **Angiomyolipoma of the kidney, associated with tuberous sclerosis; AND**
         i. The member does not require immediate surgery; **AND**
         ii. Everolimus will not be used in combination with any other oncolytic medication; **AND**
      2. **Breast cancer; AND**
         i. The member is a post-menopausal woman; **AND**
         ii. The member has advanced or metastatic disease (Stage III or IV); **AND**
         iii. Disease is confirmed as hormone receptor positive (HR+) and HER2-negative; **AND**
         iv. The member has failed a non-steroidal aromatase inhibitor [e.g., letrozole (Femara), anastrozole (Arimidex)]; **AND**
         v. Everolimus will be used in combination with exemestane (Aromasin); **OR**
      3. **Neuroendocrine tumor; AND**
         i. Everolimus will not be used in combination with any other oncolytic medication; **AND**

ii. The disease is progressive; **AND**
    a. Is of pancreatic origin; **OR**
    b. Is of gastrointestinal or lung origin and disease is well-differentiated, non-functional, unresectable and locally advanced, or metastatic; **OR**

4. **Renal cell carcinoma; AND**
    i. The member has advanced or metastatic (Stage III or IV) disease; **AND**
    ii. The member has tried and failed <u>one</u> anti-angiogenic therapy (e.g. pazopanib [Votrient], bevacizumab [Avastin], sunitinib [Sutent], axitinib [Inlyta]); **AND**
    iii. Everolimus will be used as monotherapy **<u>OR</u>** in combination with lenvatinib (Lenvima); **OR**
5. **Subependymal giant cell astrocytoma; AND**
    i. Everolimus will not be used in combination with any other oncolytic medication

III. Everolimus (Afinitor) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
    A. Carcinoid tumor

IV. Everolimus (Afinitor, Afinitor Disperz) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
    A. Graft-versus-host disease
    B. Ependymoma
    C. Hodgkin Lymphoma or Non-Hodgkin Lymphoma
    D. Central nervous system cancers
    E. Kaposi's sarcoma
    F. Thymoma and thymic carcinoma
    G. Endometrial, ovarian, uterine cancers
    H. Prostate cancer
    I. Gastroesophageal carcinomas
    J. Waldenstrom macroglobulinemia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. **Request is for everolimus (Afinitor Disperz); AND**
    A. Generic everolimus (generic for Afinitor Disperz) is prescribed, unless member has a contraindication to generic product; **AND**
    B. A diagnosis of one of the following:

1. **Subependymal giant cell astrocytoma**; **AND**
    i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
    ii. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
2. **Partial seizure, associated with tuberous sclerosis syndrome; AND**
    i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
    ii. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in seizure frequency]; **AND**
    iii. The member will continue therapy with at least one other antiepileptic medication (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine); **OR**

IV. **Request is for everolimus (Afinitor); AND**

A. Generic everolimus (generic for Afinitor) is prescribed, unless member has a contraindication to generic product; **AND**

B. A diagnosis of one of the following:

1. **Angiomyolipoma of the kidney, associated with tuberous sclerosis; AND**
    i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
    ii. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in angiomyolipoma volume, absence of new angiomyolipoma lesion]; **OR**
2. **Breast cancer; AND**
    i. Everolimus will be used in combination with exemestane (Aromasin); **AND**
    ii. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
3. **Neuroendocrine tumor; AND**
    i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
    ii. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
4. **Renal cell carcinoma; AND**
    i. Everolimus will be used as monotherapy; **OR** in combination with lenvatinib (Lenvima); **OR**
    ii. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
5. **Subependymal giant cell astrocytoma; AND**
    i. Everolimus will not be used in combination with any other oncolytic medication; **AND**
    ii. Disease response to treatment defined by stabilization of disease or decrease in tumor size

Supporting Evidence

I. Everolimus (Afinitor, Afinitor Disperz) has been evaluated in many clinical studies for various indications; however, they were focused on oncological indications (and not for transplantation management and rejection prophylaxis). Of note, everolimus (Zortress) does not have a prior authorization and is indicated for transplantation management and rejection prophylaxis. Everolimus products (Afinitor, Afinitor Disperz, Zortress) are not interchangeable, and it is recommended that utilization stay within the products' FDA-approved indication(s). Given the much lower cost as well as timely need for transplant medication access, prior authorization for everolimus (Zortress) is not commonly utilized.

II. Everolimus (Afinitor Disperz) received FDA-approval for subependymal giant cell astrocytoma related to tuberous sclerosis complex (TSC), and TSC associated partial onset seizures for adult as well as pediatric patients. On the contrary, everolimus (Afinitor) has FDA-approval only for adult patients (18 years and older) for all approved indications.

III. Everolimus (Afinitor) has been evaluated in combination with exemestane for HR+, HER2-, advanced or metastatic breast cancer. In clinical trials, subjects had previously progressed on or after an aromatase inhibitor, such as, anastrozole or letrozole. Additionally, subjects may have received one or more previous lines of chemotherapy. The major efficacy outcome was progression-free survival (PFS) which was statistically significant versus placebo; however, an overall survival (OS) benefit was not shown.

IV. Everolimus (Afinitor) was evaluated for safety and efficacy in neuroendocrine tumors, including those of pancreatic, lung, and gastrointestinal origin. Subjects were allowed previous somatostatin analog use, and the major efficacy outcome, PFS, was statistically significant regardless of previous somatostatin use in comparison to placebo. Overall survival was not statistically different between the treatment arms.

V. Everolimus (Afinitor) has been evaluated for safety and efficacy in renal cell carcinoma in patients who have previously received sunitinib (Sutent), sorafenib (Nexavar), or both sequentially. Subjects may also have had bevacizumab (Avastin), interleukin 2, or interferon alpha. Progression-free survival was shown to be statistically significant in favor of everolimus (Afinitor); however, OS was not statistically different compared to placebo. Results may have been confounded by high rates of crossover from placebo to active therapy (80%).

VI. A phase two, randomized trial to study efficacy and safety of lenvatinib (Lenvima) in renal cell carcinoma included everolimus (Afinitor) as active comparator. Lenvatinib (Lenvima) was administered in combination with everolimus (Afinitor) to the participants in treatment arm. Subjects in treatment arm had progressed on previous anti-angiogenesis therapy (VEGF-targeted therapy) such as pazopanib [Votrient], bevacizumab [Avastin], sunitinib [Sutent], or axitinib [Inlyta]. Primary outcome of progression-free survival (PFS) was shown to be statistically significant in favor of combination of lenvatinib (Lenvima) with everolimus (Afinitor) as compared to everolimus (Afinitor) monotherapy comparator. NCCN guidelines recommend everolimus (Afinitor) in combination with lenvatinib (Lenvima) and everolimus (Afinitor) monotherapy as category 1 and category 2A recommendations, respectively.

VII. Everolimus (Afinitor) was evaluated for safety and efficacy in tuberous sclerosis complex associated renal angiomyolipomas. Response rate was statistically significant in favor of everolimus (Afinitor), as well as the time to progression compared to placebo.

VIII. Everolimus (Afinitor, Afinitor Disperz) was evaluated in tuberous sclerosis completed-associated subependymal giant cell astrocytomas. Subjects included were of pediatric and adult populations. The primary outcome was SEGA response rate, which was statistically significant in favor of everolimus (Afinitor, Afinitor Disperz).

IX. Everolimus (Afinitor Disperz) was evaluated as an adjunct therapy for partial onset seizures associate with tuberous sclerosis complex (TSC). Subjects included were refractory to at least two conventional antiepileptic medications.

X. All strengths of Afinitor and Afinitor Disperz now have an AB-rated generic available. Medical necessity for brand Afinitor or Afinitor Disperz will be indicated by a contraindication to generic as intolerance to the generic is an indicator of intolerance to brand, given their therapeutic equivalence.

Investigational or Not Medically Necessary Uses

I. Carcinoid tumor
   A. Everolimus (Afinitor) was evaluated in a clinical trial for safety and efficacy for carcinoid tumor. The primary efficacy outcome was not reached, and overall survival outcomes favored placebo. At this time efficacy of everolimus (Afinitor) in this setting is not known to be clinically beneficial.

II. Everolimus (Afinitor, Afintor Disperz) has not been sufficiently evaluated for safety and/or efficacy, and/or is in clinical trials for the following indications:
   A. Graft-versus-host disease
   B. Ependymoma
   C. Hodgkin Lymphoma or Non-Hodgkin Lymphoma
   D. Central nervous system cancers
   E. Kaposi's sarcoma
   F. Thymoma and thymic carcinoma
   G. Endometrial, ovarian, uterine cancers
   H. Prostate cancer
   I. Gastroesophageal carcinomas
   J. Waldenstrom macroglbulinemia

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to add in generic Afinitor Disperz and new generic Afinitor 10mg, updated all indications to allow brand coverage only if medical necessity established for brand over generic. Updated renewal section to carry over regimen requirements from initial (e.g., monotherapy use).	10/2021
Updated policy for renal cell carcinoma to allow after trial and failure of one prior anti-angiogenic therapy rather than only sorafenib (Nexavar) or sunitinib (Sutent); and combination of everolimus (Afinitor) with lenvatinib (Lenvima); Updated supporting evidence to include clinical data; Added supporting evidence for FDA-approvals based on age for everolimus (Afinitor) and everolimus (Afinitor Disperz)	10/2020
Generic everolimus 2.5 mg, 5 mg, and 7.5 mg added to the policy, with brand coverage only if medical necessity established for brand over generic.	01/2020
Prior authorization criteria transitioned to policy format, specialist providers updated to include neurologist, Addition of trial of conventional antiepileptic therapies prior to payment consideration for everolimus (Afinitor Disperz), addition of age requirement for everolimus (Afinitor), updated QLL for everolimus (Afinitor Disperz) to be calculated upon clinical review.	12/2019
Afinitor Disperz with indications added to criteria, formatting update and quantity limits changed to mirror available package sizes.	05/2018
Criteria created	05/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP017

Description
Alprolix, Idelvion, and Rebinyn are extended half-life factor IX products for the treatment and prevention of bleeding in patients with hemophilia B.

Length of Authorization
- Initial: 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- Renewal: 12 months (for prophylaxis); 6 months (for on-demand)

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
Alprolix, coagulation factor IX (recombinant, Fc fusion protein	250, 500, 1000, 2000, 3000, 4000 IU	**On-demand Treatment**δ**:** Up to 100 IU/dL for the first dose, then again every 6 to 10 hours for another dose. Dosing is then every 24 hours for three days, then every 48 hours until healing is achieved **Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg once weekly or 100 IU/kg once every ten days • <12 years: Up to 60 IU/kg once weekly. More frequent or higher doses may be required **Perioperative Management**δ**:** • *Minor surgery*: Up to 80 IU/dL as a single infusion, then every 24 to 48 hours if needed until bleeding stops • *Major surgery*: Up to 100 IU/dL as the initial dose, then repeat dose after 6 to 10 hours and then every 24 hours for the first three days. After day three, the dosing may be extended to every 48 hours until healing is achieved	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 315 IU/kg every 28 days • <12 years: Up to 255 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Idelvion, coagulation factor IX (recombinant, albumin fusion protein	250, 500, 1000, 2000, 3500 IU	**On-demand Treatment*:** Up to 100 IU/dL every 48-72 hours for seven to 14 days until bleeding stops **Routine Prophylaxis:** • ≥12 years: Up to 40 IU/kg once weekly. Patients who are well controlled may be changed to 50-75 IU/kg every 14 days • <12 years: Up to 55 IU/kg every seven days **Perioperative Management*:** • *Minor*: Up to 80 IU/dL every 48 to 72 hours for at least one day until healing is achieved • *Major*: Up to 100 IU/dL every 48 to 72 hours for 7 to 14 days, or until bleeding stops and healing is achieved	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 170 IU/kg every 28 days • <12 years: Up to 230 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Rebinyn, coagulation factor IX (recombinant, GlycoPEGylated	500, 1000, 2000, 3000 IU	**On-demand Treatment:** Up to 80 IU/kg for the initial dose. Additional doses of 40 IU/kg can be given. **Routine Prophylaxis:** • 40 IU/kg once weekly **Perioperative Management:** • *Minor*: Preoperative dose of up to 40 IU/kg. Additional doses can be given if needed. • *Major*: Preoperative dose of up to 80 IU/kg. Repeated doses of 40 IU/kg (in one to three day intervals) within the first week after surgery may be administered.	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** Up to 170 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

‡Allows for +5% to account for assay and vial availability

δ One unit per kilogram body weight increases the circulating Factor IX level by 1% (IU/dL). Estimate the required dose or the expected in vivo peak increase in Factor IX level expressed as IU/dL (or % of normal) using the following: IU/dL (or % of normal) = [Total dose (IU)/Body Weight (kg)] x Recovery (IU/dL per IU/kg)

* One IU of Idelvion per kg body weight is expected to increase the circulating activity of factor IX as follows: adolescents and adults: 1.3 IU/dL per IU/kg; pediatrics (<12 years): 1 IU/dL per IU/kg. Determine the initial dose using the following: Required dose (IU) = body weight (kg) x desired factor IX rise (%of normal or IU/dL) x (reciprocal of recovery (IU/kg per IU/dL))

Initial Evaluation

I. Extended half-life factor IX products may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **hemophilia B (congenital factor IX deficiency)** and the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Use of extended half-life factor IX is planned for one of the following indications:
         i. On-demand treatment and control of bleeding episodes **AND** the number of factor IX units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
         ii. Perioperative management of bleeding; **OR**
         iii. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
            a. Member has severe hemophilia B (defined as factor IX level of <1%); **OR**
            b. Member has had more than one documented episode of spontaneous bleeding; **AND**
      3. Prior treatment with a standard half-life factor IX product administered at the FDA approved dose for at least 50 exposure days was ineffective for the treatment or prevention of bleeding episodes; **OR**
      4. There is clinical documentation that all available standard half-life factor IX products are inappropriate; **AND**
      5. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; **AND**
      6. Dose and frequency do not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval

II. Extended half-life factor IX products are considered investigational when used for all other conditions.

Renewal Evaluation

I. For **on-demand treatment** and **routine prophylaxis**:
   i. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline; **AND**
   ii. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is documented plan to address inhibitors; **AND**
   iii. *For **on-demand treatment only**,* the dose and frequency is not greater than the routine prophylactic dose outlined in the Quantity Limit Table above

Supporting Evidence

I. Hemophilia B (factor IX deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. The availability of factor replacement products has dramatically improved care for those with hemophilia B.

II. There are varying severities of hemophilia B depending on the level of factor produced by the patient. Hemophilia B is divided into the following categories based on severity:
   i. **Severe**: <1% factor activity (<0.01 IU/mL)
   ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
   iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL

III. There are three general approaches to bleeding management in those with hemophilia B:
   - Episodic ("on demand") treatment that is given at the time of clinically evident bleeding
   - Perioperative management of bleeding for those undergoing elective surgery/procedures
   - Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia B is to replace the deficient coagulation factor either through episodic ("on demand") treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor IX products are the treatment of choice for hemophilia B as recommended by The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia B. Therapy should be initiated early with the goal of keeping the trough factor IX level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. The safety and efficacy of the extended half-life products were established based on open-label, non-randomized trails. Alprolix and Idelvion demonstrated effectiveness in reducing annualized bleeding rates when used prophylactically compared to on-demand treatment.

VI. Rebinyn has been shown to stop or prevent bleeding in on-demand, perioperative settings, and prophylaxis. Prophylaxis use was approved based on two, phase 3 studies. Paradigm 2 was a multinational, randomized, single-blind trial using 2 prophylaxis groups (10 and 40 IU/kg once weekly) and a single on-demand group. Patients chose either prophylaxis or on-demand treatment and patients choosing prophylaxis were randomized 1:1 to either 10 or 40 IU/kg once weekly. The primary efficacy endpoint was hemostatic effect when treating a bleeding episode (patient reported) and assessing prophylactic effect via annualized bleeding rates (ABRs). The primary safety efficacy was development of FIX inhibitors. A total of 74 patients were enrolled with 67 completing the study. None of the withdrawal patients were due to adverse effects. No patients developed inhibitors. The median ABR was 2.93 and 1.04 for the 10 IU/kg and 40 IU/kg groups, respectively.

VII. Paradigm 4 was an open-label, non-randomized, multi-center extension trial. In addition to the 3 previous treatment arms, a fourth was added as 80 IU/kg every 2 weeks. Patients were able to change treatment arms based on clinical changes to disease. Length of treatment was equivalent to at least 50 exposure days. Primary endpoint was evaluation of factor inhibitors

and secondary endpoint of treatment efficacy and prophylaxis. A total of 71 patients completed the extension, no patients developed inhibitors and no safety concerns were raised. There was 94.6% success rate in treated bleeds. Median ABR was similar for the 40 IU/kg group across paradigm 2 and paradigm 4 with little difference in ABR between the 10 IU/kg and 40 IU/kg group.

VIII. Extended half-life factor IX products were developed to extend the half-life and allow for longer infusion intervals. The majority of published clinical trial evidence evaluating extended half-life products have included previously treated patients with a minimum of 50 exposure days and no history of inhibitors.

IX. There is no evidence that extended half-life factor replacement products are safer or more effective than standard half-life products. There are no head-to-head trials comparing extended half-life products and standard half-life products to definitively establish superior safety or efficacy.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of extended half-life factor IX products in any other condition.

References

1. Alprolix® [Prescribing Information]. Waltham, MA: Bioverativ; July 2019
2. Idelvion® [Prescribing Information]. Kankakee, IL: CSL Behring; May 2018
3. Rebinyn® [Prescribing Information]. Plainsboro, NJ: Novo Nordisk; August 2022
4. Collins PW, Young G, Knobe K, et al. Recombinant long-acting glycoPEGylated factor IX in hemophilia B: a multinational randomized phase 3 trial (paradigm 2). Blood. 2014; 124(26):3880-6. doi:10.1182/blood-2014-05-573055.
5. Young G, Collins PW, Colberg T, et al.Nonacog beta pegol (N9-GP) in haemophilia B: A multinational phase III safety and efficacy extension trial (paradigm 4). Thromb Res. 2016; 141:69-76. doi:10.1016/j.thromres.2016.02.030.
6. National Hemophilia Foundation. Hemophilia B. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-B. Accessed July 8, 2019.
7. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
8. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy and supportive evidence of Rebinyn for use in routine prophylaxis	06/2023
New policy created for extended half-life factor products	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP029

Description
Altuviiio, Adynovate, Eloctate, Esperoct, and Jivi are extended half-life factor VIII products for the treatment and prevention of bleeding in patients with hemophilia A.

Length of Authorization
- Initial: 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- Renewal: 12 months (for prophylaxis); 6 months (for on-demand)

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
Altuviiio, antihemophilic factor (recombinant), fc-vwf-xten fusion protein-ehtl	250, 500, 750, 1000, 2000, 3000, 4000 IU	**On-demand Treatment:** • Up to 50 IU/kg every 2 to 3 days until bleeding is resolved **Routine Prophylaxis:** • 50 IU/kg once a week **Perioperative Management:** • *Minor* (e.g., tooth extraction): single dose of 50 IU/kg followed by additional doses of 30 to 50 IU/kg after 2 to 3 days as needed until bleeding is resolved • *Major* (e.g., intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Single dose of 50 IU/kg followed by additional doses of 30 to 50 IU/kg every 2 to 3 days as needed for perioperative management	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** 200 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Adynovate, antihemophilic factor (recombinant), PEGylated	250, 500, 750, 1000, 1500, 2000, 3000 IU	**On-demand Treatment:** Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:**	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:**

		• ≥12 years: Up to 50 IU/kg two times per week • <12 years: 55 IU/kg two times per week with a maximum of 70 IU/kg **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 50 IU/kg within one hour before surgery; Repeat after 24 hours as needed until bleeding is resolved *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint-replacement): Up to 60 IU/kg within one hour before operation; Repeat every 8-24 hours (6 to 24 hours for patients <12 years of age) until adequate round healing	• ≥12 years: Up to 420 IU/kg every 28 days • <12 years: Up to 590 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Eloctate, antihemophilic factor (recombinant), Fc fusion protein	250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000, 6000 IU	**On-demand Treatment:** Up to 50 IU/kg every 12 to 24 hours (every 8 to 24 hours in patients <6 years of age) until bleeding is resolved **Routine Prophylaxis:** • ≥6 years: Up to 65 IU/kg every three to five days • <6 years: Up to 65 IU/kg every three to five days. More frequent or higher doses (up to 80 IU/kg) may be required **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 40 IU/kg every 24 hours (every 12-24 hours for patients <6 years of age) for at least 1 day until healing is achieved *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint-replacement): Preoperative dose of up to 60 IU/kg followed by a repeat dose of up to 50 IU/kg after 8-24 hours (6-24 for patients <6 years of age) and then every 24 hours until adequate wound healing (at least 7 days)	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥6 years: Up to 820 IU/kg every 28 days • <6 years: Up to 1,010 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Esperoct, antihemophilic factor (recombinant), glycopegylated	500, 1000, 1500, 2000, 3000 IU	**On-demand Treatment:** • ≥12 years: Up to 50 IU/kg per dose • <12 years: Up to 65 IU/kg per dose **Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg every four days • <12 years: Up to 65 IU/kg twice weekly **Perioperative Management:** *Minor and Major surgery:* Up to 50 IU/kg for those ≥12 years of age and up to 65IU/kg for those < 12 years of age	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 368 IU/kg every 28 days • <12 years: Up to 546 IU/kg every 28 days P**erioperative Management:** Up to the number of doses requested for 28 days
Jivi, antihemophilic factor (recombinant), PEGylated	500, 1000, 2000, 3000 IU	**On-demand Treatment:** Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:** • ≥12 years: Up to 40 IU/kg two times per week • <12 years: Not FDA approved **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 30 IU/kg within every 24 hours for at least 1 day until healing as achieved *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint-replacement): Up to 50 IU/kg every 12-24 hours until adequate wound healing is complete, then continue therapy for at least another 7 days	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 340 IU/kg every 28 days • <12 years: Not FDA approved **Perioperative Management:** Up to the number of doses requested for 28 days

‡Allows for +5% to account for assay and vial availability

Initial Evaluation

I. **Extended half-life factor VIII products** may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **hemophilia A (congenital factor VIII deficiency)** and the following are met:
      1. Treatment is prescribed by, or in consultation with, a hematologist; **AND**
      2. Use of extended half-life factor VIII is planned for one of the following indications:

i. On-demand treatment and control of bleeding episodes **AND** the number of factor VIII units requested does **not** exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
ii. Perioperative management of bleeding; **OR**
iii. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
a. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
b. Member has had more than one documented episode of spontaneous bleeding; **AND**
iv. Dose and frequency do not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval; **AND**

3. Prior treatment with a standard half-life factor VIII product administered at the FDA-approved dose for at least 50 exposure days was ineffective for the treatment or prevention of bleeding episodes; **OR**
i. There is clinical documentation that all available standard half-life factor VIII products are inappropriate; **AND**
4. Provider attests that the member is being monitored appropriately for the presence of inhibitors to clotting factors; **AND**
i. Provider attests that the member has an absence of inhibitors or has a low-responding inhibitor titer (≤5 Bethesda units); **OR**
ii. Provider attests that there is a documented plan to address inhibitors If high-responding inhibitors (≥5 Bethesda units) are detected; **AND**
5. If the request is for Jivi, the member is 12 years of age or older and has been previously treated with another factor VIII product

II. Extended half-life factor VIII products are considered investigational when used for all other conditions.

Renewal Evaluation

I. For **on-demand treatment** and **routine prophylaxis**:
i. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline; **AND**
ii. Provider attests that the member is being monitored appropriately for the presence of inhibitors to clotting factors; **AND**
i. Provider attests that the member has an absence of inhibitors or has a low-responding inhibitor titer (≤5 Bethesda units); **OR**
ii. Provider attests that there is a documented plan to address inhibitors If high-responding inhibitors (≥5 Bethesda units) are detected; **AND**
iii. *For **on-demand treatment only***, the dose and frequency are not greater than the routine prophylactic dose outlined in the Quantity Limit Table above

Supporting Evidence

I. Hemophilia A (factor VIII deficiency) is an X-linked inherited coagulation factor deficiency that results in lifelong bleeding disorders. The availability of factor replacement products has dramatically improved care for those with hemophilia A.

II. There are varying severities of hemophilia A depending on the level of factor produced by the patient, these are divided into the following:
   i. **Severe**: <1% factor activity (<0.01 IU/mL)
   ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
   iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL

III. There are three general approaches to bleeding management in those with hemophilia A:
   - Episodic ("on demand") treatment that is given at the time of clinically evident bleeding
   - Perioperative management of bleeding for those undergoing elective surgery/procedures
   - Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia A is to replace the deficient coagulation factor either through episodic ("on demand") treatment given at the time of bleeding or through continuous prophylaxis to prevent bleeding. Recombinant factor VIII products are the treatment of choice for hemophilia A as recommended by The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals aged one and older with severe hemophilia A. Therapy should be initiated early with the goal of keeping the trough factor VIII level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. The safety and efficacy of the extended half-life products were established based on open-label, non-randomized trails. All are effective for reduction in annualized bleeding rates when used prophylactically compared to on-demand treatment.

VI. Extended half-life factor VIII products were developed to extend the half-life and allow for longer infusion intervals. The majority of published clinical trial evidence evaluating extended half-life products have included previously treated patients with a minimum of 50 exposure days and no history of inhibitors.

VII. Efanesoctocog alfa (Altuviiio) is an extended half-life recombinant factor VIII (rFVIII) formulation that was recently FDA-approved for the treatment of adults and children with hemophilia A for routine prophylaxis, on-demand treatment, and perioperative management of bleeding. Unlike other extended half-life FVIII replacement products, Efanesoctocog alfa (Altuviiio) follows a consistent once-weekly intravenous (IV) infusion dosing of 50 IU/kg.

VIII. Efanesoctocog alfa (Altuviiio) is the first recombinant fusion protein independent of von Willebrand Factor (VWF) interactions and is expected to provide a longer half-life than EHL. Efanesoctocog alfa (Altuviiio) is expected to be an alternative to SHL and EHL FVIII replacement with favorability due to once-a-week administration. As of June 2023, the World Federation of Hemophilia (WFH) guidelines for the management of hemophilia have not yet been updated to include efanesoctocog alfa (Altuviiio).

IX. After initiation of a factor replacement therapy, all patients are routinely monitored for development of Inhibitors to clotting factors. are measured by the Bethesda assay or the Nijmegen-modified Bethesda assay.2,3 • The definition of a positive inhibitor is a Bethesda titer of >0.6 Bethesda units (BU) for FVIII and ≥0.3 BU for FIX.1,4 • Inhibitor measurement may be performed during replacement therapy by assays utilizing heat treatment techniques.5 (See Chapter 3: Laboratory Diagnosis and Monitoring – Coagulation laboratory testing – Inhibitor testing.) • A low-responding inhibitor is an inhibitor

X. There is no evidence that extended half-life factor replacement products are safer or more efficacious than standard half-life products. However, there are no head-to-head trials comparing extended half-life products and standard half-life products to definitively establish superior safety or efficacy.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of extended half-life factor VIII products in any other condition.

References

1. Adynovate® [Prescribing Information]. Westlake Village, CA: Shire; May 2018
2. Afstyla® [Prescribing Information]. Kankakee, IL: CSL Behring; September 2017
3. Esperoct® [Prescribing Information]. Novo Nordisk Inc: Plainsboro, NJ. October 2019.
4. Eloctate® [Prescribing Information]. Waltham, MA: Bioverativ Therapeutics; December 2017
5. Jivi® [Prescribing Information]. Whippany, NJ: Bayer; August 2018
6. National Hemophilia Foundation. Hemophilia A. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed July 5, 2019.
7. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
8. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.
9. Von Drygalski A, Chowdary P, et al. XTEND-1 Trial Group. Efanesoctocog Alfa Prophylaxis for Patients with Severe Hemophilia A. N Engl J Med. 2023 Jan 26;388(4):310-318.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Standard Half-life Factor VIII Products – Hemophilia A	Hemophilia A

Policy Implementation/Update:

Action and Summary of Changes	Date
Efanesoctocog alfa (Altuviiio) added to the policy; updated criteria related to presence of inhibitors	08/2023
Esperoct added to policy	05/2020
New policy created for extended half-life factor products	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP019

Description

Alphanate, Humate-P, and Wilate are factor VIII concentrates containing von Willebrand factor (VWF) for the treatment of von Willebrand disease (vWD) and/or hemophilia A.

Length of Authorization

- Initial: 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- Renewal: 12 months (for prophylaxis); 6 months (for on-demand)

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
Alphanate, antihemophilic factor/von Willebrand factor complex (human)	250, 500, 1000, 1500, 2000 IU FVIII	**Control and prevention of bleeding – hemophilia A**[δ]: Up to 50 IU factor VIII/kg twice daily for at least three to five days. Following this, factor VIII levels should be maintained at 25 IU factor VIII/kg twice daily until healing has been achieved. Major hemorrhages may require treatment for up to ten days. Intracranial hemorrhages may require prophylaxis therapy for up to six months.	**Control and prevention of bleeding in hemophilia A:** Up to the number of doses requested every 28 days
		Perioperative management – hemophilia A: Up to 50 IU factor VIII/kg prior to surgery, then up to 50 IU factor VIII/kg twice daily for the next seven to ten days, or until healing has been achieved	**Perioperative management in hemophilia A:** Up to the number of doses requested for 28 days
		Control and prevention of bleeding and perioperative management – vWD[γ]: Pre-operative/pre-procedure dose: • Adults: Up to 60 IU VWF:RCo/kg body weight • Pediatrics: Up to 75 IU VWF:RCo/kg body weight Maintenance: • Adults: Up to 60 IU VWF:RCo/kg body weight at eight to 12 hour intervals as clinically needed for at least three to seven days	**Control and prevention of bleeding and perioperative management in vWD:** Up to the number of doses requested for 28 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		• Pediatrics: Up to 75 IU VWF:RCo/kg body weight at eight to 12 hour intervals as clinically needed for at least three to seven days	
Humate-P, antihemophilic factor/von Willebrand factor complex (human)	600, 1200, 2400 IU vWF:RCo	**Control and prevention of bleeding – hemophilia A*:** • Minor: Up to 15 IU factor VIII:C/kg to achieve a factor VIII: C plasma level of approximately 30% of normal. One infusion may be sufficient. If needed, half of the loading dose may be given one or twice daily for one to two days • Moderate: Up to 25 15 IU factor VIII:C/kg to achieve a factor VIII: C plasma level of approximately 50% of normal, followed by 15 IU factor VIII:C/kg every eight to 12 hours for the first one to two days to maintain the factor VIII:C plasma level at 30% of normal. Continue the same dose one or twice for up to seven days or until adequate wound healing is achieved • Major: Initially up to 50 IU factor VIII:C/kg, followed by up to 25 IU factor VIII:C/kg every eight hours to maintain the factor VIII:C plasma level at 80-100% of normal for seven days. Continue the same dose one or twice daily for another seven days to maintain the factor VIII:C level at 30-50% of normal **Control and prevention of bleeding – vWD:** Up to 80 IU vWF:RCo (corresponding to 17 to 33 IU factor VIII in Humate-P) per kg body weight every eight to 12 hours. Adjust as needed based on the extent and location of bleeding. Repeat doses as long as necessary. **Perioperative management – vWD:** <u>Loading</u>: • Major: vWF:RCo target peak plasma level – 100 IU/dL; Target factor VIII:C activity – 80-100 IU/dL	**Control and prevention of bleeding – hemophilia A:** Up to the number of doses requested every 28 days **Control and prevention of bleeding – vWD:** Up to the number of doses requested every 28 days **Perioperative management – vWD:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		• Minor: vWF:RCo target peak plasma level – 50-60 IU/dL; Target factor VIII:C activity – 40-50 IU/dL • Emergency: vWF:RCo target peak plasma level – 100 IU/dL; Target factor VIII:C activity – 80-100 IU/dL. Administer a dose of 50-60 IU vWF:RCo/kg body weight <u>Maintenance</u>: Initial maintenance dose should be half the loading dose, irrespective of additional dosing required to meet factor VIII:C targets. Subsequent doses should be based on the patient's vWF:RCo and factor VIII levels	
Wilate, von Willebrand factor/coagulation factor VIII complex (human)		**Control of bleeding episodes – vWD**€: Up to 60 IU/kg initially, followed by up to 40 IU/kg every 12 to 24 hours until vWF:Rco and factor VIII activity trough levels > 50%, for up to five to seven days **Perioperative management of bleeding – vWD**: Up to 60 IU/kg initially, followed by up to 40 IU/kg every 12 to 24 hours until wound healing achieved, up to six days or more. vWF:Rco and factor VIII activity trough levels > 50% and peak levels 100% until wound healing is achieved, up to six days or more	**Control of bleeding episodes – vWD:** Up to the number of doses requested every 28 days **Perioperative management of bleeding – vWD:** Up to the number of doses requested for 28 days

‡Allows for +5% to account for assay and vial availability

δ Dose (IU) = body weight (kg) x desired factor VIII rise (IU/dL or % normal) x 0.5 (IU/kg per IU/dL)

ɣ The ratio of VWF:RCo to factor VIII varies by lot, so with each new lot, check the IU vWF:RCo/Vial to ensure accurate dosing

* One IU of factor VIII activity per kg body weight will increase the circulating factor VIII level by approximately 2 IU/dL

Ψ Target peak plasma vWF:RCo level – baseline plasma vWF:RCo level) – body weight (kg)/in vivo recovery. If the in vivo recovery is not available, assume an in vivo recovery of 2 IU/dL per IU/kg and calculate the loading dose as follows: (100 – baseline plasma vWF:RCo) x body weight (kg)/2

€ The ratio between vWF:RCo and factor VIII activities is approximately 1:1. The dosage should be adjusted according to the extent and location of the bleeding.

Initial Evaluation

von Willebrand Disease

I. **Alphanate** or **Humate-P** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologists; **AND**
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
   C. Use is planned for one of the following indications:
      1. Treatment of spontaneous and trauma-induced bleeding episodes; **OR**
      2. Used as surgical bleeding prophylaxis during major or minor procedures when desmopressin (DDAVP) is either ineffective or contraindicated; **AND**
      3. **Alphanate** will not be used for severe (type 3) vWD undergoing major surgery

II. **Wilate** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologists; **AND**
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
   C. Use is planned for one of the following indications:
      1. Perioperative management of bleeding; **OR**
      2. For the treatment of spontaneous and trauma-induced bleeding episodes when one of the following is met:
         i. Member has severe vWD; **OR**
         ii. Member has mild or moderate vWD and the use of desmopressin (DDAVP) is known or suspected to be ineffective or contraindicated; **AND**
   D. Wilate will not be used for the routine prophylactic treatment of spontaneous bleeding episodes; **AND**
   E. Wilate is not being used for hemophilia A

Hemophilia A (congenital factor VIII deficiency)

I. **Alphanate** or **Humate-P** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   B. A diagnosis of hemophilia A has been confirmed by blood coagulation testing; **AND**
   C. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding episodes **AND** the number of factor VIII/VWF units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
      2. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
         i. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
         ii. Member has had more than one documented episode of spontaneous bleeding; **OR**
      3. Perioperative management of bleeding; **AND**

D. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; **AND**
E. Dose and frequency does not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval

II. Alphanate, Humate-P, and Wilate are considered investigational when used for any other condition.

Renewal Evaluation

I. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline

Supporting Evidence

von Willebrand Disease

I. Von Willebrand disease (vWD) is the most common of the inherited bleeding disorders. Although vWD is common, only a fraction of patients seek medical attention due to bleeding symptoms due to the mild nature of the disease in many patients, and to the lack of bleeding challenges.
II. There are three types of inherited vWD:
    - Type 1 – The most common type that accounts for about 70% of cases. It reflects a quantitative deficiency of von Willebrand factor (vWF). The clinical presentation varies from mild to moderately severe.
    - Type 2 – Accounts for 25-30% of cases and is characterized by several qualitative abnormalities of vWF (e.g. altered size rations or biologic properties).
    - Type 3 – The most severe type of disease with very low or undetectable levels of vWF. Patients typically present with severe bleeding involving both the skin and mucous membrane surfaces and soft tissues and joints. Replacement therapy with vWF is usually required.
III. Choice of therapy begins with an accurate and complete diagnosis of vWD, plus patient-specific factors must be taken to account (e.g. history of bleeding, response to prior therapies).
IV. A trial of desmopressin (DDAVP) should be considered in all patients with type 1 and most with type 2, but not in patients with type 3 vWD. Typically, minor bleeding episodes can be treated with DDAVP without further therapeutic intervention. Major surgery typically requires replacement with vWF. However, Alphanate is not indicated for patients with severe vWD undergoing major surgery.
V. Patients with type 3 vWD, those with more severe type 1, and many of those with certain subtypes of type 2 disease often require replacement therapy with a vWF-containing product to control bleeding. However, vWF is not generally given as long-term prophylaxis like is done in patients with hemophilia A.

VI. The safety and efficacy of factor VIII/vWF complex products were established based on open-label, non-randomized trails. All replacement are effective in restoring hemostasis.

Hemophilia A

I. Hemophilia A (factor VIII deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. The availability of factor replacement products has dramatically improved care for those with hemophilia A.

II. There are varying severities of hemophilia A depending on the level of factor produced by the patient. Hemophilia A is divided into the following categories based on severity:

    i. **Severe**: <1% factor activity (<0.01 IU/mL)
    ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
    iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL

III. There are three general approaches to bleeding management in those with hemophilia A:

    i. Episodic ("on demand") treatment that is given at the time of clinically evident bleeding
    ii. Perioperative management of bleeding for those undergoing elective surgery/procedures
    iii. Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia A is to replace the deficient coagulation factor either through episodic ("on demand") treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor VIII products are the treatment of choice for hemophilia A as recommended by The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia A. Therapy should be initiated early with the goal of keeping the trough factor VIII level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. The safety and efficacy of the standard half-life products were established based on open-label, non-randomized trails. All replacement products can produce satisfactory hemostasis.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of factor VIII/vWF complex products in any other condition.

References

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8. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	Date
New policy created for factor VIII/vWF complex products	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP280

Description

Fecal microbiota spores, live-brpk (Vowst™) is an orally administered microbiome therapy composed of purified Firmicutes spores.

Length of Authorization

- Initial: One-time fill
- Renewal: None

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
fecal microbiota spores, live-brpk (Vowst)	Reduction of recurrence risk of Clostridioides difficile (C. difficile) infection	Capsule	12 capsules/30 days

Initial Evaluation

I. **Fecal microbiota spores, live-brpk (Vowst)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a gastroenterologist or infectious disease specialist; **AND**
   C. A diagnosis of **recurrent Clostridioides difficile infection** when the following are met:
      1. Provider attestation that the member has had two or more prior *recurrent C. difficile* episodes in the past 12 months; **AND**
      2. Member had complete remission of the most recent *C. difficile* infection episode with oral antibiotics (e.g., vancomycin, fidaxomicin); **AND**
      3. Provider attestation that the member does not have active *C. difficile* infection (defined as ≤3 unformed stools for 2 or more consecutive days); **AND**
      4. Member has <u>not</u> received a *C. difficile* prophylaxis therapy (e.g., fecal microbiota transplantation (FMT), fecal microbiota, live-jslm (Rebyota), bezlotoxumab (Zinplava)) within the previous 3 months

II. Fecal microbiota spores, live-brpk (Vowst) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Treatment of active Clostridioides difficile infection
   B. Non-recurrent Clostridioides difficile infection
   C. In combination with other Clostridioides difficile prophylaxis regimens (e.g. FMT, bezolotoxumab, Rebyota)
   D. When used for more than one treatment course per 6 months

Renewal Evaluation

I. N/A

Supporting Evidence

I. Fecal microbiota spores, live-brpk (Vowst) was studied in clinical trials in adult patients. Safety and efficacy of Vowst has not been established in the pediatric population.

II. Diagnosis and management of recurrent C. difficile infection require detailed clinical examination in combination with advanced testing (e.g., stool toxin assay). C. difficile has a high rate of recurrence and is highly contagious if not adequately contained and treated. Given the complexities of diagnosis and treatment of the condition, supervision of treatment by an infectious disease specialist or gastroenterologist (GI) is required.

III. Recurrent C. difficile infection can be defined as the reappearance of C. difficile symptoms within a few days, to up to 12 weeks, after symptom resolution. While there is not a definite definition and time frame for C. difficile recurrence across clinical practice and scientific literature, reappearance of symptoms within 8-12 weeks of symptom resolution is often used within clinical trials assessing C. difficile treatment and recurrence prevention. The majority of clinical trials included in the American College of Gastroenterology (ACG) and the C. Difficile Clinical Guidelines and Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA) C. Difficile Clinical Practice Guidelines, used a window between 8 and 12 weeks; however, sustained clinical response and rate of recurrence have been measured out to 24 weeks (6 months) in some trials. Risk factors for recurrent C. difficile infections are antibiotic exposure, older age, recent hospitalization, weakened immune system, and history of C. diff infection. Roughly 1/6 patients will experience a recurrence after an initial infection.

IV. Vowst is an oral microbiome therapy studied in ECOSPOR III, a Phase III, double-blind, randomized placebo-controlled trial with 182 adult patients (18 years and older) with recurrent C. difficile infection that had symptom resolution following standard of care antibiotic treatment with vancomycin or fidaxomicin.

V. Within the ECOSPOR III trial, a qualifying episode of C. difficile was defined as: ≥ 3 unformed stools per day for 2 consecutive days, a positive C. difficile stool toxin assay, C. difficile standard of care (SOC) antibiotic therapy (defined as 10 to 21 days of treatment with vancomycin [125 mg QID] or fidaxomicin [200 mg BID], and an adequate clinical response following SOC antibiotic therapy, defined as < 3 unformed stools in 24 hours for 2 or more consecutive days. Recurrence was defined as ≥ 3 episodes of C. difficile infection within the previous 12 months inclusive of the current episode. The primary efficacy endpoint was the superiority of Vowst versus placebo in reducing the risk of C. difficile recurrence up to 8 weeks after dosing. Rate of C. difficile recurrence at 8 weeks for Vowst treatment group was 12% (n=11) and that for placebo was 40% (n=37), with relative risk reduction of 0.32 (95% CI, 0.18 to 0.58; p<0.001).

VI. Patients that received human monoclonal antibody C. difficile toxin (e.g., Zinplava) or fecal microbiota transplantation (FMT) within previous 3 months prior to the study were excluded from the ECOSPOR III trial. The efficacy and safety of concurrent use of Vowst and other C. difficile prophylaxis therapies (e.g., FMT or bezlotoxumab (Zinplava), fecal microbiota, live-jslm (Rebyota) has not been evaluated and remains unknown at this time.

VII. While toxin assay diagnostic testing was used within ECOSPOR III, NAAT, which includes PCR testing, is commonly used in clinical practice within a multistep algorithm and is supported by both ACG Clinical Guidelines and IDSA/SHEA C. Difficile Clinical Practice Guidelines.

VIII. In the ECOSPOR III trial population, the overall adverse events (AE) reported for Vowst were similar to those for placebo. Most common AE for Vowst were gastrointestinal disorders (88%), fatigue (59%), chills (21%), decreased appetite (29%), and infection (20%).

IX. Vowst is an alternative to fecal microbiota, live-jslm (Rebyota), bezlotoxumab (Zinplava), or FMT with expected favorability due to oral administration and purported safety advantage compared to FMT. Rebyota is administered via rectal enema, and bezlotoxumab is administered intravenously. FMT may be administered through colonoscopy, capsule, or enema. Head-to-head trials have not been conducted between different C. difficile prophylaxis treatment options, however indirect comparison between trials suggests similar efficacy of recurrence prevention between agents.

Investigational or Not Medically Necessary Uses

I. Vowst has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Treatment of Clostridioides difficile infection
      i. ECOSPOR III did not review Vowst for safety and efficacy in the setting of treatment of C. difficile infection. Vowst is a microbiome therapy and would not have efficacy in treating an active infection without the use of standard of care antibiotics (e.g., vancomycin and fidaxomicin).
   B. Non-recurrent Clostridioides difficile infection
      i. Safety and efficacy have not been established for Vowst for non-recurrent C. difficile. ACG C. difficile guidelines and IDSA/SHEA C. difficile guidelines recommends FMT and Zinplava only for recurrent C. difficile infection, and not for primary prevention of C. difficile infection.
   C. In combination with other Clostridioides difficile regimens (e.g., FMT, bezlotoxumab, Rebyota)
      i. There is lack of safety and efficacy data when C. difficile prophylaxis regimens are used concurrently. Clinical trials evaluating C. difficile prophylaxis treatments (PUNCH CD3 for Rebyota, Modify I and II for bezlotoxumab (Zinplava), ECOSPOR III and IV for Vowst) excluded patients that had been previously treated (within 3 months of study enrollment), or planned to concurrently use other C. difficile prophylaxis treatment options, including fecal microbiota transplant. The safety profile of combination therapy is unknown at this time with potential safety

concerns. Additionally, efficacy of combination has not been established in any clinical trials to date or real-world data.

D. When used for more than one treatment course per 6 months
    i. Repeat dosing of Vowst was not studied in ECOSPOR III. In the open-label extension trial, ECOSPOR IV, there were only 4 patients that had repeat dosing of Vowst after having C. difficile recurrence within 8 weeks that were previously enrolled in ECOSPOR III. Additionally, rates of recurrence beyond six months or safety and efficacy of retreatment with Vowst has not been established. Due to lack of adequate safety and efficacy data to establish an appropriate timeline for retreatment, retreatment with Vowst within 6 months will not be allowed.

References

1) Feuerstadt P, Louie TJ, Lashner B, et al. SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection. *N Engl J Med*. 2022; 386(3):220-229.
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Seres Therapeutics, Inc. ECOSPOR IV: An Open-Label Extension of Study SERES-012 and Open-Label Program for Evaluating SER-109 in Subjects With Recurrent Clostridioides Difficile Infection (RCDI). clinicaltrials.gov. Published May 24, 2022. Accessed December 5, 2022. https://clinicaltrials.gov/ct2/show/NCT03183141.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	2/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP083

Split Fill Management*

Description

Fedratinib (Inrebic) is an orally administered kinase inhibitor with activity against both wild-type and mutated Janus-associated kinase 2 (JAK2) and FMS-like tyrosine kinase 3 (FLT3).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
fedratinib (Inrebic)	Intermediate- or high-risk myelofibrosis	100 mg capsules	120 capsules/30 days

Initial Evaluation

I. **Fedratinib (Inrebic)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
   C. A diagnosis of **intermediate- or high-risk myelofibrosis (MF)** when the following are met:
      1. Splenomegaly is present and baseline spleen volume is documented; **AND**
      2. Documentation of disease-related symptoms (e.g., fatigue, shortness of breath, bruising, bleeding, fever, bone pain); **AND**
      3. Platelet count, measured within the past 30 days, is greater than or equal to, 50 x 10^9/L; **AND**
      4. Treatment with ruxolitinib (Jakafi) has been ineffective or not tolerated.

II. Fedratinib (Inrebic) is considered investigational when used for all other conditions, including but not limited to:
   A. Low risk myelofibrosis
   B. Polycythemia vera
   C. Graft versus host disease
   D. Lymphoproliferative neoplasms
   E. Solid tumors (e.g., prostate, colorectal, lung)
   F. Acute myeloid leukemia (AML)
   G. Chronic lymphocytic leukemia, small lymphocytic lymphoma
   H. COVID-19

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of intermediate- or high-risk myelofibrosis (has not transformed to AML); **AND**
IV. Member has exhibited improvement in or stability of disease-related symptoms (e.g., fatigue, shortness of breath, bruising, bleeding, fever, bone pain).

Supporting Evidence

I. Myelofibrosis (MF) is a cancer of the bone marrow. Symptoms are non-specific (e.g., fatigue, shortness of breath, bleeding) and splenomegaly is common. Over time MF may progress to acute myeloid leukemia (AML). There are five risk levels of disease that correlate with prognosis, and treatment is based on risk. When patients are not eligible for allogeneic stem cell transplant, symptom targeted therapy may be used in those with intermediate or higher risk MF. Symptomatic therapies include hydroxyurea and JAK inhibitors: ruxolitinib (Jakafi), fedratinib (Inrebic), and pacritinib (Vonjo). JAK inhibitors have only been sufficiently evaluated in patients with at least intermediate-risk MF and have unknown clinical value for lower risk disease. JAK inhibitors do not reverse fibrosis or prolong survival but may reduce spleen size and improve disease-related symptoms. In absence of splenomegaly and symptoms, these medications have unknown application. Given the specialized diagnosis, treatment, and monitoring, prescribing by, or in consultation with, a specialist is required.
II. Fedratinib (Inrebic) and ruxolitinib (Jakafi) are approved for MF when platelet count is ≥ 50 x 10^9/L. These medications cause thrombocytopenia and are recommended to be discontinued if the platelet count drops below 50 x 10^9/L. Pacritinib (Vonjo), has a unique approval, and was approved under the accelerated approval pathway based on spleen volume reduction (SVR) when platelet count is under 50 x 10^9/L (severe thrombocytopenia). These therapies have only been evaluated in adults; use in pediatrics or adolescents has unknown value or consequences. Outside of a clinical trial setting, therapy should only be utilized in adults.
III. Fedratinib (Inrebic) was evaluated as an initial treatment in patients with intermediate-2 or high-risk MF (JAKARTA) and as a second-line treatment in patients who are ruxolitinib (Jakafi) resistant or intolerant (JAKARTA-2).
    - JAKARTA: Phase 3, double-blind, randomized, placebo-controlled trial with 289 total patients. The primary and secondary endpoints were superior to placebo: spleen volume reduction of 35% and at least a 50% reduction in total symptom score.
    - JAKARTA-2: Single-arm, open-label, non-randomized, Phase 2 trial in ruxolitinib (Jakafi) resistant or intolerant patients, which showed patients were able to achieve spleen volume reduction of 35% as well as a 50% or greater reduction in TSS.
    - Dose interruptions due to adverse events occurred in 21% of patients, dose reductions in 19%, and permanent discontinuation in 14%. Split-fill is applied.

IV. As of February 2022, NCCN guidelines recommend treatment with fedratinib (Inrebic) or ruxolitinib (Jakafi) in higher risk MF when platelet count is greater than 50 x 10^9/L (Category 1).

V. Fedratinib (Inrebic) has shown to reduce spleen size and improve disease-related symptoms; however, reduction of spleen volume alone without associated improvement in symptoms has unknown clinical value. Therapy should be initiated in presence of disease-related symptoms in those that are not candidates for transplant, and it is appropriate to continue treatment when therapy has stabilized or improved symptoms.

VI. Fedratinib (Inrebic) uniquely carries a black box warning for encephalopathy including Wernicke's, due to seven cases of Wernicke's encephalopathy during clinical trials. Providers should monitor patients for risk prior to starting fedratinib (Inrebic) and during therapy. In patients that have elevated risk or develop encephalopathy on treatment, alternative JAK inhibitors may be considered for use.

VII. There is no evidence of superiority for any of the three JAK inhibitors for MF; however, when balancing safety and cost effectiveness, use of ruxolitinib (Jakafi) prior to coverage consideration of fedratinib (Inrebic) is required.

Investigational or Not Medically Necessary Uses

I. Fedratinib (Inrebic) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Low risk myelofibrosis
   B. Polycythemia vera
   C. Graft versus host disease
   D. Lymphoproliferative neoplasms
   E. Solid tumors (e.g., prostate, colorectal, lung)
   F. Acute myeloid leukemia (AML)
   G. Chronic lymphocytic leukemia, small lymphocytic lymphoma
   H. COVID-19

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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2. National Comprehensive Cancer Network. NCCN Guidelines: Myeloproliferative Neoplasms Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf Updated February 28, 2022
3. UpToDate, Inc Management of primary myelofibrosis. UpToDate [database online]. Waltham, MA. Last updated Dec 06, 2021.Available at: http://www.uptodate.com/home/index.html.

4. Celgene Corporation [online press release]. U.S. FDA Approves INREBIC® (Fedratinib) as First New Treatment in Nearly a Decade for Patients with Myelofibrosis. Available at: https://ir.celgene.com/press-releases/press-release-details/2019/US-FDA-Approves-INREBIC-Fedratinib-as-First-New-Treatment-in-Nearly-a-Decade-for-Patients-With-Myelofibrosis/default.aspx. Updated August 16, 2019.
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6. Pardanani A, Harrison C, Cortes JE, et al. Safety and Efficacy of Fedratinib in Patients with Primary or Secondary Myelofibrosis: A Randomized Clinical Trial. JAMA Oncol. 2015;1(5):643-51.
7. Harrison CN, Schaap N, Vannucchi AM, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study. Lancet Haematol. 2017;4(7):e317-e324.
8. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366(9):799-807.
9. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: An updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. Am J Hematol. 2020 Jun;95(6):594-603. doi: 10.1002/ajh.25777. Epub 2020 Apr 17. PMID: 32129512; PMCID: PMC7317815.
10. Vonjo [Prescribing Information]. CTI Biopharma Corp. Seattle, WA. February 2022.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
ruxolitinib (Jakafi)	Intermediate- or high-risk myelofibrosis
	Polycythemia vera
	Graft versus-host disease (acute or chronic)
pacritinib (Vonjo)	Intermediate- or high-risk myelofibrosis

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to new formatting changes including addition of related policy. Reviewed for new indications and appropriateness of policy criteria. Updated supporting evidence. Simplified required diagnosis, to "Int. or high risk MF". Added an age edit to align with the labeled indication/age and known safety profile (i.e., adults). Added requirement of both: splenomegaly AND disease related symptoms. Added requirement of prior ruxolitinib (Jakafi) treatment. Updated renewal criteria to remove requirement of SVR reduction.	5/2022
Criteria created	9/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP203

Description

Fenfluramine (Fintepla) is an orally administered amphetamine derivative serotonin 5HT-2 receptor agonist.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit*
fenfluramine (Fintepla)	Dravet Syndrome	2.2 mg/ml solution	360 ml/30 days Monthly quantity (in mL) to allow for a maximum of 26 mg (12 mL) per day
	Lennox-Gastaut Syndrome		

**The maximum daily dose differs with concomitant stiripentol and clobazam with a maximum daily dose of 17 mg (7.7mL) per day.*

Initial Evaluation

I. **Fenfluramine (Fintepla)** may be considered medically necessary when the following criteria are met:
   A. Member is two years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. Documentation of baseline seizure frequency and severity**; AND**
   D. Documentation of the member's weight that has been measured in the past three months (necessary for dose calculation); **AND**
   E. Provider attestation fenfluramine (Fintepla) will not be used in combination with cannabidiol (Epidiolex); **AND**
   F. A diagnosis of one of the following:
      1. **Dravet syndrome; AND**:
         i. <u>All</u> of the following have been ineffective, not tolerated or are contraindicated (‡ Please note: These agents may be subject to prior authorization and may require an additional review):
            a. valproate
            b. clobazam
            c. cannabidiol (Epidiolex)‡
            d. stiripentol (Diacomit)‡; **OR**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

2. **Lennox-Gastaut Syndrome**; **AND**
    i. Two of the following have been ineffective, not tolerated or all are contraindicated (‡ Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
        a. valproate
        b. lamotrigine
        c. rufinamide‡
        d. clobazam
        e. felbamate
        f. topiramate**; AND**
    ii. Treatment with cannabidiol (Epidiolex)‡ has been ineffective, not tolerated or contraindicated

II. Fenfluramine (Fintepla) is considered investigational when used for all other conditions, including but not limited to:
    A. Epileptic encephalopathies associated with SCN1A mutations
    B. Seizure disorders other than Dravet syndrome and Lennox-Gastaut syndrome
    C. Use in combination with cannabidiol (Epidiolex)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation fenfluramine (Fintepla) will not be used in combination with cannabidiol (Epidiolex)**; AND**
IV. Documentation of the member's weight that has been measured in the past three months (necessary for dose calculation); **AND**
V. Provider attests member has exhibited improvement or stability of disease symptoms (e.g., reduction in seizure frequency).

Supporting Evidence

I. Fenfluramine (Fintepla) is FDA-approved for use in Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) for patients aged two years and older. Fenfluramine was originally introduced as a weight-loss agent at higher doses and was pulled from the market due to reports of cardiovascular adverse events (i.e., valvular heart disease and pulmonary arterial hypertension). Given the serious adverse safety profile of fenfluramine (Fintepla), and lack of evaluation in patients under two years of age, use outside of the FDA-approved two years of age and older is not recommended.

II. Both Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are associated with treatment-resistant seizures of multiple types, neurodevelopmental delay, and profound cognitive impairment. Despite the use of numerous antiseizure medications (ASMs) in these conditions, ASMs tend to have limited efficacy. Due to these conditions being treatment refractory, high-touch care and monitoring required, fenfluramine (Fintepla) must be prescribed by, or in consultation with a neurologist.

III. Fenfluramine (Fintepla) may be used as monotherapy, concomitantly with stiripentol (Diacomit), or concomitantly as triple-therapy with stiripentol (Diacomit) and clobazam (in DS). However, concomitant use with cannabidiol (Epidiolex) has not been studied in DS nor LGS. The efficacy and safety of fenfluramine (Fintepla) used in combination with cannabidiol (Epidiolex) remains unknown.

IV. Dravet syndrome:

- Dravet syndrome is a rare pediatric genetic epilepsy syndrome characterized by refractory epilepsy and neurodevelopmental problems starting in infancy. Dravet syndrome is commonly misdiagnosed as other conditions such as cerebral palsy, Lennox-Gastaut syndrome, or vaccine encephalopathy.
- Fenfluramine (Fintepla) was studied in two randomized, double-blind, placebo-controlled Phase 3 trials in 206 patients aged two to 18 years with Dravet syndrome, where convulsive seizures were not completely controlled by current AED therapy.
- Trial one (Lagae L, et al. 2019) was a Phase 3, randomized, double-blind, placebo-controlled, multicohort, multi-country trial that studied 119 patients ages two to 18 years, who had at least four convulsive seizures in a four-week period for the past 12 weeks prior to screening and were stable for at least four weeks prior to screening and throughout the trial on valproate, clobazam, topiramate, or levetiracetam. This trial excluded patients who were on concomitant stiripentol (Diacomit) therapy. Patients were randomized 1:1:1 to either fenfluramine (Fintepla) 0.7 mg/kg/day, fenfluramine (Fintepla) 0.2 mg/kg/day, or matching placebo twice daily. Patients in the trial had a mean baseline convulsive seizure frequency of 40.3 per 28 days and a mean baseline of 2.4 concomitant AEDs. The primary efficacy outcome was the reduction in mean monthly convulsive seizure frequency (MCSF) over the 14-week treatment period with fenfluramine (Fintepla) 0.7 mg/kg/day versus placebo. A key secondary endpoint was the reduction in MCSF over the 14-week treatment period with fenfluramine 0.2 mg/kg/day versus placebo. The primary end point result was a 62.3% (95% Cl -47.7 to -72.8) greater reduction in mean MCSF over the 14-week treatment period with fenfluramine 0.7 mg/kg/day versus placebo ($p<0.0001$). The key secondary endpoint result was a 32.4% (95% Cl -6.2 to -51.3) greater reduction in mean MCSF over the 14-week treatment period with fenfluramine (Fintepla) 0.2 mg/kg/day versus placebo ($p=0.0209$).
- Trial two (Nabbout R, et al. 2019) was a Phase 3, randomized, double-blind, placebo-controlled, multi-country trial that studied 87 patients ages two to 18 years, who were receiving concomitant stiripentol (Diacomit), valproate, clobazam, levetiracetam, or topiramate, and who had a stable baseline with six or more convulsive seizures during the six-week baseline, with two or more seizures in the first three weeks and two or more seizures in the second three weeks. Less than 10% of the subjects were reported to have received one of the following

concomitant AED's: acetazolamide, clonazepam, diazepam, ethosuximide, felbamate, gamma-aminobutyric acid, lorazepam, phenobarbital, pregabalin, or zonisamide. Patients were randomized 1:1 to either fenfluramine (Fintepla) 0.4 mg/kg/day or matching placebo twice daily. Patients in the trial had a mean baseline convulsive seizure frequency of 14 versus 10.7 in the fenfluramine (Fintepla) versus placebo arm. The primary efficacy outcome was the difference between fenfluramine (Fintepla) and placebo on the change in mean MCSF from baseline to the 15-week combined titration and maintenance (T+M) periods. A key secondary endpoint was the proportion achieving 50% or greater reduction from baseline levels in MCSF. The primary endpoint was 54% (95% CI, 35.6%-67.2%) achieved greater reduction in mean MCSF between the baseline and T + M periods with fenfluramine versus placebo ($p<0.001$). Results of the key secondary endpoint of reduction in mean MCSF in the fenfluramine group, 23 of 43 (54%) versus the placebo group, two of 44 (5%) ($p <0.001$).

- The NICE guidelines for Dravet syndrome, recommend valproate as first-line therapy, then clobazam, cannabidiol (Epidiolex), and stiripentol (Diacomit) as second-line therapy. These guidelines have not been updated to include fenfluramine (Fintepla). In addition to these guidelines, the international consensus on diagnosis and treatment of Dravet syndrome recommend first-line treatment with valproate, second-line with stiripentol (Diacomit), clobazam, or fenfluramine (Fintepla), and third-line with cannabidiol (Epidiolex).
- Based on the established safety, efficacy, and cost effectiveness of valproate, clobazam, cannabidiol (Epidiolex), and stiripentol (Diacomit) relative to fenfluramine (Fintepla), trial of two generics, cannabidiol (Epidiolex), and stiripentol (Diacomit) is required before approval of fenfluramine (Fintepla).

V. Lennox-Gastaut syndrome:

- Lennox-Gastaut syndrome is associated with severe seizures in childhood that typically present before eight years of age. There are a variety of causes including cortical malformations, tumors, neurocutaneous syndromes (i.e., tuberous sclerosis complex), encephalopathies, meningitis, and head injuries.
- Fenfluramine (Fintepla) was studied in a Phase 3 randomized, double-blind, placebo-controlled trial in 263 patients aged two to 35 years with Lennox-Gastaut syndrome who were using stable antiseizure regimens. Patients were eligible to enroll if they had: onset of seizures at age 11 years or younger, multiple seizure types including tonic or atonic, stable 4-week seizure baseline with 2 or more drop seizures per week, abnormal cognitive development, and medication history showing electroencephalogram evidence of abnormal background activity with slow spike-and-wave pattern. The trial excluded patients with degenerative neurological disease, history of hemiclonic seizures in the first year of life, only drop seizure clusters, and previous or current cardiovascular abnormalities. Patients were randomized 1:1:1 into fenfluramine (Fintepla) 0.7 mg/kg/day, 0.2 mg/kg/day or placebo stratified by weight less than 37.5 kg or greater than 37.5. The population characteristics included: median age of 13 years (range 2-35 years), median drop seizure frequency per 28 days 85 in 0.7 mg/kg/day, 83 in 0.2 mg/kg/day, and 53 in placebo. A mean previous antiseizure medication use of 7-8 medications. Concomitant seizure medications >20% included valproate, clobazam, lamotrigine,

rufinamide and levetiracetam. The primary efficacy outcome was the percentage change from baseline in drop seizure frequency for patients in the 0.7 mg/kg/day compared to placebo. The secondary efficacy endpoints were percentage change from baseline in frequency of drop seizures in the 0.2 mg/kg/day group, a 50% or greater response rate, and the proportion of patients who achieved improvement on the Clinical Global Impressions-Improvement (CGI-I) scale. The study met the primary efficacy endpoint, patients who received 0.7 mg/kg/day achieved a statistically significant median difference in drop seizure frequency of -19.9% (95% CI, -31 to -8.7, P=.001) compared to placebo. The study achieved statistically significant results in the secondary endpoint of 50% or greater reduction in drop seizure frequency, with 25% (P=.02) achieving greater than 50% reduction in the 0.7 mg/kg/day and 28% (P=.005) in the 0.2 mg/kg/day groups compared to 10% in placebo. Additionally, 26% (P=.001) of patients in 0.7 mg/kg/day group had a clinically meaningful improvement in CGI-I of much improved or very much improved compared to 20% in the 0.2 mg/kg/day group and 6% in placebo.

- The American Epilepsy Society guidelines for Lennox-Gastaut syndrome, recommend use of lamotrigine, topiramate, felbamate with clobazam, and rufinamide as add-on therapy, they do not make recommendations for sequential therapy. The NICE guidelines for LGS recommend use of valproate as well as lamotrigine, cannabidiol (Epidiolex), clobazam, rufinamide, topiramate, and felbamate (though not licensed for use in the UK).
- Based on the established safety, efficacy, and cost effectiveness of valproate, lamotrigine, rufinamide**,** clobazam, felbamate, topiramate, and cannabidiol (Epidiolex) relative to fenfluramine (Fintepla), trial of two generic agents and cannabidiol (Epidiolex) is required before approval of fenfluramine (Fintepla).

VI. Fenfluramine (Fintepla) is a Schedule IV controlled substance that is only available through a restricted program called the Fintepla REMS. Fenfluramine (Fintepla) carries a black-box warning for valvular heart disease (VHD) and pulmonary arterial hypertension (PAH). Echocardiogram assessments are required before, during, and after treatment with fenfluramine (Fintepla).

Investigational or Not Medically Necessary Uses

I. Fenfluramine (Fintepla) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Epileptic encephalopathies associated with SCN1A mutations
   B. Seizure disorders other than Dravet syndrome and Lennox-Gastaut syndrome

Appendix

I. Table 1: fenfluramine (Fintepla) Recommended Titration Schedule

	Without concomitant stiripentol		**With concomitant stiripentol and clobazam**	
	Weight-based Dosage	**Maximum Total Daily Dosage**	**Weight-based Dosage**	**Maximum Total Daily Dosage**

Initial Dosage	0.1 mg/kg twice daily	26 mg	0.1 mg/kg twice daily	17 mg
Day 7	0.2 mg/kg twice daily	26 mg	0.15 mg/kg twice daily	17 mg
Day 14	0.35 mg/kg twice daily	26 mg	0.2 mg/kg twice daily	17 mg

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
cannabidiol (Epidiolex)	Lennox-Gastaut syndrome Dravet syndrome Tuberous Sclerosis Complex

stiripentol (Diacomit)	Dravet syndrome
vigabatrin (Sabril, Vigadrone)	Refractory complex partial epileptic seizure, adjunct therapy West syndrome (infantile spasms)

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication (Lennox-Gastaut syndrome), added weight-based dosing to QL for Dravet syndrome, updated initial and renewal evaluation criteria (Dravet syndrome), updated supporting evidence, added related policies table.	08/2022
Policy created	11/2020

Policy Type: PA Pharmacy Coverage Policy: UMP185

Description
Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®) is an opioid agonist FDA approved for the treatment of breakthrough cancer pain in those who are tolerant to, or already receiving, constant opioid treatment for continual cancer pain.

Length of Authorization
- Initial: Up to 12 months
- Renewal: Up to 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
fentanyl citrate (Abstral)	100 mcg sublingual tablet	Chronic pain associated with cancer	120 tablets/30 days
	200 mcg sublingual tablet		120 tablets/30 days
	300 mcg sublingual tablet		120 tablets/30 days
	400 mcg sublingual tablet		120 tablets/30 days
	600 mcg sublingual tablet		120 tablets/30 days
	800 mcg sublingual tablet		120 tablets/30 days
fentanyl citrate (Actiq)	200 mcg lozenge handle	Chronic pain associated with cancer	120 lozenges/30 days
	400 mcg lozenge handle		120 lozenges/30 days
	600 mcg lozenge handle		120 lozenges/30 days
	800 mcg lozenge handle		120 lozenges/30 days
	1200 mcg lozenge handle		120 lozenges/30 days
	1600 mcg lozenge handle		120 lozenges/30 days
fentanyl citrate (Fentora)	100 mcg buccal tablet	Chronic pain associated with cancer	120 tablets/30 days
	200 mcg buccal tablet		120 tablets/30 days
	400 mcg buccal tablet		120 tablets/30 days
	600 mcg buccal tablet		120 tablets/30 days
	800 mcg buccal tablet		120 tablets/30 days
fentanyl citrate (Lazanda)	100 mcg nasal spray	Chronic pain associated with cancer	15 bottles/30 days
	400 mcg nasal spray		15 bottles/30 days
fentanyl citrate (Subsys)	100 mcg sublingual spray	Chronic pain associated with cancer	4 cartons/30 days
	200 mcg sublingual spray		4 cartons/30 days
	400 mcg sublingual spray		4 cartons/30 days
	600 mcg sublingual spray		4 cartons/30 days
	800 mcg sublingual spray		4 cartons/30 days
	1200 mcg sublingual spray		4 cartons/30 days
	1600 mcg sublingual spray		4 cartons/30 days
fentanyl citrate (fentanyl citrate)	200 mcg lozenge handle	Chronic pain associated with cancer	120 lozenges/30 days
	400 mcg lozenge handle		120 lozenges/30 days
	600 mcg lozenge handle		120 lozenges/30 days

	800 mcg lozenge handle		120 lozenges/30 days
	1200 mcg lozenge handle		120 lozenges/30 days
	1600 mcg lozenge handle		120 lozenges/30 days

Initial Evaluation

I. Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, fentanyl citrate) may be considered medically necessary when the following criteria are met:
   A. Member has a diagnosis of **chronic pain associated with cancer**; **AND**
   B. Member is enrolled into the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) program**; AND**
   C. Member is 18 years of age or older; **OR**
      1. If request is for fentanyl citrate (Actiq), member is 16 years of age or older; **AND**
   D. Medication is prescribed by, or in consultation with, an oncologist or pain specialist; **AND**
   E. Member is opioid tolerant; **AND**
   F. Member is currently experiencing breakthrough cancer pain, for which fentanyl citrate is being prescribed to treat; **AND**
   G. The provider has recorded baseline and ongoing assessments of measurable, objective pain scores and function scores. These should be tracked serially in order to demonstrate clinically meaningful improvements in pain and function; **AND**
   H. The patient has been screened for mental health disorders, substance use disorder, naloxone use; **AND**
   I. The provider has checked the Prescription Drug Monitoring Program (PDMP) for any other opioid use and concurrent use of benzodiazepines and other sedatives

II. Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, fentanyl citrate) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Non-tolerant opioid members
   B. Any indication that is not for treatment of breakthrough pain in patients experiencing chronic pain associated with cancer

Renewal Evaluation

I. See initial evaluation section.

Supporting Evidence

I. Based off clinical trials, there is currently no evidence to support the use of fentanyl citrate (Abstral®, Fentora®, Lazanda®, Subsys®) in any age group below 18 years of age, with the exception of fentanyl citrate (Actiq®, fentanyl citrate) which was studied in those aged 16 years and older.

II. Due to the FDA indication, Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS), and strict dosing guidelines, these agents are not to be prescribed without the consultation or direct supervision of a pain specialist or oncologist.
III. All fentanyl citrate products, and the parties involved in their use (i.e., outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors) are required to be enrolled into the TIRF REMS program, in accordance with FDA guidelines.
IV. The policy aligns with recommendations of the Centers for Disease Control, the Washington State Agency Medical Directors Group, and the Bree Collaborative around safe and appropriate opioid prescribing.
V. This policy is in full compliance with UMP's regulations and mandates regarding the chronic use of opioids.
VI. This policy applies to all groups under UMP, including Public Employees Benefit Board (PEBB) and School Employees Benefits Board (SEBB).

Investigational or Not Medically Necessary Uses

I. Fentanyl citrate (Abstral) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraines dental pain, or use in the emergency department
II. Fentanyl citrate (Actiq)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraines and dental pain
III. Fentanyl citrate (Fentora)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain, including headache/migraine and dental pain
IV. fentanyl citrate (Lazanda)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraine and dental pain, or in emergency department
V. fentanyl citrate (Subsys)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraine and dental pain, or in emergency department

Appendix

I. Table 1: Product dosing schedule and conversion from lozenge (Actiq) to other formulation

Product Name	Titration Dosing Schedule
fentanyl citrate (Abstral)	**Start:** 100mcg, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half

	hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Please see chart below for conversion when switching from Actiq to Abstral*	
	200mcg	2x 100mcg, *or* 1x 200mg tab
	300mcg	3x 100mcg, *or* 1x 300mg tab
	400mcg	4x 100mcg, *or* 2x 200mcg, *or* 1x 400mg tab
	600mcg	3x 200mcg, *or* 1x 600mg tab
	800 mcg	4x 200mcg, *or* 1x 800mg tab
Initial Dosing Recommendations for Patients on ACTIQ		
Current ACTIQ Dose (mcg)		**Initial Abstral Dose (mcg)**
200		100 mcg
400		200 mcg
600		200 mcg
800		200 mcg
1200		200 mcg
1600		400 mcg
Product Name		**Titration Dosing Schedule**
fentanyl citrate (Actiq)	**Start:** 200mcg taken over 15 minutes, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 200mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Note: No more than six units is allowed to be dispensed at one time until maintenance dose is found.*	
	400 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	600 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	800 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	1200 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	1600 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
Product Name		**Titration Dosing Schedule**

fentanyl citrate (Fentora)	**Start:** 100mcg, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Please see chart below for conversion when switching from Actiq to Fentora.*	
	200 mcg buccal tablet 2x 100mcg, *or*	1x 200mg tab
	400 mcg buccal tablet	4x 100mcg, *or* 2x 200mg tab, *or* *1x 400mg tab*
	600 mcg buccal tablet	3x 200mcg, *or* 1x 600mg tab
	800 mcg buccal tablet	4x 200mcg, *or* 1x 800mg tab
Initial Dosing Recommendations for Patients on ACTIQ		
Current ACTIQ Dose (mcg)		**Initial Fentora Dose (mcg)**
200		100 mcg
400		100 mcg
600		200 mcg
800		200 mcg
1200		2x 200 mcg
1600		2x 200 mcg
For patients converting from ACTIQ doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg FENTORA tablet and should proceed using multiples of this tablet strength		
Product Name		**Titration Dosing Schedule**
fentanyl citrate (Lazanda)	**Start:** 100mcg (one spray in each nostril) if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Due to differences in pharmacokinetic properties and individual variability, do not switch patients on a mcg per mcg basis from any other fentanyl product to Lazanda as Lazanda is not equivalent with any other fentanyl product, nor is Lazanda a generic version of any other fentanyl product.*	
	200 mcg nasal spray *Note: Only comes in a 100mcg and 400mcg bottle, these strengths are achieved by intervals of 100mcg or 400mcg*	2 x 100 mcg spray (1 in each nostril)
	400 mcg nasal spray	1 x 400 mcg
	800 mcg nasal spray *Note: Only comes in a 100mcg and 400mcg bottle, these strengths are achieved by intervals of 100mcg or 400mcg*	2 x 400mcg (1 in each nostril)
Product Name		**Titration Dosing Schedule**

fentanyl citrate (Subsys)	**Start:** 100mcg, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Please see chart below for conversion when switching from Actiq to Subsys.*	
	100 mcg sublingual spray	1 × 100 mcg unit
	200 mcg sublingual spray	1 × 200 mcg unit
	400 mcg sublingual spray	1 × 400 mcg unit
	600 mcg sublingual spray	1 × 600 mcg unit
	800 mcg sublingual spray	1 × 800 mcg unit
	1200 mcg sublingual spray	2 × 600 mcg unit
	1600 mcg sublingual spray	2 × 800 mcg unit

Initial Dosing Recommendations for Patients on ACTIQ	
Current ACTIQ Dose (mcg)	**Initial Subsys Dose (mcg)**
200	100 mcg
400	100 mcg
600	200 mcg
800	200 mcg
1200	400 mcg
1600	400 mcg

a. For patients converting from Actiq doses 400 mcg and below, titration should be initiated with 100 mcg SUBSYS and should proceed using multiples of this strength.
b. For patients converting from Actiq doses of 600 and 800 mcg, titration should be initiated with 200 mcg SUBSYS and should proceed using multiples of this strength.
c. For patients converting from Actiq doses of 1200 and 1600 mcg, titration should be initiated with 400 mcg SUBSYS and should proceed using multiples of this strength

Product Name	**Titration Dosing Schedule**	
fentanyl citrate (fentanyl citrate)	**Start:** 200mcg taken over 15 minutes, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 200mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Note: No more than six units is allowed to be dispensed at one time until maintenance dose is found.*	
	200 mcg lozenge handle	1 × 200 mcg unit
	400 mcg lozenge handle	1 × 400 mcg unit
	600 mcg lozenge handle	1 × 600 mcg unit
	800 mcg lozenge handle	1 × 800 mcg unit
	1200 mcg lozenge handle	1 × 1200 mcg unit
	1600 mcg lozenge handle	2 × 1600 mcg unit

References

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5. Subsys® [Prescribing Information]. Chandler, AZ: Insys Therapeutics, Inc. October 2019.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Removed attestation criteria following UMP guidance, as cancer is exempt diagnosis for the attestation requirement. Per UMP guidance, left in baseline and ongoing pain assessments, mental health and substance abuse screening, and provider check of Prescription Drug Monitoring Program (PDMP) for any other opioid use and concurrent use of benzodiazepines and other sedatives.	06/2020
Converted to policy, added in REMS question, age limitation question, and clarified prescribing provider specialty needed for approval.	04/2020
Previous reviews	11/15/13, 12/28/17
Criteria created	12/2011

Policy Type: PA/SP Pharmacy Coverage Policy: UMP204

Description

Fostemsavir (Rukobia) is an orally administered gp120 attachment inhibitor.

Length of Authorization

I. Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
fostemsavir (Rukobia)	600 mg extended-release tablets	Human immunodeficiency virus type 1 (HIV-1) infection	60 tablets/30 days

Initial Evaluation

I. Fostemsavir (Rukobia) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an infectious disease or HIV specialist; **AND**
   C. Provider attestation that fostemsavir (Rukobia) will be used in combination with at least one other antiretroviral medication; **AND**
   D. Member has a diagnosis of **human immunodeficiency virus type 1 (HIV-1) infection** when all of the following are met:
      1. Provider attests the member is heavily treatment-experienced as indicated by treatment failure, contraindication, intolerance, and/or resistance to medications in three or more classes of HIV therapies; **AND**
      2. Provider attests the member has two or less remaining medications that are fully active and available to construct a viable treatment regimen; **AND**
      3. The member is failing their current treatment regimen, as defined by HIV-1 RNA viral load greater than, or equal to, (≥) 200 copies/mL; **AND**
      4. The member does not have concurrent untreated hepatitis B infection.

II. Fostemsavir (Rukobia) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of disease response to treatment defined by improvement or stability of disease symptoms [e.g., decreased HIV-1 RNA, increased CD4 cell count from baseline].

Supporting Evidence

I. Fostemsavir (Rukobia) has not been studied in randomized controlled trials in pediatric patients <18 years of age.
II. In the pivotal Phase 3 trial (BRIGHTE), subjects were given fostemsavir (Rukobia) in combination with other antiretroviral(s). Per the National Institute for Health recommendations, HIV-1 infections should never be treated with monotherapy. Fostemsavir (Rukobia) is not approved as monotherapy and must be used in combination with other antiretroviral(s).
III. In the BRIGHTE trial, subjects were included if they had documented resistance, contraindication, or intolerance to three or more antiretroviral classes and had two or less fully active and available antiretroviral agents in two or fewer classes of which a treatment regimen could be constructed. Fostemsavir (Rukobia) is only approved for use in heavily treatment-experienced individuals.
IV. The primary efficacy endpoint in the BRIGHTE trial was the adjusted mean $\log_{10}$ change in HIV-1 RNA from baseline after Day 8 which was -0.17 in the placebo group and -0.79 in the fostemsavir (Rukobia) group (difference: -0.625; 95% CI: -0.810, -0.441; p<0.0001). Increase in CD4 count was found to be clinically significant after 96 weeks. The mean increase was 204.7 c/mm3 and 119.1 for randomized and non-randomized cohorts, respectively. Patients with the lowest CD4 counts at baseline (<20 c/mm3) showed the largest increase by week 96 with a mean of 239.8 c/mm3, a clinically meaningful improvement.
V. In clinical trials HIV-1 RNA suppression was seen after Day 8, thus the initial authorization of three months ensures that there is adequate time to respond to treatment and that the therapy remains safe and effective.
VI. The National Institute for Health defines virologic failure as the inability to maintain suppression of HIV RNA <200 copies/mL and persistent viral loads at this level are often indicative of the viral evolution and drug-resistance mutations.
VII. Subjects with chronic, untreated hepatitis B (HBV) co-infection were excluded from the BRIGHTE trial. Elevations in hepatic transaminases were more commonly observed in subjects with HBV co-infection and consistent with HBV reactivation, particularly when anti-hepatitis therapy was discontinued.

Investigational or Not Medically Necessary Uses

I. Fostemsavir (Rukobia) has not been sufficiently studied for safety and efficacy for any other condition to date.

References

1. Rukobia [Prescribing Information]. Research Triangle Park, NC: ViiV Healthcare. July 2020.
2. NIH AIDSInfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV (2019)
3. Rukobia (fostemsavir) Integrated Review. FDA. 2020
4. Fostemsavir in adults with multi-drug resistant HIV-1 infection (BRIGHTE). *N Engl J Med*. 2020 Mar 26;382(13):1232-1243. (NCT 02362503)

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of HIV-specialist to criterion 1B, addition of establishing therapy through a different health plan in the renewal criteria, removal of requirement for HIV resistance assessment from renewal criteria as response to treatment is already being assessed via decrease HIV RNA, addition of supporting evidence V.	03/2021
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP290

Split Fill Management*

Description

Fruquintinib (Fruzaqla) is a selective vascular endothelial growth factor (VEGF) receptor kinase inhibitor.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
fruquintinib (Fruzaqla)	Metastatic colorectal cancer (mCRC)	1 mg cap	84 caps/28 days
		5 mg cap	21 caps/28 days

Initial Evaluation

I. **Fruquintinib (Fruzaqla)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Medication is not used in combination with any other oncology therapy; **AND**
   D. A diagnosis of **metastatic colorectal cancer (mCRC)**; **AND**
      1. The member has been previously treated with a fluoropyrimidine (e.g., fluorouracil, capecitabine, etc.), oxaliplatin, and irinotecan-based chemotherapy; **AND**
      2. The member has been previously treated with an anti-VEGF therapy (e.g. bevacizumab, Zaltrap, Cyramza, etc.); **AND**
      3. Treatment with trifluridine-tipiracil (Lonsurf) has been ineffective, contraindicated, or not tolerated; **AND**
      4. The tumor has been tested and is documented to be RAS mutant-type; **OR**
         i. The tumor has been tested and is documented to be RAS wild-type; **AND**
            a. The tumor is a right-sided tumor; **OR**
            b. The tumor is a left-sided tumor; **AND**
               i. The member has been previously treated with an anti-EGFR therapy (e.g., cetuximab, panitumumab)

II. **Fruquintinib (Fruzaqla)** is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:

A. Fruquintinib (Fruzaqla) used in combination with another oncology therapy
B. Gastroesophageal junction adenocarcinoma
C. Breast cancer
D. Non-small cell lung cancer (NSCLC)
E. Soft tissue sarcoma
F. Advanced pancreatic cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Clinical documentation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
IV. Medication is not used in combination with any other oncology therapy

Supporting Evidence

I. Colorectal cancer (CRC) is the third most prevalent cancer worldwide and the second most common cause of cancer death in the United States. Initial clinical presentation as mCRC occurs in approximately 20% of patients and nearly 70% of patients with localized disease eventually develop metastases. In 2023, approximately 150,000 individuals will be diagnosed with CRC and over 50,000 individuals will die from the disease. Given the complexity of management of mCRC, the treatment of mCRC must be initiated by, in or consultation with, an oncologist.
II. CRC originates from the epithelial tissue of the colon, and it may develop either on the right side or left side of the colon. Therapeutic responses, disease progression, and overall survival vary depending on the position of the tumor. The difference between left and right tumors can be attributed to anatomical and developmental origin, or distinct carcinogenic factors (such as difference in bacterial population) or a combination of both. Multiple retrospective analyses (CRYSTAL, FIRE-3, and Canadian NCIC CO.17 trial) found that left-sided CRC has a better prognosis and responds better to anti-EGFR therapy compared to right-sided CRC. Studies have demonstrated that anti-EGFR therapies improved the overall survival in patients with left-sided KRAS wild type tumors, but not in patients with right-sided wild type tumors.
    - Right-sided tumors occur in the ascending colon, and proximal two thirds of the transverse colon and mutations in the DNA mismatch repair pathway are commonly observed. These tumors generally have a flat histology and are harder to diagnose, which may result in more advanced and larger tumors at diagnosis. Right-sided CRC patients do not respond well to anti-EGFR therapy. Microsatellite DNA mismatch repair pathway (MSI or dMMR) may be an important prognostic factor to consider when deciding whether to use adjuvant chemotherapy in patients with stage II disease.
    - Left-sided tumors occur in the descending and sigmoid colon, and distal one third of the transverse colon and chromosomal instability pathway-related mutations, such as KRAS, APC, PIK3CA, p53 mutations, are more commonly observed. These tumors generally have polypoid-like morphology, which makes them easier to diagnose in

early stages of carcinogenesis. Up to 85% of CRC are left-sided tumors. Left-sided CRC patients benefit more from targeted therapies such as anti- epidermal growth factor receptor (EGFR) therapy, due to the pathway-related mutation.

III. Fruquintinib (Fruzaqla) is the fifth FDA-approved anti-VEGF agent indicated for treatment of mCRC. Fruquintinib (Fruzaqla) is the first and only selective inhibitor of all three VEGF receptor kinases for previously treated mCRC regardless of biomarker status. It is FDA-approved for the treatment of metastatic colorectal cancer (mCRC) previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, anti-VEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. Fruquintinib (Fruzaqla) is an oral capsule given once daily for 21 days out of a 28-day cycle.

IV. The National Comprehensive Cancer Network (NCCN) guidelines recommend fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy with or without bevacizumab as first and second line therapy, with immune checkpoint inhibitors, anti-epidermal growth factor receptor (EGFR) agents if RAS wildtype, and anti-VEGF therapy. NCCN guidelines recommend fruquintinib (Fruzaqla) as a third line treatment (category 2A) for mCRC, joining trifluridine-tipiracil (Lonsurf) ± bevacizumab and regorafenib (Stivagra) as category 2A recommended agents. NCCN guidelines recommend anti-EGFR therapy prior to fruquintinib (Fruzaqla) in mCRC, RAS wild type, left-sided tumors.
    - NCCN guidelines remain silent on the best sequence of therapy in the third- and fourth-line setting. The FRESCO-2 trial permitted previous treatment with trifluridine-tipiracil (Lonsurf) prior to randomization, and 91% of participants received prior trifluridine-tipiracil (Lonsurf) therapy. As the majority of participants had prior trifluridine-tipiracil (Lonsurf) therapy, requiring step through trifluridine-tipiracil (Lonsurf) is both clinically appropriate and cost-effective.

V. Fruquintinib (Fruzaqla) was studied in a Phase 3, international, multicenter, randomized (2:1), double-blinded, placebo-controlled study (FRESCO-2) in 691 patients with mCRC who had received all current standard approved cytotoxic and targeted therapies [fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, anti-VEGF therapy, and anti- EGFR therapy (if RAS wild type)] and progressed on, or were intolerant to, trifluridine-tipiracil and/or regorafenib. Participants were randomized to receive fruquintinib (Fruzaqla) 5mg daily in addition to best supportive care (BSC) or placebo with BSC. Baseline characteristics were similar between both groups: median age 64 years, 63% of patients had RAS mutation, median number of previous therapies was four (96% of patients received previous anti-VEGF therapy and all participants received trifluridine-tipiracil (Lonsurf) and/or regorafenib (Stivara). The median OS was 7.4 months for the fruquintinib-treated group compared to 4.8 months for the placebo group, HR 0.66 (95% CI 0·55–0·80; p<0·0001).

VI. Fruquintinib (Fruzaqla) was also studied in a randomized, double-blinded, placebo-controlled, multicenter, Phase 3 clinical trial completed in China (FRESCO). A total of 416 participants aged 18-75 years with mCRC that progressed after 2 lines of chemotherapy were randomized in a 2:1 ratio to receive either fruquintinib (Fruzaqla) 5mg daily plus best supportive care or placebo with best supportive care. Median overall survival was significantly prolonged with fruquintinib (Fruzaqla) compared with placebo (9.3 months [95% CI, 8.2-10.5] vs 6.6 months [95% CI, 5.9-8.1]); HR 0.65 (95% CI, 0.51-0.83; P<0.001). However, at the time of the study, standard treatment practices for metastatic colorectal cancer in China were not the same as the standard treatment practices in the United States. Only one-third of the patients had received previous anti-VEGF therapy, and none had received trifluridine–tipiracil or regorafenib.

VII. The safety profile of fruquintinib (Fruzaqla) is similar to that of other FDA-approved anti-VEGF agents indicated for mCRC. Adverse events did occur more frequently in the fruquintinib

(Fruzaqla) group compared to placebo. The most common adverse events were hypertension (37% vs 9%), asthenia (34% vs 23%), and hand-foot syndrome (19% vs 3%). A total of 93 (20%) patients who received fruquintinib (Fruzaqla) and 49 (21%) who received placebo discontinued treatment due to adverse events (asthenia and gastrointestinal perforation, proteinuria, and elevated LFTs).

VIII. The use of fruquintinib (Fruzaqla) has not been studied in combination with other oncology therapies, and due to lack of safety and efficacy data with a combination regimen, these agents should not be used together.

Investigational or Not Medically Necessary Uses

I. Fruquintinib (Fruzaqla) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Fruquintinib (Fruzaqla) used in combination with another oncology therapy. Fruquintinib (Fruzaqla) was studied as monotherapy in the FRESCO and FRESCO-2 trials.
   B. Gastroesophageal junction adenocarcinoma
      i. Fruquintinib plus paclitaxel demonstrated improvements in progression-free survival, objective response rate, disease control rate, and more, in patients with advanced gastric or gastroesophageal junction adenocarcinoma in a Phase 3 FRUTIGA study. Results are to be shared with the China National Medical Products Administration.
   C. Breast cancer
      i. There is an ongoing open-label study evaluating fruquintinib in HER2- breast cancer (NCT03251378)
   D. NSCLC
      i. There was a withdrawn trial evaluating fruquintinib in NSCLC
   E. Soft tissue sarcoma
      i. There is a recruiting trial evaluating fruquintinib in chemotherapy resistant soft tissue sarcoma in China (NCT05142631)
   F. Advanced pancreatic cancer – Phase 2 trial evaluating fruquintinib in advanced pancreatic cancer in China

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Dasari A, Lonardi S, Garcia-Carbonero R, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. Lancet. 2023;402(10395):41-53.
2. Li J, Qin S, Xu RH, et al. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. JAMA. 2018;319(24):2486-2496.

3. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (Versions 4.2023 – Nov 16, 2023). 2023 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on December 1, 2023.
4. Fruzaqla (fruquintinib) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals; November 2023.
5. UpToDate, Inc. Systemic therapy for nonoperable metastatic colorectal cancer: Approach to later lines of systemic therapy. UpToDate [database online]. Waltham, MA. Last updated October 19, 2023. Available at: http://www.uptodate.com/home/index.html.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
regorafenib (Stivara®) Policy	Gastrointestinal stromal tumor, metastatic colorectal cancer, hepatocellular carcinoma
trifluridine/tipiracil (Lonsurf®) Policy	Stomach or esophagogastric adenocarcinoma, metastatic colorectal cancer
encorafenib (Braftovi®), binimetinib (Mektovi®) Policy	Malignant melanoma (BRAF V600E mutation), metastatic colorectal cancer with BRAF V600E mutation

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2024

Policy Type: PA/SP Pharmacy Coverage Policy: UMP266

Split Fill Management*

Description

Futibatinib (Lytgobi) is an orally administered selective inhibitor of fibroblast growth factor receptor 1-4 (FGFR) and targets tumors harboring an FGFR2 fusion or other rearrangements.

Length of Authorization

- N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
futibatinib (Lytgobi)	Intrahepatic cholangiocarcinoma, advanced or metastatic, with FGFR2 fusion or rearrangement	12 mg dose pack (84 tablets of 4 mg)	84/28
		16 mg dose pack (112 tablets of 4 mg)	112/28
		20 mg dose pack (140 tablets of 4 mg)	140/28

Initial Evaluation

I. Futibatinib (Lytgobi)is considered investigational when used for all conditions, including but not limited to Intrahepatic cholangiocarcinoma (iCCA).

Renewal Evaluation

I. N/A

Supporting Evidence

I. Futibatinib (Lytgobi) is a selective inhibitor of fibroblast growth factor receptor 1-4 (FGFR), FDA-approved for adult patients with previously treated, unresectable, locally advanced, or metastatic intrahepatic cholangiocarcinoma (iCCA) harboring an FGFR2 fusion or other rearrangements. Futibatinib (Lytgobi) is a once-daily orally administered tablet.

II. Futibaitinib (Lytgobi) is the third FGFR2 inhibitor and joins infigratinib (Truseltiq) and pemigatinib (Pemazyre), which are indicated for previously treated patients with advanced or metastatic CCA. It should be noted that as of March 2023, infigratinib (Truseltiq) is scheduled to be withdrawn from the US market.

III. The FDA approval for futibatinib (Lytgobi) is limited only to the treatment of iCCA. On the other hand, pemigatinib (Pemazyre) carris a broader FDA-approved indication for the treatment of CCA (iCCA and eCCA). National Comprehensive Cancer Network (NCCN) guidelines have included Futibaitinib (Lytgobi) alongside pemigatinib (Pemazyre) and infigratinib (Truseltiq) as a subsequent-line therapy, useful in CCA with FGFR2 mutations (Category 2A).

IV. Futibaitinib (Lytgobi) was studied in an ongoing open-label, single-arm, multi-cohort phase 1/ 2 trial (N= 103). Patients with unresectable, advanced, or metastatic iCCA, who had received at least one prior platinum-based systemic therapy were administered futibatinib (Lytgobi) for a median of 9.1 months. At median follow-up, an objective response rate (ORR) of 41.7% (95% CI, 32, 52) was reported, with all participants reporting a partial response (PR). Additionally, a median PFS of 8.9 months and median OS of 20 months were observed.

V. Futibaitinib (Lytgobi) was FDA-approved under the accelerated approval pathway. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

VI. The quality of evidence is considered low due to single-arm, open-label study design with unknown impact on clinically meaningful outcomes such as morbidity, mortality, health-related quality-of-life, or symptom improvement in treated patients. OS remains an exploratory outcome due to the observational study design and requires confirmation in a subsequent clinical trial. Additionally, the efficacy of futibatinib (Lytgobi) in comparison with, as well as after progression on pemigatinib (Pemazyre) remains unknown.

VII. Most CCA patients present with advanced-stage or unresectable tumors at diagnosis, wherein platinum-based chemotherapy (cisplatin with gemcitabine and/ or durvalumab (Imfinzi)) remains the standard of care. For patients, who progress on the first-line therapy, FOLFOX is the preferred subsequent-line option, along with 5-fluorouracil (5-FU), capecitabine, and paclitaxel as alternatives. Targeted therapies may be considered as subsequent-line options based on the presence of amenable mutations (e.g., entrectinib (Rozlytrek) and larotrectinib (Vitrakvi) for CCA with NTRK gene fusions).

VIII. Currently, there are other clinical trials (Phase 1b / 2) ongoing for futibatinib (Lytgobi) in the settings of metastatic breast cancer, cholangiocarcinoma, endometrial cancer, urothelial cancer etc. as a monotherapy as well as in combination with other agents (e.g., binimitinib, pembrolizumab). These clinical trials are in early phases and as of January 2023, data is not available for review.

IX. Single-arm, open-label clinical trial may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, Overall Response Rate (ORR), despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. ORR is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.

X. Targeted therapies in oncology have garnered interest in recent years and may be considered part of a paradigm shift in the management of CCA based on histology and actionable driver mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Acquired resistance to current molecularly targeted therapies presents a major clinical challenge. Additionally, the targeted therapy approach is also susceptible to failure due to escape mutations. To date, the clinical data for FGFR2 inhibitors do not support robust conclusions regarding their safety, efficacy, and long-term impact on disease outcomes.

XI. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines note that the best management for any patient with cancer is in a clinical trial setting, and participation in a trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading healthcare facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced iCCA. Despite the accelerated FDA approval, continued approval of futibatinib (Lytgobi) as a subsequent-line treatment of iCCA, remains contingent upon verification of clinical benefit in confirmatory trials.

Investigational or Not Medically Necessary Uses

I. Futibatinib (Lytgobi) has not been sufficiently studied for safety and efficacy for any condition to date.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Goyal L, Meric-Bernstam F, Hollebeque A, et al. Updated results of the FOENIX-CCA2 trial: Efficacy and safety of futibatinib in intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions/rearrangements. J Clin Oncol 2022;40: Abstract 4009.
2. Meric-Bernstam F, Bahleda R, Hierro C, Sanson M, Bridgewater J, Arkenau HT, Tran B, Kelley RK, Park JO, Javle M, He Y, Benhadji KA, Goyal L. Futibatinib, an Irreversible FGFR1-4 Inhibitor, in Patients with Advanced Solid Tumors Harboring *FGF*/*FGFR* Aberrations: A Phase I Dose-Expansion Study. Cancer Discov. 2022 Feb;12(2):402-415. doi: 10.1158/2159-8290.CD-21-0697. Epub 2021 Sep 22. PMID: 34551969.
3. Lytgobi. Package insert. Taiho Pharmaceutical Co. Ltd; September 2022.
4. National Comprehensive Cancer Network. Hepatobiliary Cancers (Version 3.2022). NCCN. October 14, 2022. Accessed November 7, 2022. hepatobiliary.pdf (nccn.org)

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
pemigatinib (Pemazyre)	Previously treated, unresectable, locally advanced, or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2023

Policy Type: PA Pharmacy Coverage Policy: UMP197

Description
Gabapentin ER (Gralise) is an orally administered anticonvulsant. Gabapentin enacarbil (Horizant) is a prodrug of gabapentin.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
gabapentin ER (Gralise)	300 mg tablets	Postherpetic neuralgia	60 tablets/30 days
	450 mg tablets		
	600 mg tablets		
	750 mg tablets		
	900 mg tablets		
	300 mg-600mg tablets Blister/Starter Pack		33 tablets (1 pack)/30 days
generic gabapentin ER	300 mg capsules	Postherpetic neuralgia	60 capsules/30 days
	600 mg capsules		
gabapentin enacarbil (Horizant)	300 mg tablets	Postherpetic neuralgia; Restless leg syndrome	30 tablets/30 days
	600 mg tablets		60 tablets/30 days

Initial Evaluation

I. **Gabapentin ER (Gralise) or gabapentin enacarbil (Horizant)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. A diagnosis of one of the following:
      1. **Postherpetic neuralgia (PHN); AND**
         i. Treatment with gabapentin, greater than or equal to, 1800 mg per day has been ineffective, contraindicated, or not tolerated; **AND**
         ii. Treatment with pregabalin has been ineffective, contraindicated, or not tolerated; **AND**
         iii. If the request is for brand gabapentin ER (Gralise) 300mg or 600mg, treatment with generic gabapentin ER 300mg or 600mg has been ineffective, not tolerated, or contraindicated; **OR**
            a. Request is for 450mg, 750mg, 900mg, or 300mg-600mg starter pack; **OR**

2. **Moderate-to-severe primary restless leg syndrome**; **AND**
    i. Request is for gabapentin enacarbil (Horizant); **AND**
    ii. Treatment with **all** of the following has been ineffective, contraindicated, or not tolerated:
        a. pramipexole; **AND**
        b. ropinirole; **AND**
        c. pregabalin

II. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) are considered investigational when used for all other conditions, including but not limited to:
    A. Diabetic peripheral neuropathy
    B. Postmastectomy pain syndrome
    C. Seizures
    D. Other neuropathic pain

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of one of the following:
    A. Restless Leg Syndrome (RLS); **AND**
        1. Member has exhibited improvement or stability of restless leg syndrome symptoms [e.g., improved pain, sleep, fatigue]; **OR**
    B. Postherpetic neuralgia (PHN); **AND**
        1. Member has exhibited improvement or stability of symptoms [e.g. improved pain, skin sensitivity].

Supporting Evidence

I. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for safety and efficacy in pediatric patients under the age of 18 years.
II. A phase 3, placebo-controlled, randomized trial has shown gabapentin ER (Gralise) to be efficacious in decreasing pain associated with postherpetic neuralgia over placebo (p=0.013). Phase 4 studies have similarly suggested effectiveness in pain reduction in patients with postherpetic neuralgia.
III. A phase 3, placebo-controlled, randomized trial has shown gabapentin enacarbil (Horizant) to be efficacious in reducing pain associated with postherpetic neuralgia over placebo (p=0.013) after 13 weeks.
IV. Guidelines for postherpetic neuralgia recommend immediate release gabapentin as a first line treatment option. It is recommended patients trial gabapentin IR before switching to an extended-release gabapentin product such as gabapentin ER (Gralise) or gabapentin enacarbil (Horizant).

V. Standard of care for treatment of postherpetic neuralgia includes use of pregabalin as first line therapy.

VI. A phase 4, placebo-controlled randomized trial found gabapentin enacarbil (Horizant) to improve restless leg syndrome symptoms on patient reported scales (IRLS) over placebo (p=0.014) as well as clinician-assessed (CGI-I) scales (p=0.004) after 12 weeks of treatment.

VII. Restless leg syndrome guidelines, as published by the American Academy of Neurology (AAN), recommend dopamine agonists (e.g. pramipexole, ropinirole, rotigotine) and gabapentin enacarbil (Horizant) as first line treatment options. A small (n=39) double-blind, placebo-controlled trial investigated a possible reduced response to gabapentin enacarbil (Horizant) following long-term dopaminergic treatment. A significant difference (p=0.045) in restless leg syndrome symptoms (IRLS) was found between dopamine treatment-naïve and dopamine treatment-experienced individuals when treated with gabapentin enacarbil (Horizant). Patients who were dopamine-experienced had been treated with a dopamine agonist for at least 90% of the past 5 consecutive years. Although gabapentin enacarbil (Horizant) is recommend as a first-line therapy along with dopamine agonists, due to the small sample size, as well as the unknown effects of shorter-term uses of dopamine agonists on gabapentin enacarbil (Horizant) responses, enacarbil (Horizant) should not be chosen as a first-line agent over a dopamine agonist.

VIII. Restless leg syndrome guidelines as published by the American Academy of Neurology (AAN) also lists pregabalin as having moderate evidence for use in treatment of RLS aligned with ropinirole, a dopamine agonist.

Investigational or Not Medically Necessary Uses

I. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   - A. Diabetic peripheral neuropathy
     - i. A placebo-controlled, randomized trial found no significant difference in efficacy from placebo and three different doses of gabapentin enacarbil (Horizant) in subjects with diabetic peripheral neuropathy.
   - B. Postmastectomy pain syndrome
     - i. A small (n=21) open-label study found a small positive improvement in pain intensity after 8 weeks with gabapentin ER (Gralise). Further placebo-controlled, randomized trials are needed to validate efficacy and safety for this indication.
   - C. Seizures
     - i. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for efficacy and safety in the treatment of seizures.
   - D. Other neuropathic pain
     - i. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for efficacy and safety in the treatment of neuropathic pain not associated with postherpetic neuralgia or restless leg syndrome.

References

1. Gralise [Prescribing Information]. Menlo Park, CA: Depomed. September 2012.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Added new 300mg and 600mg gabapentin ER to the QL table; Added step through generic gabapentin ER before use of Gralise when using the 300mg or 600mg tablets/capsules	01/2024
Added new 450mg, 750mg, 900mg once-daily tab Gralise strengths to the QL table	05/2023
Update to new policy format, addition of pregabalin as required agent to try and fail, removal of renal status related criteria	10/2020
Previous review	11/2011

Policy Type: PA/SP Pharmacy Coverage Policy: UMP260

Description

Ganaxolone (Ztalmy) is an orally administered neuroactive steroid gamma-aminobutyric acid A ($GABA_A$) receptor positive modulator.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
ganaxolone (Ztalmy)	Seizures associated with CDKL5 Deficiency Disorder (CDD)	50 mg/mL oral suspension	≤ 28 kg: Monthly quantity (in mL) to allow for a maximum of 63 mg/kg per day
			> 28 kg: Monthly quantity (in mL) to allow for a maximum of 1800 mg (36 mL) per day

Initial Evaluation

I. **Ganaxolone (Ztalmy)** may be considered medically necessary when the following criteria are met:
   A. Member is two years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. Documentation of the member's weight, measured in the past three months (necessary for dose calculation); **AND**
   D. Will be used in combination with one or more antiseizure medications (e.g., clobazam [Onfi], valproate [Depakote], levetiracetam [Keppra], etc.); **AND**
   E. A diagnosis of **cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)** as evidenced by all of the following:
      1. Documentation of pathogenic or likely pathogenic CDKL5 mutation; **AND**
      2. Provider attestation that seizure onset occurred by one year of age; **AND**
      3. Provider attestation that member has motor and cognitive delays; **AND**
      4. Documentation of baseline seizure frequency and severity**; AND**
      5. Seizures are refractory to three or more antiseizure medications (e.g., clobazam [Onfi], valproate [Depakote], lamotrigine [Lamictal], levetiracetam [Keppra], rufinamide [Banzel], topiramate [Topamax], felbamate [Felbatol], stiripentol [Diacomit], zonisamide [Zonergan], vigabatrin [Sabril]).

II. Ganaxolone (Ztalmy) is considered investigational when used for all other conditions, including but not limited to:
   A. Infantile Spasms or West Syndrome
   B. Rett Syndrome
   C. Lennox-Gastaut Syndrome, Dravet Syndrome, Tuberous Sclerosis Complex
   D. Other non-FDA approved seizure disorders

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of the member's weight that has been measured in the past three months (necessary for dose calculation); **AND**
IV. Ganaxolone (Ztalmy) will continue to be used in combination with one or more antiseizure medications; **AND**
V. Member has exhibited improvement or stability of seizure frequency or severity.

Supporting Evidence

I. Length of authorization for initial approval is six months as clinical benefits of ganaxolone (Ztalmy) were evaluated at 17 weeks in the pivotal trial. Six months is sufficient for assessment of treatment response and to initiate medication renewal request.
II. Ganaxolone (Ztalmy) is FDA-approved for use in patients two years of age and older. Safety and efficacy of ganaxolone (Ztalmy) in younger patients has not been evaluated. Other antiseizure medications have been evaluated for safety and efficacy in as early as infancy.
III. Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare genetic disorder caused by a mutation in the CDKL5 gene, which is responsible for normal brain development and function, that results in severe developmental delay, intellectual disability, and seizures. CDD presents as early as three months after birth, primarily in the form of frequent, refractory spasms and seizures of various types. Additionally, motor and cognitive dysfunction become more prevalent over time, including behavioral dysregulation, movement disorders, hypotonia, visual impairment, sleep abnormalities, and gastrointestinal problems. CDKL5 gene mutations have also been identified in patients with infantile spasms, Rett, West and Lennox Gastaut Syndrome, autism and intractable epilepsy. However, CDD is a distinct disease characterized by symptoms of motor/cognitive delays and epilepsy with various seizure types within the first year of life. Given significant overlap with other types of developmental encephalopathies, treatment-resistant epilepsy, and movement disorders, diagnosis of CDD is made through presence of a pathogenic or likely pathogenic variant in the CDKL5 gene, presence of motor/cognitive delays, and onset of epilepsy within the first year of life.

IV. Given the specialized, high-touch care and monitoring required for CDD patients, ganaxolone (Ztalmy) must be prescribed by, or in consultation with, a neurologist.

V. There are no formal guidelines for management of CDD. Additionally, there are no currently available disease-modifying therapies for CDD, therefore treatment is supportive. Common treatment strategies for CDD-associated seizures include ketogenic diet, vagus nerve stimulator (VNS) placement, pharmacologic therapy with antiseizure medications, ACTH, or steroids, and neurosurgery. Experts recommend first-line therapy with a broad-spectrum antiseizure medication (e.g., valproate, levetiracetam, clobazam, zonisamide), and proceed with second trial or combination therapy as appropriate; VNS and neurosurgery are reserved for drug-resistant seizure. Seizure in CDD is known to be medically refractory, therefore it is common for CDD patients to have tried and continue to take multiple antiseizure medications concurrently. While ganaxolone (Ztalmy) is the only FDA-approved therapy for treatment of CDD-associated seizures, patients in the clinical program were required to be refractory to two or more antiseizure medications, the majority did not achieve clinically meaningful seizure reduction, and comparative efficacy to other antiseizure medications is unknown. Therefore, given the known extent of efficacy, established safety profile, and cost effectiveness of other antiseizure medications, at least three adequate efficacy trials are required prior to ganaxolone. Considering an abundance of available antiseizure medications, intolerance and early discontinuation do not meet definition of adequate efficacy trial.

VI. Ganaxolone (Ztalmy) was studied in one 17-week international, randomized, double-blind, placebo-controlled Phase 3 study: MARIGOLD. A total of 101 patients aged 2-21 years with molecularly confirmed CDD and a history of early-onset seizures uncontrolled by two or more antiseizure medications were enrolled. Use of up to four concomitant antiseizure medications during the study was allowed if stable on dose for at least one month, while patients being treated with glucocorticoids or ACTH were excluded. Population characteristics were as follows: 79% female, median age six years, median seven previous antiseizure medication trials, median two concomitant antiseizure medications including valproic acid, levetiracetam, clobazam and vigabatrin. The primary endpoint was percent change in median 28-day major motor seizure frequency (MMSF), with a 30.7% reduction in the ganaxolone group compared to a 6.9% reduction in the placebo group (P=0.0036). Secondary endpoints included proportion of patients with ≥ 50% reduction in 28-day MMSF, otherwise known as clinically meaningful reduction in seizure frequency, and quality of life as assessed through the Clinical Global Impression of Improvement (CGI-I) score by clinician and caregiver, none of which were met. Most common adverse events were somnolence, pyrexia, and upper respiratory tract infection; ganaxolone (Ztalmy) is a controlled substance due to abuse and dependence potential and has a warning for somnolence/sedation. Overall, the benefit of ganaxolone (Ztalmy) is modest and potential confounding background therapy limits application and usefulness in the intended population.

VII. During clinical trials, participants received ganaxolone (Ztalmy) as an adjunct to antiseizure therapy, with the majority taking a median of two concomitant antiseizure medications. Background seizure medications included, but were not limited to, valproate, levetiracetam, clobazam, vigabatrin, clonazepam, topiramate, zonisamide, rufinamide, lamotrigine, oxcarbazepine, etc. Only one patient in the ganaxolone group was taking ganaxolone as monotherapy. As such, efficacy and safety of ganaxolone as monotherapy remain unknown.

Investigational or Not Medically Necessary Uses

I. Ganaxolone (Ztalmy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Infantile Spasms or West Syndrome
   B. Rett Syndrome
   C. Lennox-Gastaut Syndrome, Dravet Syndrome, Tuberous Sclerosis Complex
   D. Other non-FDA approved seizure disorders

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
cannabidiol (Epidiolex®) Policy	Lennox-Gastaut Syndrome
	Dravet Syndrome
	Tuberous Sclerosis Complex
vigabatrin (Sabril®, Vigadrone®) Policy	West Syndrome (Infantile Spasms)
	Refractory complex partial epileptic seizure, adjunct therapy
stiripentol (Diacomit®) Policy	Dravet Syndrome
fenfluramine (Fintepla®) Policy	Dravet Syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP294

Description

Gepirone ER (Exxua) is an orally administered selective serotonin 1A (5HT1A) receptor agonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
gepirone ER (Exxua)	Major depressive disorder (MDD)	18.2 mg tablets	30 tablets/30 days
		36.3 mg tablets	
		54.5 mg tablets	
		72.6 mg tablets	

Initial Evaluation

I. **Gepirone ER (Exxua)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. A diagnosis of **major depressive disorder (MDD)** when the following are met:
      1. Treatment with at least <u>two</u> medications in each of the following drug classes has been ineffective, contraindicated, or not tolerated:
         i. Selective serotonin reuptake inhibitors [SSRIs] (e.g., citalopram, fluoxetine, paroxetine, sertraline)
         ii. Serotonin-norepinephrine reuptake inhibitors [SNRIs] (e.g., desvenlafaxine succinate, duloxetine, venlafaxine)
         iii. Atypical antidepressants (e.g., bupropion, mirtazapine, vilazodone); **AND**
      2. Treatment with vortioxetine (Trintellix)* has been ineffective, contraindicated, or not tolerated. (<u>Please note:</u> medications notated with an asterisk may require step therapy or non-formulary requirements prior to approval)

II. Geprione ER (Exxua) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Generalized anxiety disorder (GAD)
   B. Substance use disorder
   C. Other psychiatric conditions

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g., reduced HAMD-17 score, reduced suicidal thoughts/ideation, no ED or inpatient admissions]

Supporting Evidence

I. The FDA-approval of gepirone ER (Exxua) was based on two randomized, double-blind, placebo-controlled trials in a total of 457 adult patients with moderate to severe MDD. The primary efficacy outcome was change from baseline (CFB) in Hamilton Depression Rating Scale (HAMD-17) total score at week 8. Key secondary endpoints included CFB in Montgomery-Asberg Depression Rating Scale (MADRS), and Clinical Global Impression-Severity (CGI-S) scale. All primary and key secondary outcomes were met and considered statistically significant. However, the numerical difference of CFB in the HAMD-17 score between gepirone ER (Exxua) and placebo did not meet the threshold for a clinically meaningful benefit (difference of 4 to 6 points) in either pivotal trial.

	Study 1 [134001]		Study 2 [FKGBE007]	
	Gepirone ER (N=101)	Placebo (N=103)	Gepirone ER (N=116)	Placebo (N=122)
CFB in HAMD-17 score	-9.77	-7.43	-10.2	-8.0
p-value	*P = 0.18*		*P=0.032*	
CFB MADRS	-12.28	-9.22	-13.7	-9.9
p-value	*P = 0.024*		*P=0.008*	
CFB CGI-S	-1.28	-0.88	-1.3	-0.09
p-value	*P = 0.016*		*P=0.015*	

II. Gepirone ER (Exxua) has been studied across numerous clinical trials over the past 30 years, with multiple attempts at gaining FDA approval dating back to the 1990s, and three failed attempts to secure approval prior to the successful submission in 2023.
III. Looking at the totality of evidence, there were 12 short-term trials conducted in the 1990s and early 2000s that have previously been included in FDA submission for approval; only two trials are considered positive, three uninformative, and seven negative. The four active-controlled trials did not detect a statistically significant change compared to placebo or active control for either the pre-specified endpoint or the ad-hoc primary analysis for HAMD-17 conducted by the FDA for comparison purposes. Interestingly, a statistically significant difference was detected in favor of the active control compared to gepirone ER (Exxua) in the ad-hoc analysis. Regardless of the active control result in the ad-hoc analysis, gepirone ER (Exxua) failed to meet the primary endpoint in both analyses compared to placebo and active control. Therefore, these trials are considered failed and negatively impact the quality of evidence. Therefore, the quality of evidence is considered low as there are multiple well-designed trials with mixed results in the efficacy of gepirone ER (Exxua).

IV. Although the results of the two pivotal trials showed a statistically significant change from baseline in HAMD-17 scores, this did not correlate to a clinically meaningful change compared to placebo. Due to a lack of clinically meaningful impact on depressive symptoms compared to placebo, in addition to multiple failed clinical trials with an active control, the value of gepirone ER (Exxua) as compared to standard of care antidepressant therapy remains unknown at this time and will be realized in real-world settings.

V. The majority of adverse events reported during the clinical program were considered mild or moderate in severity. The most reported adverse events during clinical trials for gepirone ER (Exxua) versus placebo, respectively, included dizziness (49% vs. 10%), nausea (35% vs. 13%), headache (31% vs. 20%), sleepiness (15% vs. 14%), and insomnia (14% vs. 5%). Gepirone ER (Exxua) carries labeled contraindications for prolonged QTc interval or long QT syndrome, hepatic impairment, and combination use with MAOIs and strong CYP3A4 inhibitors. Gepirone ER (Exxua) also carries a black box warning for increased risk of suicidal thoughts and behaviors, especially in the pediatric and young adult populations.

VI. Notably, sexual side effects were not widely reported during the clinical trial period. Therefore, gepirone ER (Exxua) may be seen as a favorable treatment option for patients who have experienced sexual side effects with a previous antidepressant. Although gepirone ER (Exxua) may have a lower incidence of sexual side effects associated with its use, bypassing treatment alternatives due to potential side effects is not considered a viable clinical rationale.

VII. For the treatment of MDD, American Psychiatric Association (APA) recommends either psychotherapy or a second-generation antidepressant (i.e., SSRI, SNRI, bupropion) for first-line therapy, switching to another antidepressant medication for second-line therapy, and augmentation with another antidepressant medication or adding psychotherapy for third-line therapy. Alternatively, augmentation with an antipsychotic may also be considered in the third line and subsequent therapy. Treatment effectiveness with generic antidepressants has been established by clinical trials and substantiated by real-world use. Therefore, the use of multiple generic antidepressants and lower cost branded antidepressants remains a reasonable approach to therapy and prioritizes use of high-value therapeutic options.

Investigational or Not Medically Necessary Uses

I. Gepirone ER (Exxua) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Generalized anxiety disorder (GAD)
   B. Substance use disorder
   C. Other psychiatric conditions

Appendix

I. Generic antidepressants by class

Selective Serotonin Reuptake Inhibitors (SSRIs)	Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)	Atypical Antidepressants
Citalopram	Desvenlafaxine succinate	Bupropion (IR/SR/XL)
Escitalopram	Duloxetine	Mirtazapine
Fluoxetine	Venlafaxine (IR/ER)	Trazodone
Fluvoxamine (IR/ER)		Vilazodone

Paroxetine (IR/CR)		
Sertraline		

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2. Center for Drug Evaluation and Research. Application Number 021164Orig1s000 Multi-Discipline Review. Multidisciplinary Review and Evaluation: NDA 021164. Updated September 22, 2023. Available At: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/021164Orig1s000MultidisciplineR.pdf
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Related Policies

Policy Name	Disease state
esketamine (Spravato™) Policy	Treatment resistant depression (TRD) and Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2024

Policy Type: PA/SP Pharmacy Coverage Policy: UMP032

Split Fill Management*

Description

Gilteritinib (Xospata) is an orally administered FLT3 Tyrosine Kinase Inhibitor.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
gilteritinib (Xospata)	Relapse/Refractory FLT3-mutated Acute Myeloid Leukemia (AML)	40 mg tablets	90 tablets/30 days

Initial Evaluation

I. **Gilteritinib (Xospata)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. A diagnosis of **relapsed/refractory FLT3-mutated acute myeloid leukemia** and all of the following are met:
      1. The disease is classified as relapsed/refractory AML **AND**
      2. Will not be used in combination with any other oncolytic medication; **AND**
      3. FLT3 mutation status has been detected by an FDA-approved test (e.g., LeukoStrat CDx FLT3 mutation Assay by Invivoscribe Technologies,Inc.)

II. Gilteritinib (Xospata) is considered investigational when used for all other conditions, including but not limited to:
   A. Gilteritinib (Xospata) as monotherapy or in combination (e.g., azacitidine) for newly diagnosed AML
   B. AML in the absence of FLT3 mutation
   C. AML in combination with other therapies in the relapsed/refractory setting

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off of being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., no signs of disease progression, no signs of unacceptable toxicity); **AND**
IV. Gilteritinib (Xospata) will not be used in combination with any other oncolytic medication

Supporting Evidence

I. The ADMIRAL trial only included adult patients and gilteritinib is only approved for treatment in adult patients who have relapsed or refractory AML with FLT3 mutations. The safety and efficacy of gilteritinib in the pediatric population has not been established, and clinical trials including pediatric patients are still ongoing at this time. Given the lack of safety and efficacy data in this patient population, use of gilteritinib is restricted to adults 18 years and older.
II. Many treatment options exist for AML. Initial and further line therapies in this setting are contingent upon patient specific characteristics, disease-risk, and cytogenetic stratification. Given the complexities involved with the diagnosis and management of AML, treatment with gilteritinib must be initiated and/or supervised by an oncologist or hematologist.
III. Gilteritinib (Xospata) was studied in a phase III, randomized controlled trial, which included 138 adult patients with relapse or refractory FMS-like tyrosine kinase 3 gene (FLT3) mutated AML against salvage chemotherapy (i.e., had not reached CR following treatment). The efficacy of XOSPATA was established on the basis of the rate of complete remission (CR)/CR with partial hematological recovery (CRh), the duration of CR/CRh (DOR), and the rate of conversion from transfusion dependence to transfusion independence at the first interim analysis in the ADMIRAL trial (n=138). The final analysis of the ADMIRAL included 371 adult patients randomized 2:1 to receive gilteritinib 120mg daily or a prespecified chemotherapy regimen. Overall survival data were included in the final analysis, measured from the data of randomization until death by any cause. Patients randomized to the XOSPATA arm had significantly longer survival compared to the chemotherapy arm (HR 0.64; 95% CI: 0.49 – 0.83; 1-sided p-value: 0.0004), with median OS of 9.3 months vs 5.6 months for chemotherapy.
IV. Compared to salvage chemotherapy, gilteritinib had higher incidence of any, grade ≥3 adverse events, and serious adverse events for reported adverse events. Common adverse events of grade 3 or higher in the gilteritinib group were febrile neutropenia (45.9% vs 36.7%), anemia (40.7% vs 30.3%), and thrombocytopenia (22.8% vs 16.5%) for gilteritinib compared to salvage chemotherapy. In the Gilteritinib arm, 30.9% of patients experienced febrile neutropenia deemed as a serious adverse event, compared to 8.3% for chemotherapy. Due to the high incidence of any and serious adverse events, split fill management is required.
V. There were 251 deaths in the safety population of 355 patients, including 170 deaths among 246 patients (69.1%) in the gilteritinib group and 81 deaths among 109 patients (74.3%) in the chemotherapy group. In the intention-to-treat population, mortality at 30 days and at 60 days was 2.0% and 7.7%, respectively, in the gilteritinib group and 10.2% and 19.0%, respectively, in the chemotherapy group.
VI. Subjects included were adults with confirmed FLT3-mutated AML as detected by an FDA-approved test, (e.g., LeukoStrat® CDx *FLT3* Mutation Assay). Use of gilteritinib (Xospata) in

assigned subjects was as monotherapy only. Currently, there are no literature available on safety and efficacy outside of this setting.

VII. The NCCN guidelines for the treatment of AML was updated in March 2023, which recommends gilteritinib monotherapy for relapsed/refractor disease with FLT3 mutation at a category 1 recommendation. For patients that are not a candidate for intensive induction therapy with FLT3 mutated AML, gilterinib + azacitidine combination treatment is the only category 2B therapy, with other monotherapy and combination therapy regimens receiving category 2A recommendations (e.g., LDAC + ventoclax, or azacitidine monotherapy, decitabine monotherapy, sorafenib monotherapy, or azacitidine/decitabine + sorafenib). In the post allogeneic HCT, AML in remission with history of FLT3-ITD mutation setting, sorafenib is recommended (category 2A), while gilterinib (category 2B) due to a lack of safety and efficacy data supporting the use of gilteritinib in this setting.

Investigational or Not Medically Necessary Uses

I. Newly diagnosed AML
   A. There is lack of evidence for the use of gilteritinib (Xospata) as monotherapy in patients with newly diagnosed AML. The LACEWING Trial, a phase III, randomized, open-label study compared the efficacy and safety of gilteritinib with azacitidine against azacytidine alone in newly diagnosed AML patients with FLT3 mutation not eligible for intensive induction chemotherapy. The primary outcome was OS. At the interim analysis, the study failed to demonstrate a difference in median OS between the treatment arms for gilteritinib + azacitidine (9.82 months) versus azacitidine monotherapy (8.87 months) (HR, 0.916, 95% CI, 0.529-1.585; P=0.753), and the study was closed based on protocol-specified boundary for futility. The Median event-free survival was 0.03 months in both arms.

II. AML in the absence of FLT3 mutation
   A. Clinical trials have only evaluated gilteritinib (Xospata) in patients that have a confirmed FLT3 mutation by an FDA-approved test.

III. AML in combination with other therapies in the relapsed/refractory setting
   A. There is a lack of well-designed phase II/III clinical trials supporting the safety and efficacy of gilteritinib (Xospata) outside of the monotherapy in the relapsed/refractory setting. Clinical trials evaluating gilteritinib (Xospata) combination therapy are still ongoing. There is a Phase IB non-randomized, open label, single-arm trial accessing the safety and efficacy of venetoclax (Venclexta) in combination with gilteritinib (Xospata) in patients with R/R AML, however without a comparison arm to gilteritinib monotherapy, it is difficult to determine the safety and efficacy value of combination therapy versus monotherapy at this time.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side*

effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
midostaurin (Rydapt®)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with cytarabine/daunorubicin induction and cytarabine consolidation
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Unresectable Liver Carcinoma
	Advanced Renal Cell Carcinoma
	Locally Recurrent or Metastatic Progressive Thyroid Cancer
	Advanced Soft Tissue Sarcoma
	Recurrent, High-risk or Metastatic Endometrial Carcinoma
Quizartunib (Brand)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with 7+3 induction and cytarabine consolidation

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated supporting evidence, renewal criteria language and formatting.	06/2023
Previous Reviews	01/2019; 02/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP206

Split Fill Management*

Description

Glasdegib (Daurismo) is an orally administered hedgehog pathway inhibitor that inhibits Smoothened proteins involved in hedgehog signal transduction. As a result, glasdegib reduces the amount of CD25+/CD33+ blasts in the bone marrow.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
glasdegib (Daurismo)	Acute myeloid leukemia, newly diagnosed	25 mg tablets	60 tablets / 30 days
		100 mg tablets	30 tablets / 30 days

Initial Evaluation

I. **Glasdegib (Daurismo)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND**
   B. A diagnosis of newly diagnosed acute myeloid leukemia (AML); **AND**
      1. Member is 75 years or older; **OR**
      2. Provider attests that the member has comorbidities that preclude intensive induction chemotherapy (e.g., baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2 or greater, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, or creatine clearance <30 mL/min); **AND**
      3. Treatment will be used in combination with low-dose cytarabine (LDAC)

II. Glasdegib (Daurismo) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute Myeloid Leukemia – Previously treated
   B. Monotherapy use or used in combination with azacitidine or decitabine

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., became independent of red blood cell and platelet transfusion, or exhibited tumor response)

Supporting Evidence

I. Standard of care intensive induction chemotherapy for treatment of AML consists of a 7-day continuous infusion of cytarabine and daunorubicin and can induce complete response (CR) rates as high as ≥80% with a 5-year overall survival (OS) of ~40–50% in younger patients without adverse cytogenetic or molecular risk factors. Elderly or unfit patients tend to have poorer outcomes due to the inability to tolerate intensive therapy, deleterious genetic changes, comorbidities, or ineligibility for allogenic hematopoietic stem cell transplant.
II. Medical fitness is a key determinant of management of AML and influence the goals of care and choice of therapy. Determination of medical fitness is based on assessment of performance status using the Eastern Cooperative Oncology Group performance scale (ECOG PS) and physiological fitness (assessment of comorbid conditions, activities of daily living, cognition, etc. by the Charlson comorbidity index [CCI]). The ECOG PS ranges from 0-4, zero being fully active with no performance restrictions, and four being completely disabled, cannot carry out any self-care or totally confided to bed. The CCI predicts the ten-year mortality of a patient who has comorbid conditions. The maximum CCI score is 24 with three grades: 1-2 mild, 3-4 moderate, and ≥5 severe. Fitness categories fall into three groups: medically fit and able to tolerate intensive induction treatment for AML (ECOG PS 0-2 or CCI 0-2), medically unfit, but not frail and are unlikely to tolerate intensive antileukemic therapy (ECOG PS 3 or CCI 3), and frail, those whose comorbid conditions would not permit treatment (ECOG PS ≥3 or CCI ≥3).
III. Glasdegib (Daurismo) is FDA-approved, in combination with LDAC, for the treatment of newly diagnosed AML in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.
IV. Glasdegib (Daurismo) was studied in a multicenter, open-label, randomized study (BRIGHT AML 1003). Participants included were 55 years and older with newly diagnosed AML and met one of the following: at least 75 years old, severe cardiac disease, baseline ECOG PS of 2, or a baseline serum creatinine > 1.3 mg/dL. Participants were randomized 2:1 to receive glasdegib (Daurismo) 100mg daily with low-dose cytarabine 20mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle (N=77), or low-dose cytarabine alone (N=28) until disease progression or unacceptable toxicity. Both arms had similar baseline characteristics with a mean age of 76.5 years, mostly white male, and history of secondary AML (53%). The active arm had 41 participants (53%) and the cytarabine arm had 18 participants (47%) with ECOG PS score of 2. The study did not include patients with an ECOG PS of 3, severe renal, or hepatic impairment, all of which are comorbidities that would preclude use of intensive chemotherapy.

V. The primary endpoint was OS from the date of randomization to death from any cause with a mean follow-up of 20 months. The active arm had a median OS of 8.3 months (95% CI 4.4-12.2) and cytarabine arm 4.3 months (95% CI, 1.9-5.7), hazard ratio (HR) 0.46 (95% CI, 1.9-5.7), p=0.0002. The complete response rate (CR) in the active arm was 18.2% (95% CI, 10.3-28.6) and 2.6% (95% CI, 0.1-13.8) in the cytarabine group.

VI. Serious adverse events were reported in 79% of participants in the active arm with the most common adverse reactions being neutropenia (29%), pneumonia (23%), hemorrhage (12%), anemia (7%), and sepsis (7%). A total of 36% of participants receiving glasdegib (Daurismo) discontinued treatment due to pneumonia (6%), febrile neutropenia (4%), sepsis (4%), sudden death (2%), myocardial infarction (2%), nausea (2%), and renal insufficiency (2%).

VII. Glasdegib (Daurismo) has not been studied in patients with severe renal impairment or moderate-to-severe hepatic impairment. Glasdegib (Daurismo) can cause embryo-fetal death or severe birth defects when administered to a pregnant woman and is not recommended for use during pregnancy.

VIII. NCCN guidelines preferred hypomethylating agents (HMA) (e.g. azacitidine, decitabine) plus venetoclax for treatment of AML in patients who are not candidates for intensive induction therapy. Preferred treatment includes azacitidine plus venetoclax (category 1) and decitabine and venetoclax (category 2A). Phase III trials demonstrated that azacitidine and decitabine are associated with greater overall survival (OS) compared to conventional care regimens (LDAC, intensive induction chemotherapy, or best supportive care). Other recommended treatment options include LDAC plus venetoclax, azacitidine or decitabine monotherapy, glasdegib plus LDAC, and best supportive care (category 2A).

Investigational or Not Medically Necessary Uses

I. Acute Myeloid Leukemia – Previously treated
   A. Pivotal trials leading to FDA approval were specifically in the previously untreated setting. Use in the relapsed/refractory setting is not supported by clinical trials nor cited within NCCN AML guidelines.

II. Monotherapy use or used in combination with azacitidine or decitabine
   A. Monotherapy use or use in combination with azacitidine or decitabine is not supported within guidelines or clinical evidence. The clinical trial evaluating glasdegib and decitabine was terminated due to failure to accrue participants. BRIGHT AML 1012 (NCT02367456) was a multicenter open label phase 1b study that evaluated the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of glasdegib when combined with azacitidine in patients with previously untreated Higher Risk Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), or Chronic Myelomonocytic Leukemia (CMML). Overall response rates in the AML and MDS cohorts were 30.0% and 33.3%, respectively; 47.4% and 46.7% of patients who were transfusion dependent at baseline achieved independence. Median overall survival (95% confidence interval) was 9.2 (6.2-14.0) months and 15.8 (9.3-21.9) months.

therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
venetoclax (Venclexta®)	Newly diagnosed acute myeloid leukemia (AML)
IDH inhibitors	Relapsed or refractory Acute Myeloid Leukemia (AML), Newly diagnosed AML, locally advanced or metastatic cholangiocarcinoma
midostaurin (Rydapt)	Acute Myeloid Leukemia (AML) newly diagnosed with FLT3 mutation, Systemic mast cell disease
azacitidine (Onureg®)	Acute Myeloid Leukemia (AML), maintenance treatment after first complete remission

Policy Implementation/Update:

Action and Summary of Changes	Date
No clinical changes. Wording of comorbidities that may preclude newly diagnosed AML patients from intensive induction chemotherapy has been updated to improve flow and reduce misinterpretation. The supporting evidence has been updated to reflect current guideline recommendations and reflect pivotal trials. The reference section has been updated to include NCCN guidelines for AML and reflect changes.	06/2023
Policy created.	01/2019

Policy Type: PA Pharmacy Coverage Policy: UMP044

Description

Glycopyrronium (Qbrexza) is an anticholinergic that works to reduce sweating by inhibiting the action of acetylcholine on sweat glands.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
glycopyrronium (Qbrexza)	Topical 2.4% single-use pre-moistened cloth	Primary axillary hyperhidrosis	30 cloths/30 days	203316 203275

Initial Evaluation

I. Glycopyrronium (Qbrexza) may be considered medically necessary when the following criteria below are met:
   A. Member is nine years of age or older; **AND**
   B. The medication is prescribed by or in consultation with a dermatologist; **AND**
   C. Member has a confirmed diagnosis of primary axillary hyperhidrosis; **AND**
   D. Member has a history of medical complications such as skin infections or significant functional impairments due to condition; **OR**
   E. Member has a significant impact to activities of daily living due to condition; **AND**
   F. Member has tried and failed or have a contraindication to both of the following:
      1. Over-the-counter topical antiperspirant therapy (e.g. Drysol Solution, Hypercare Solution, or Aluminum Chloride Hexahydrate 20% Solution); **AND**
      2. Oral anticholinergics (e.g. oxybutynin tablet, glycopyrrolate tablet)

Renewal Evaluation

I. Member has experienced a reduction in spontaneous axillary sweat production; **AND**
II. Member has experienced an improvement in activities of daily living.

Supporting Evidence

I. Glycopyrronium (Qbrexza) is the first topical anticholinergic agent FDA-approved for treatment of axillary hyperhidrosis. The drug was studied in two, phase III, randomized, double-blind, vehicle controlled, parallel group trials, ATMOS-1 (N=344) and ATMOS-2 (N=353) evaluating daily glycopyrronium (Qbrexza) application to each axilla over 4 weeks. ASDD responder rate at week 4 was significantly greater for glycopyrronium (Qbrexza) versus vehicle in both trials.
    - ATMOS-1: 52.8% vs 28.3%; *P*=<0.001
    - ATMOS-2: 66.1% vs 26.9%; *P*=<0.001

II. Safety and efficacy of glycopyrronium (Qbrexza) has been established in patients older than nine years of age.

III. Glycopyrronium (Qbrexza) is FDA approved in the setting of primary hyperhidrosis. Secondary causes of hyperhidrosis should be ruled out. Patients with generalized, secondary hyperhidrosis usually present as adults and report sweating that occurs both while awake and sleeping. Medications should be carefully reviewed, as many can cause generalized sweating

IV. Topical antiperspirants offer a localized treatment approach with a favorable side effect profile compared to other therapies. Although glycopyrronium (Qbrexza) is a topical formulation, it carries a similar side effect profile to oral anticholinergics (e.g. oxybutynin).

References

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Policy Implementation/Update:

Date Created	October 2018
Date Effective	November 2018
Last Updated	September 2019
Last Reviewed	09/2019

Action and Summary of Changes	**Date**
Transition from criteria to policy	09/2019
Criteria created	10/2018

Policy Type: PA Pharmacy Coverage Policy: UMP021

Description

Elagolix and relugolix are oral gonadotropin-releasing hormone (GnRH) antagonists.

Length of Authorization

- Initial: Three months
- Renewal:
  i. Elagolix (Orilissa) 150 mg: Up to 12 months; maximum total (lifetime) fills should not exceed #24 30-day fills
  ii. Elagolix (Orilissa) 200 mg: Up to three months; maximum total (lifetime) fills should not exceed #6 30-day fills
  iii. Elagolix/estradiol/norethindrone acetate (Oriahnn) and relugolix/estradiol/norethindrone (Myfembree): Up to 12 months; maximum total (lifetime) fills should not exceed #24 28-day fills

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
elagolix (Orilissa)	Moderate to severe pain associated with endometriosis	150mg tablets	30 tablets/30 days
		200mg tablets	60 tablets/30 days
elagolix/estradiol/ norethindrone acetate (Oriahnn)	Treatment of heavy menstrual bleeding associated with uterine fibroids	300 mg/1 mg/0.5 mg tablets	56 tablets/28 days
relugolix/estradiol/ norethindrone (Myfembree)	Heavy menstrual bleeding associated with uterine fibroids (leiomyoma) Moderate to severe pain associated with endometriosis	40 mg/1 mg/0.5 mg tablets	28 tablets/28 days

Initial Evaluation

I. **Elagolix (Orilissa), elagolix/estradiol/norethindrone acetate (Oriahnn) and relugolix/estradiol/norethindrone (Myfembree)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an obstetrician/gynecologist; **AND**
   C. Member does **not** have history of osteoporosis (defined as a T-score less than or equal to -2.5 or Z-score less than -1.5 at the lumbar spine, femoral neck or total hip); **AND**

D. Provider attestation that the member has not previously been treated with a full course of a GnRH antagonist (i.e., Orilissa, Oriahnn, Myfembree); **AND**
E. A diagnosis of one of the following:
    1. **Moderate-to-severe pain associated with endometriosis; AND**
        i. Request is for elagolix (Orilissa) or relugolix/estradiol/norethindrone (Myfembree); **AND**
        ii. Treatment with one of the following has been ineffective, contraindicated, or not tolerated:
            a. Nonsteroidal anti-inflammatory drugs (NSAIDs); **OR**
            b. Hormonal contraceptives (oral, IUD, implant, etc.); **AND**
        iii. If the request is for elagolix (Orilissa) and continued use of estrogen containing contraceptives is planned in combination, the provider acknowledges that the efficacy of both the contraceptive and elagolix (Orilissa) may be decreased (use of non-hormonal contraceptives is recommended); **OR**
    2. **Heavy menstrual bleeding associated with uterine fibroids; AND**
        i. Request is for elagolix/estradiol/norethindrone acetate (Oriahnn) or relugolix/estradiol/norethindrone (Myfembree); **AND**
        ii. At least one hormonal contraceptive (oral, IUD, implant, etc.) has been ineffective, not tolerated, or ALL are contraindicated; **AND**
        iii. Treatment with tranexamic acid has been ineffective, not tolerated, or is contraindicated

II. Elagolix and/or relugolix is considered investigational when used for all other conditions, including but not limited to:
    A. Polycystic ovary syndrome
    B. Fertility treatment

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If so, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation that the member has not previously received treatment with a full course of a GnRH antagonist (i.e., Orilissa, Oriahnn, Myfembree); **AND**
IV. **Elagolix (Orilissa)**:
    A. Member has experienced a clinical improvement in pain symptoms relating to endometriosis; **AND**
        1. If the request is for elagolix (Orilissa) 150 mg; the member has not received treatment with elagolix (Orilissa) 150 mg for more than 24 months; **OR**

2. If the request is for elagolix (Orilissa) 200 mg**;** the member has not received treatment with elagolix (Orilissa) 200 mg for more than 6 months; **OR**

V. **Elagolix/estradiol/norethindrone acetate (Oriahnn)**:

B. Member has exhibited improvement in symptoms (reduction in menstrual blood loss, pain reduction, improved quality of life, etc.); **AND**

1. The member has not received treatment for more than 24 months

VI. Relugolix/estradiol/norethindrone (Myfembree):

C. Member has exhibited improvement in symptoms (reduction in menstrual blood loss, pain reduction, improved quality of life, etc.); **AND**

1. The member has not received treatment for more than 24 months

Supporting Evidence

I. Elagolix and Relugolix combination oral gonadotropin-releasing hormone (GnRH) antagonists have been evaluated in several clinical trials in adults. The safety and efficacy in pediatric patients have not been established and FDA approvals for these agents are limited to adult members.

II. Endometriosis and uterine fibroids are complex diseases and given the potential for long term side effects of GnRH antagonists, supervision of treatment/consultation by a gynecologist or obstetrician is required.

III. Clinical trials evaluating elagolix with or without estradiol/norethindrone excluded patients with a Z-score less than -1.5 at the lumbar spine, femoral neck, or total hip. Bone loss of more than 5% was seen in lumbar spine, total hip, and femoral neck within six months of treatment. Clinical trials evaluating relugolix/estardiol/norethindrone (Myfembree) excluded patients with Z-score less than -2.0 at the lumbar spine, femoral neck, or total hip. Bone loss of approximately 1% was seen in the lumbar spine within 6 months and consistent through 2 years of treatment. Bone loss studies have not yet been completed to evaluate elagolix (Orilissa) and elagolix/estradiol/norethindrone acetate (Oriahnn) in combination with bone loss prevention treatments.

IV. **Elagolix (Orilissa)** is an oral GnRH antagonist for the management of moderate to severe pain associated with endometriosis. The drug was studied in two randomized, double-blind, placebo-controlled, Phase 3, trials (Study EM-1 and Study EM-2; Elaris Endometriosis I and II).

- At three months, both elagolix (Orilissa) 150 mg and 200 mg regimens showed a higher proportion of responders compared to placebo. Both treatment arms showed statistically significant differences in greater mean decreases in non-menstrual pelvic pain scores from baseline at six months.
- The FDA-approved maximum duration of use for 150 mg tablets is 24 months, though clinical trials only studied up to 12 months. The FDA-approved maximum duration of use for 200 mg tablets is six months. These FDA maximum durations of treatment are recommended due to loss of bone marrow density as seen in clinical trials. Bone loss of more than 5% was seen in lumbar spine, total hip, and femoral neck within six months of treatment. Studies have not yet been completed to evaluate in combination with bone loss prevention treatments.
- Due to the mechanism of action, use of estrogen containing contraceptives are expected to reduce the efficacy of elagolix (Orilissa); likewise, use of elagolix (Orilissa) will reduce

efficacy of estrogen containing oral contraceptives. To avoid drug interactions, use of non-hormonal contraceptives during treatment with elagolix (Orilissa) is recommended.

V. For the treatment of heavy menstrual bleeding associated with uterine fibroids there is a lack of randomized trial data demonstrating the effectiveness of medical therapies. Treatment options include hormonal contraceptives (oral, IUD, implant, etc.), ulipristal acetate (Ella), mifepristone (Korlym, Mifeprex), GnRH agonists (leuprolide depot (Lupron), nafarelin acetate (Synarel), goserelin acetate (Zoladex), etc.), raloxifene (Evista), and danazol. GnRH agonists are an effective medical therapy but due to side effects are primarily used as preoperative therapy. Surgical treatment options are available, but often patients become incapable of reproduction.

VI. Uterine fibroids are commonly experienced by women that are premenopausal, and are associated with heavy menstrual bleeding, pain, and anemia. Management strategies for uterine fibroids include hysteroscopic fibroid resection, estrogen-progestin contraceptives, progestin-releasing intrauterine devices, progestin-only contraceptives, tranexamic acid, GnRH agonists (e.g., Lupron), GnRH antagonists (e.g., Oriahnn, Myfembree), uterine artery embolization, hysterectomy, and endometrial ablation.

VII. Treatment choice is dependent on fibroid size, patient age, fertility preference, symptoms, and other patient related factors. Hysterectomy is the only definitive cure, but myomectomy may be preferred for women with submucosal fibroids wishing to preserve the uterus. Medication therapy may be preferred for management to either prolong time to surgery or as preoperative treatment in preparation for surgery. Given the complex treatment choices and risks associated with each, therapy should be directed by or in consultation with a specialist.

VIII. The most common medication therapy utilized for the management of uterine fibroids includes estrogen-progestin contraceptives (e.g., pills, rings, patches) and progestin IUDs. These interventions do not change affect the pathology of the fibroids, but they are accepted as a standard management strategy to reduce the heavy menstrual bleeding. Tranexamic acid is a nonhormonal treatment that may be used during menstruation to reduce heavy bleeding.

IX. As the safety profiles often limit their use, GnRH agonists and antagonists are second-line medications. GnRH agonists (e.g., Lupron) are often used for a few months preoperatively to reduce fibroid size, or to bridge a patient into menopause. For GnRH antagonists, there are two products available: relugolix/estradiol/norethindrone (Myfembree), and elagolix/estradiol/norethindrone (Oriahnn). Acute tolerability is generally more favorable, but long-term safety and efficacy data are limited. Additionally, there is a known decrease in bone mineral density (BMD) which limits treatment duration. Furthermore, the safety of utilizing GnRH antagonists subsequently at their full FDA-approved duration is unknown, and would be expected to exacerbate the decrease in BMD.

X. For the treatment of pain associated with endometriosis there are no studies supporting one treatment, or treatment combination, over another. Treatment choice is based upon symptom severity, patient preferences, medication side effects, treatment efficacy, contraceptive needs, costs, and availability. Treatments commonly used first-line are NSAIDs and continuous hormonal contraceptives because these therapies are low-risk, have few side effects, and provide relief of symptoms for many women. Second-line treatments include GnRH agonists (leuprolide depot (Lupron), nafarelin acetate (Synarel), goserelin acetate (Zoladex), etc.), progestins, and danazol.

XI. **Elagolix/estradiol/norethindrone acetate (Oriahnn)** was evaluated in two six-month, randomized, double-blind, placebo-controlled, Phase 3 trials (Elaris UF-1 and Elaris UF-2) and one six-month, extension trial (Elaris UF-EXTEND). The primary efficacy outcome was the percentage of women who had menstrual blood loss (MBL) volume <80 mL during the final month and ≥ 50% reduction in MBL volume from baseline to the final month.

- In Elaris UF-1, the primary outcome was 68.5%, 84.1%, and 8.7% (p<0.001) for elagolix/estradiol/norethindrone acetate (Oriahnn) plus hormonal therapy, elagolix alone, and placebo, respectively. In Elaris UF-2, the primary outcome was 76.5%, 76.9%, 10.5% (p<0.001) for elagolix/estradiol/norethindrone acetate (Oriahnn), elagolix alone, and placebo, respectively. In Elaris UF-EXTEND, the primary outcome was 87.9% for elagolix/estradiol/norethindrone acetate (Oriahnn). The hormonal therapy that was used in combination with elagolix was estradiol/norethindrone (Activella, Amabelz, Combipatch, Lopreeza, Mimvey Lo, and Mimvey).
- The most common adverse events noted for elagolix/estradiol/norethindrone acetate (Oriahnn) were hot flashes, night sweats, nausea, and headache; however, elagolix/estradiol/norethindrone acetate (Oriahnn) had lower rates of hot flashes and night sweats compared to elagolix (Orilissa). Elagolix/estradiol/norethindrone acetate (Oriahnn) also had a reduced change from baseline in bone mineral density compared to elagolix (Orilissa). Elaris UF-1 had similar rates of discontinuation due to adverse events across all treatment arms; however, in Elaris UF-2, elagolix (Orilissa) had a discontinuation rate of 12.6% compared to 8.5% and 5.3% for elagolix/estradiol/norethindrone acetate (Oriahnn) and placebo, respectively. Elaris UF-EXTEND had lower rates of adverse events in the final six months compared to Elaris UF-1 and UF-2.
- The FDA has indicated that use of Oriahnn should be limited to 24 months due to the risk of continued bone loss with use, which may not be reversible.

XII. **Relugolix/estradiol/norethindrone (Myfembree)** was evaluated in the setting of heavy menstrual bleeding associated with uterine fibroids (leiomyoma) and moderate to severe pain associated with endometriosis.

- **Uterine Fibroids**: Relugolix/estradiol/norethindrone (Myfembree) was evaluated in two Phase 3, double-blind, randomized, placebo-controlled trials over 24 weeks (LIBERTY 1 and LIBERTY 2). Therapy was evaluated in premenopausal women with heavy menstrual bleeding and diagnosis of uterine fibroids, confirmed via ultrasonography. Patients with osteoporosis or osteopenia were excluded.
- Primary outcome: percentage of participants with treatment response (blood loss volume < 80 mL and ≥ 50% reduction in volume). Secondary outcomes: proportion of patients reaching amenorrhea, change in blood loss volume, pain, distress from bleeding and pelvic discomfort, and participants that had a change in hemoglobin of 2 g/dL or more in those that had anemia at baseline. These outcomes were statistically and clinically significant over placebo. In clinical trials, relugolix/estradiol/norethindrone (Myfembree) did not reduce uterine fibroid volume.
- Relugolix was also evaluated as monotherapy in a randomized, blinded, non-inferiority (NI) trial vs. leuprorelin (Lupron). Relugolix showed to be NI to leuprorelin (Lupron) in the following outcomes: blood loss, amenorrhea, uterine volume, fibroid volume,

hemoglobin improvement, pain, and quality of life. Estrogenic AE and decrease in BMD were notable; thus, the manufacturer is pursuing combination therapy with estradiol and norethindrone to mitigate these concerns. A limitation of the trial is the majority of patients received leuprorelin (Lupron) 1.88 mg, rather than the standard U.S. dose of 3.75 mg. Comparative safety and efficacy data to the 3.75 mg dose of leuprorelin (Lupron) is currently unknown.

- **Endometriosis:** Relugolix/estradiol/norethindrone (Myfembree) was evaluated in two replicate, phase 3, randomized, double-blind, placebo-controlled trial over 24 weeks (SPIRIT 1 and SPIRIT 2). Therapy was evaluated in pre-menopausal women aged 18 – 50 years with moderate to very severe dysmenorrhea and non-menstrual pelvic pain associated with endometriosis. Patients were excluded from the trial if they had a history of Z-score consistent with osteoporosis or osteopenia.
- The co-primary outcomes were the proportion of responders based on dysmenorrhea NRS score and non-menstrual pelvic pain (NMPP) NRS score at the end of treatment. In both trials, relugolix/estradiol/norethindrone (Myfembree) demonstrated a statistically significant benefit in dysmenorrhea and NMPP compared to placebo. In SPIRIT 1, 75% of patients in the relugolix-CT group and 27% of patients in the placebo group were considered dysmenorrhea responders (95% CI 39.3-56.0; p<0.0001) while 59% of patients in the relugolix-CT group and 40% of patients in the placebo group were considered NMPP responders (95% CI 9.5-28.2; p<0.0001). In SPIRIT 2, 75% of patients in the relugolix-CT group and 30% of patients in the placebo group were considered dysmenorrhea responders (95% CI 36.2-53.5; p<0.0001) while 66% of patients in the relugolix-CT group and 43% of patients in the placebo group were considered NMPP responders (95% CI 14.0-32.8; p<0.0001).
- An extension trial (SPIRIT LTE) was conducted to assess the long-term efficacy and safety of relugolix with estradiol/norethindrone (relugolix-CT) for the treatment of moderate to severe pain associated with endometriosis up to 104 weeks. Participants were required to have completed 24 weeks of participation in either SPIRIT 1 or SPIRIT 2; all eligible patients were assigned to receive relugolix-CT during the 80-week, open-label treatment period. SPIRIT LTE used the same co-primary endpoints as the SPIRIT 1 and SPIRIT 2 trials. For the co-primary endpoint of dysmenorrhea responders, at the end of 104 weeks of treatment, 84.8% and 83.0% of patients in the relugolix-CT and delayed relugolix-CT groups, respectively were considered dysmenorrhea responders; at the end of 80 weeks of treatment, 80.4% of patients who initially received placebo were considered dysmenorrhea responders. For the co-primary endpoint of NMPP responders, 75.8% of patients in the relugolix-CT group and 71.7% of patients in the delayed relugolix-CT group were considered NMPP responders; in patients initially treated with placebo, 73.1% were considered NMPP responders at week 52. No new safety signals were identified during the long-term extension period.

XIII. In both the LIBERTY and SPIRIT trials, rate of overall AEs was consistent for placebo and active therapy. No deaths occurred in the trials and serious AEs were rare. In the LIBERTY trials, there were a few cases of ankle fracture in those that received relugolix/estradiol/norethindrone (Myfembree). At week 24 the BMD at lumbar spine and total hip were similar between groups. AE leading to treatment discontinuation occurred in 4-11% of patients. Common AE included the

following: hot flash (6-11% vs. 4-8% for placebo) and hypertension (5% vs. 0% for placebo). Other AEs that occurred in ≥ 5% of patients included headache, arthralgia, cough, nausea, URI, nasopharyngitis, fatigue, and anemia. Long term safety is currently unknown but will be better understood with results from long-term safety extension trials. The FDA has indicated that use of Myfembree should be limited to 24 months due to the risk of continued bone loss with use, which may not be reversible.

XIV. Elagolix (Orilissa), elagolix/estradiol/norethindrone acetate (Oriahnn), and relugolix/estradiol/norethindrone (Myfembree) are contraindicated in pregnant patients due to an increased risk of early pregnancy loss.

Investigational or Not Medically Necessary Uses

I. Elagolix and/or relugolix has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Polycystic ovary syndrome
   B. Fertility treatment

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
relugolix (Orgovyx™)	Prostate cancer
Gonadotropin-releasing hormone (GnRH)	Endometriosis, Central Precocious Puberty (CPP), Advanced Prostate Cancer, Uterine leiomyoma (fibroids), Advanced breast cancer in premenopausal women, Reduction of endometrial thickness prior to endometrial ablation, Gender Dysphoria

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria updated to include Myfembree for the indication uterine fibroids and moderate to severe pain with endometriosis; Changed policy name to 'GnRH Antagonists in Gynecologic Conditions'.	11/2022
Criteria updated to require specialist prescriber, removal of check on pregnancy status and menopausal status, and addition of assessment for prior use of GnRH antagonist relugolix. Supporting evidence updated, and format of policy updated to follow new standards. Experimental and investigational section added.	05/2021
Removed criteria: "Must be used in combination with an estradiol/norethindrone acetate product (Activella, Combipatch, Mimvey Lo, etc.)" from the indication heavy menstrual bleeding associated with uterine fibroids	12/2020
Added criteria for treatment of heavy menstrual bleeding associated with uterine fibroids, added requirements for premenopause and confirmation member is not pregnant. Also added NSAIDS as an option for trial and failure for pain associated with endometriosis.	12/2019
Transition from criteria to policy	09/2019
Criteria created	10/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP092

Description
The listed treatments are synthetic gonadotropin-releasing hormone (GnRHs) analogs that exhibit a potent reversible inhibition of gonadotropin secretion through suppression of testicular and ovarian steroidogenesis.

Length of Authorization and Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit	Duration of approval
nafarelin (Synarel)	Endometriosis	2 mg/mL nasal spray	16 mL/30 days	6 months
	Central Precocious Puberty		40 mL/30 days	6 months
leuprolide acetate (Lupron)	Central Precocious Puberty	1 mg/0.2mL kit	1 kit/14 days	6 months
Leuprolide acetate (Lupron Depot)	Endometriosis, Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	3.75 mg/syringe kit	1 syringe kit/30 days	6 months for all indications EXCEPT - 3 months for uterine leiomyoma -2 months for Endometrial Thickness
	Advanced Prostate Cancer, Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Advanced Prostate Cancer, Advanced Breast Endometrial Thickness, Uterine leiomyoma, Central Precocious Puberty, Gender Dysphoria	11.25 mg/syringe kit	1 syringe kit/90 days	6 months for all indications EXCEPT - 3 months for Uterine Leiomyoma -2 months for Endometrial Thickness
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	6 months
	Advanced Prostate, Cancer Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/120 days	6 months

	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	6 months
Leuprolide acetate (Lupron Depot-Ped)	Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	11.25 mg/syringe kit	1 syringe kit/30 days OR 1 syringe kit/90 days	6 months
	Central Precocious Puberty	15 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/90 days	6 months
	Central Precocious Puberty	45 mg/syringe kit	1 syringe kit/180 days	6 months
Leuprolide acetate (Eligard)	Advanced Prostate Cancer	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	6 months
	Advanced Prostate Cancer	30 mg/syringe kit	1 syringe kit/120 days	6 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	6 months
Leuprolide-norethindrone (Lupaneta)	Endometriosis	3.75-5 mg/syringe	1 syringe kit/30 days	6 months
	Endometriosis	11.25-5 mg/syringe	1 syringe kit/90 days	6 months
Renewal				
nafarelin (Synarel)	Central Precocious Puberty	2 mg/mL nasal spray	40 mL/30 days	6 months
leuprolide acetate	Central Precocious Puberty	1 mg/0.2mL kit (each kit contains 2.8 mL of leuprolide acetate and 14 disposable syringes)	1 kit/14 days	6 months
Leuprolide acetate (Lupron Depot)	Endometriosis, Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	3.75 mg/syringe kit	1 syringe kit/30 days	- 12 months for Advanced Breast Cancer and Gender Dysphoria EXCEPT - 6 months for Endometriosis (**MAX #1 renewal allow**) - NO RENEWAL for Uterine leiomyoma and Endometrial Thickness

	Advanced Prostate Cancer, Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	12 months
	Advanced Prostate Cancer, Advanced Breast Endometrial Thickness, Uterine leiomyoma, Central Precocious Puberty, Gender Dysphoria	11.25 mg/syringe kit	1 syringe kit/90 days	- 12 months for Advanced Breast Cancer, Central Precocious Puberty, and Gender Dysphoria EXCEPT - 6 months for Endometriosis (**MAX #1 renewal**) - NO RENEWAL for Uterine leiomyoma and Endometrial Thickness
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	12 months
	Advanced Prostate, Cancer Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/120 days	12 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	12 months
Leuprolide acetate (Lupron Depot-Ped)	Central Precocious Puberty	7.5 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	11.25 mg/syringe kit	1 syringe kit/30 days OR 1 syringe kit/90 days	6 months
	Central Precocious Puberty	15 mg/syringe kit	1 syringe kit/30 days	6 months
	Central Precocious Puberty	30 mg/syringe kit	1 syringe kit/90 days	6 months
	Central Precocious Puberty	45 mg/syringe kit	1 syringe kit/180 days	6 months
Leuprolide acetate (Eligard)	Advanced Prostate Cancer	7.5 mg/syringe kit	1 syringe kit/30 days	12 months
	Advanced Prostate Cancer	22.5 mg/syringe kit	1 syringe kit/90 days	12 months
	Advanced Prostate Cancer	30 mg/syringe kit	1 syringe kit/120 days	12 months
	Advanced Prostate Cancer	45 mg/syringe kit	1 syringe kit/180 days	12 months
	Endometriosis	3.75-5 mg/syringe	1 syringe kit/30 days	6 months

Leuprolide-norethindrone (Lupaneta)	Endometriosis	11.25-5 mg/syringe	1 syringe kit/90 days	6 months (**MAX #1 renewal allow**)

Initial Evaluation

I. **Synthetic gonadotropin-releasing hormones (GnRHs)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a gynecologist, endocrinologist, or oncologist; **AND**
   B. A diagnosis of one of the following:
      1. **Endometriosis**; **AND**
         i. Member is 18 years of age or older; **AND**
         ii. Member requires pain relief and reduction of endometriotic lesions; **AND**
         iii. Treatment with an oral contraceptive has been ineffective, contraindicated, or was not tolerated; **AND**
         iv. The request is for Lupron Depot (3.75 mg, 11.25 mg), Synarel, OR Lupaneta; **OR**
      2. **Uterine leiomyoma (fibroids); AND**
         i. Member is 18 years of age or older; **AND**
         ii. The diagnosis of uterine leiomyoma has been confirmed by ultrasound or hysteroscopy; **AND**
         iii. Member requires therapy for anemia associated with preoperative management (e.g., hysterectomy, uterine artery embolization, myomectomy, hysteroscopy, etc.) of uterine leiomyoma; **AND**
         iv. Member will be on iron therapy concomitantly; **AND**
         v. The request is for Lupron Depot (3.75 mg, 11.25 mg); **OR**
      3. **Central Precocious Puberty (CPP)**; **AND**
         i. Documented onset of secondary sexual characteristics (e.g., genital maturation, pubic hair growth, and/or menses in female); **AND**
            a. Symptom onset before 8 years of age for FEMALE, 9 years of age for MALE; **AND**
         ii. FEMALE member is less than 11 years of age, MALE member is less than 12 years of age; **AND**
         iii. Member has clinical diagnosis of CPP confirmed by a pubertal response to a GnRH stimulation test or a pubertal basal level of luteinizing hormone (LH); **AND**
         iv. Provider attestation that the member has bone age advanced at least one year beyond chronological age; **OR**
      4. **Advanced prostate cancer; AND**
         i. The request is for Lupron-Depot, or Eligard; **OR**
      5. **Advanced breast cancer in premenopausal women; AND**
         i. The request is for Lupron-Depot 11.25 mg; **OR**

6. **Reduction of endometrial thickness prior to endometrial ablation; AND**
    i. The request is for Lupron Depot (3.75 mg, 11.25 mg), **OR**
7. **Gender Dysphoria**

II. Gonadotropin-releasing hormone (GnRH) analogs are considered not medically necessary when criteria above are not met and/or when used for:
    A. In vitro fertilization
    B. Premenstrual syndrome

Renewal Evaluation

I. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
II. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
III. A diagnosis of one of the following:
    A. Endometriosis; **AND**
        1. Member is responding positively to therapy (e.g., pain relief and reduction of endometriotic lesions); **AND**
        2. Provider attests that the member's bone mineral density been assessed and has been deemed appropriate to continue GnRH therapy; **AND**
        3. The total duration of treatment with a GnRH analog has not exceed a total of 12 months; **AND**
        4. The request is for leuprolide acetate (Lupron Depot) in combination with norethindrone, or Lupaneta; **OR**
    B. Central Precocious Puberty (CPP); AND
        1. Member is responding positively to therapy (e.g., lack of progression or stabilization of secondary sexual characteristics, decrease in growth rate, decrease in bone age to chronological age); **AND**
        2. Female member is less than 11 years of age; **OR**
            i. Male member is less than 12 years of age; **OR**
    C. Advanced prostate cancer; AND
        1. Provider attest that member has exhibited improvement in or stability of disease symptoms; **OR**
    D. Advanced breast cancer in premonopausal women; **AND**
        1. Provider attests that member has exhibited improvement in or stability of disease symptoms; **OR**
    E. Gender Dysphoria; AND
        1. A renewal approval of 12 months is allowed

Supporting Evidence

I. In clinical trials, leuprolide acetate (Lupron Depot), when compared to danazol 800 mg per day, significantly reduced symptoms of endometriosis (e.g., pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and induced laparoscopic improvement; however, due to decrease in bone mineral density, the total duration of therapy with leuprolide acetate for depot suspension should not exceed 12 months. If retreatment is needed after the initial six months, an addition of hormone therapy with norethindrone acetate is recommended. Clinical studies demonstrated that concurrent norethindrone acetate and calcium supplementation daily with leuprolide acetate (Lupron Depot) have shown to significantly reduce the loss of bone mineral density that occurs with GnRH treatment, without compromising the efficacy of relieving symptoms of endometriosis.

II. In a study, women with stage III-IV endometriosis were randomized to receive either laparoscopic surgery first followed by 6 months of nafarelin (Synarel) 200 mcg twice daily followed by a second-look laparoscopy (n=28) or no initial surgical procedure with nafarelin (Synarel) 200 mcg twice daily followed by a second-look laparoscopy with appropriate surgery (n=25). There was no difference in efficacy. Additionally, per label, safety and efficacy has not been established beyond 6 months.

III. In a randomized study, leuprolide acetate (Lupron depot) plus iron demonstrated clinical response (HCT of 36% or greater and Hb of 12 g/dL or greater) compared with iron alone at week 4 (40% vs 17%), week 8 (71% vs 39%), and week 12 (75% vs 49%). In the leuprolide acetate (Lupron depot) arm: excessive vaginal bleeding decreased in 80% of patients at 3 months; uterine and myoma volume decreases of 25% or greater occurred in 60% and 54% of patients, respectively; and mean fibroid diameter decreased from 6.3 cm to 5.6 cm. The use of leuprolide acetate (Lupron depot) for uterine leiyomyoma should not exceed an FDA max of 3 months therapy.

IV. Precocious puberty is defined as the onset of secondary sexual development before the age of eight years in females and nine years in males. Central precocious puberty (CPP), also known as gonadotropin-dependent precocious puberty or true precocious puberty, is caused by early maturation of the hypothalamic-pituitary-gonadal axis. CPP is characterized by sequential maturation of breasts and pubic hair in females, and maturation of the testes, penis, and pubic hair in males. Average age of puberty onset in females is 11 and 12 in males. The decision to discontinue treatment factors in the patient's bone age and height balanced with a desire to have pubertal progression with their peers.

V. GnRH stimulation tests have been the gold standard for confirmation of CPP diagnosis. However, new studies support the use of pubertal basal LH levels in diagnosis. The American Family Physician and Gonadotropin-Releasing Hormone Analogs in Children guidelines support use of basal LH levels to confirm the diagnosis of CPP after onset of symptoms. One study attempted to diagnose young girls with CPP based off pubertal basal LH levels. In over 90% of instances, basal LH levels was able to differentiate prepubertal patients from those with CPP using third-generation assays. The basal LH level threshold to diagnose CPP has not been definitively set, but a typical threshold of 0.3 U/L is used.

VI. Patients with CPP typically demonstrate early bone maturation and accelerated growth. Height velocity is considered accelerated if it exceeds 6 cm per year. As bones mature, CPP could lead to early closure of epiphysis, eventually resulting in a decreased adult height. The decision to

treat is based on pubertal progression (sexual maturation), height velocity, and rate of bone age advancement. The goal of GnRH treatment is preservation of height potential and growth to normal adult height and to address the psychosocial impact of early entry into puberty.

VII. MRI imaging is completed to rule out intracranial pathology such as hamartomas (tumor-like growth), CNS tumors, arachnoid cysts, and other lesions. Imaging can be used to identify the cause of CPP to determine if other treatments are needed. The American Academy of Pediatrics, American Family Physician, and European Society for Paediatric Endocrinology have released consensus statements that brain imaging should be performed in all boys and girls who are 6 years or younger. However, recommendations were also given to discuss the pros and cons of MRI scanning with the parents to assist in making an informed decision. Intracranial pathology occurs in up to 38% of boys and up to 6.3% in girls with CPP. A meta-analysis of CPP MRI findings found that only 1.6% of girls had CNS abnormalities required an intervention. Investigators suggest there is a lower incidence of tumors in girls older than 6 years and imaging above 6 years old will likely lead to incidental positive findings not related to CPP. Ultimately, treatment for CPP with a GnRH agent will occur independent of imaging or the presence of a tumor. Therefore MRI/imaging is not required for coverage of GnRH therapy.

VIII. In an open-label study, nafarelin acetate (Synarel) for the treatment of central precocious puberty in children, demonstrated a growth rate reduction from 11.5 cm/year to 5.8 cm/year after 6 months of therapy.

IX. In open-label studies, monthly or once every 3 months of leuprolide acetate administration in children with central precocious puberty naïve to GnRH therapy demonstrated clinical and physical signs of puberty suppression. These clinical/physical signs include stopped or regressed secondary sexual characteristics, significantly improved mean height standard deviation for bone age, and suppressed luteinizing hormone and follicle stimulating hormone.

X. In an open-label, non-comparative, multicenter clinical trial, leuprolide acetate (Lupron depot) demonstrated a reduction and maintenance in serum testosterone level to castrate range (≤50 ng/dL). In the study, serum testosterone suppressed to the castrate range within 30 days of the initial depot injection in 94% (51/54) of patients for whom testosterone suppression was achieved (2 patients withdrew prior to onset of suppression) and within 66 days in all 54 patients. In a separate open-label study (AGL9904), leuprolide acetate (Eligard) 7.5 mg, 22.5 mg, 30 mg and 45 mg demonstrated castration suppression and maintenance.

Investigational or Not Medically Necessary Uses

I. In vitro fertilization
   A. This is an excluded indication per the plan benefit.

II. Premenstrual syndrome
   A. There is currently insufficient evidence regarding safety and/or efficacy with leuprolide acetate in this setting.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added mew strength of Lupron Depo peds 45 mg syringe kit	05/2023
Addition of CPP indication to the Lupron Depot injection products with corresponding strengths of Lupron Depot Ped. Updated criteria for central precocious puberty. Changed wording in the age criteria to specify "onset of symptoms" before specified age. Included basal serum LH levels in addition to GnRH stimulation test required for confirmation of diagnosis. Removed lines "beta human chorionic gonadotropin (HCG) level and adrenal and pelvic ultrasound or testicular ultrasound" as tests are specifically performed in the peripheral setting. Added evidence to support changes. Removed criteria requiring imaging prior to treatment with GnRH analogues. Updated supporting evidence with disease state background and guideline recommendations for diagnosis and treatment.	05/2022
Criteria transitioned into policy format. With the following updates made: added supporting evidence, added indications that are medically not necessary, added renewal criteria, limit renewal for endometriosis to a total duration of 12 months, limit initial approval for uterine leiomyoma to 3 months per FDA max, require bone mineral density evaluation upon renewal for the treatment of endometriosis, require concomitant iron therapy for uterine leiomyoma indication, updated Lupron-depot strength for advanced breast cancer, and no renewal for uterine leiyomyoma and endometrial thickness.	10/2019
Previous reviews	08/2017
Policy created	10/2014

Policy Type: PA/SP Pharmacy Coverage Policy: UMP126

Description

Somatropin and somapacitan are purified polypeptide hormones of recombinant DNA origin. Somatropin is comprised of amino acids in a sequence identical to that of human growth hormone. Somapacitan includes a single substitution in the amino acid backbone to which an albumin-binding moiety is attached; it is otherwise an identical amino acid sequence to human growth hormone. Human growth hormone stimulates growth of linear bone, skeletal muscle, and organs, and stimulates erythropoietin which increases red blood cell mass, exerts both insulin-like and diabetogenic effects, and enhances the transmucosal transport of water, electrolytes, and nutrients across the gut. In short-bowel syndrome, growth hormone may directly stimulate receptors in the intestinal mucosa or indirectly stimulate the production of insulin-like growth factor-I which is known to mediate many of the cellular actions of growth hormone.

Length of Authorization

- Initial: Six months
  - i. AIDS wasting syndrome: Three months only
  - ii. Short bowel syndrome: One month only
  - iii. All other indications: Six months
- Renewal: 12 months
  - i. AIDS wasting syndrome: Three months only
  - ii. Short bowel syndrome: No renewal allowed
  - iii. All other indications: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
somatropin (Genotropin)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults • Idiopathic short stature • Prader-Willi syndrome • Small for gestational age • Turner syndrome	5 mg/mL cartridge	Pediatric GHD: 0.24 mg/kg/week Adult GHD: 0.08 mg/kg/week Idiopathic short stature: 0.47 mg/kg/week Prader-Willi syndrome: 0.24 mg/kg/week Small for gestational age: 0.48 mg/kg/week Turner syndrome:
		12 mg/mL cartridge	
somatropin (Genotropin MiniQuick)		0.2 mg/0.25 mL syringe	
		0.4 mg/0.25 mL syringe	
		0.6 mg/0.25 mL syringe	
		0.8 mg/0.25 mL syringe	
		1 mg/0.25 mL syringe	
		1.2 mg/0.25 mL syringe	
		1.4 mg/0.25 mL syringe	
		1.6 mg/0.25 mL syringe	
		1.8 mg/0.25 mL syringe	
		2 mg/0.25 mL syringe	

			0.33 mg/kg week
somatropin (Humatrope)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults • Idiopathic short stature • Short stature homeobox-containing gene (SHOX) deficiency • Small for gestational age • Turner syndrome	5 mg vial	Pediatric GHD: 0.3 mg/kg/week Adult GHD: 0.0875 mg/kg/week (0.0125 mg/kg/day) Idiopathic short stature: 0.37 mg/kg/week SHOX deficiency: 0.35 mg/kg/week Small for gestational age: 0.47 mg/kg/week Turner syndrome: 0.375 mg/kg week
		6 mg cartridge	
		12 mg cartridge	
		24 mg cartridge	
somatropin (Norditropin FlexPro)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults • Idiopathic short stature • Noonan syndrome • Prader-Willi syndrome • Small for gestational age • Turner syndrome	5 mg/1.5 mL pen injector	Pediatric GHD: 0.24 mg/kg/week Adult GHD: 0.112 mg/kg/week (0.016 mg/kg/day) Idiopathic short stature: 0.47 mg/kg/week Noonan syndrome: 0.46 mg/kg/week Prader-Willi syndrome: 0.24 mg/kg/week Small for gestational age: 0.47 mg/kg/week Turner syndrome: 0.47 mg/kg week
		10 mg/1.5 mL pen injector	
		15 mg/1.5 mL pen injector	
		30 mg/3 mL pen injector	
somatropin (Nutropin AQ)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults	5 mg/2 mL pen injector	Pediatric GHD: 0.3 mg/kg/week Adult GHD: <u>Age 18-35 years</u> 0.175 mg/kg/week

	• Growth failure associated with chronic renal insufficiency (CRI) • Idiopathic short stature • Turner syndrome	10 mg/2 mL pen injector	(0.025 mg/kg/day) <u>Age >36 years</u> 0.0875 mg/kg/week (0.0125 mg/kg/day) Chronic Renal Insufficiency: 0.35 mg/kg/week Idiopathic short stature: 0.3 mg/kg/week Turner syndrome: 0.375 mg/kg week
		20 mg/2 mL pen injector	
somatropin (Omnitrope)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults • Idiopathic short stature • Prader-Willi syndrome • Small for gestational age • Turner syndrome	5.8 mg vial	Pediatric GHD: 0.24 mg/kg/week Adult GHD: 0.08 mg/kg/week Idiopathic short stature: 0.47 mg/kg/week Prader-Willi syndrome: 0.24 mg/kg/week Small for gestational age: 0.48 mg/kg/week Turner syndrome: 0.33 mg/kg week
		5 mg/1.5 mL cartridge	
		10 mg/1.5 mL cartridge	
somatropin (Saizen)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults	5 mg vial	Pediatric GHD: 0.18 mg/kg/week Adult GHD: 0.07 mg/kg/week (0.01 mg/kg/day)
		8.8 mg vial	
somatropin (Saizen Click Easy)		8.8 mg/1.51 mL cartridge	
somatropin (Saizenprep)		8.8 mg cartridge	
somatropin (Serostim)	Wasting or cachexia associated with HIV	4 mg vial	28 vials/28 days
		5 mg vial	
		6 mg vial	
somapacitan (Sogroya)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults	5 mg/1.5 mL pen	6 mL/28 days
		10 mg/1.5 mL pen	
		15 mg/1.5 mL pen	

somatropin (Zomacton)	• Growth hormone deficiency (GHD), children • Growth hormone deficiency (GHD), adults • Idiopathic short stature • Short stature homeobox-containing gene (SHOX) deficiency • Small for gestational age • Turner syndrome	5 mg vial	Pediatric GHD: 0.3 mg/kg/week Adult GHD: 0.0875 mg/kg/week (0.0125 mg/kg/day) Idiopathic short stature: 0.37 mg/kg/week SHOX deficiency: 0.35 mg/kg/week Small for gestational age: 0.47 mg/kg/week Turner syndrome: 0.375 mg/kg week
		10 mg vial	
somatropin (Zorbtive)	Short bowel syndrome	8.8 mg vial	28 vials/28 days
Somatrogon-ghla (Ngenla)	Growth hormone deficiency (GHD), children	24mg/1.2mL pen	1.2mL/28days
		60mg/1.2mL pen	
lonapegsomatropin (Skytrofa)	Growth hormone deficiency (GHD), children	3.0 mg cartridge	4 cartridges/28 days
		3.6 mg cartridge	
		4.3 mg cartridge	
		5.2 mg cartridge	
		6.3 mg cartridge	
		7.6 mg cartridge	
		9.1 mg cartridge	
		11.0 mg cartridge	
		13.3 mg cartridge	

Growth Hormone Therapy in Children and Adolescents

Initial Evaluation

Genotropin and Omnitrope:
- There is no prior authorization required on these preferred agents unless requesting over the allowed quantity limits noted above.

I. **Somatropin (Humatrope, Norditropin, Nutropin AQ, Saizen, or Zomacton)** may be considered medically necessary for **children and adolescents** when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   B. Member's epiphyses are not closed (as confirmed by radiograph of the wrist and hand); **AND**
   C. Member has not reached final height; **AND**
   D. A diagnosis of one of the following:

1. **Short stature associated with Turner Syndrome, Prader-Willi Syndrome, Noonan Syndrome, SHOX gene deficiency, or Chronic renal insufficiency; AND**
    i. The member has short stature as confirmed by one of the following:
        a. Current height: more than two standard deviations (SD) (less than 3rd percentile) below the mean for age and gender; **OR**
        b. Growth velocity: more than two SD below the mean for age and gender over one year; **OR**
        c. Growth velocity: more than 1.5 SD sustained over two years; **OR**
        d. Delayed skeletal maturation (delayed bone age): bone age compared to chronological age is equal to, or greater than, two SD below the mean for age and gender; **AND**
    ii. Treatment with Genotropin **AND** Omnitrope has been ineffective, contraindicated, or not tolerated; **OR**
        a. Request is for Humatrope or Zomacton for SHOX gene deficiency; **OR**
        b. Request is for Nutropin AQ for chronic renal insufficiency; **OR**
        c. Request is for Norditropin in Noonan Syndrome; **OR**
        d. Request is for Norditropin in Prader-Willi Syndrome; **OR**
2. **Growth Hormone Deficiency; AND**
    i. Request is for Skytrofa; **AND**
        a. A trial with Genotropin **OR** Omnitrope of at least 12 months resulted in failure to achieve a growth velocity of at least two (2) cm/year due to lack of adherence; **OR**
        b. Member experienced intolerance, hypersensitivity, or has a contraindication to Genotropin **OR** Omnitrope that is not expected to occur with Skytrofa; **OR**
    ii. Request is for somapacitan (Sogroya) or somatrogon-ghla (Ngenla); **AND**
        a. Treatment with Genotropin **OR** Omnitrope, followed by treatment with Skytrofa, has been ineffective, contraindicated, or not tolerated; **OR**
3. **Growth failure in children born small for gestational age (SGA); AND**
    i. Member failed to manifest catch-up growth by two years of age; **AND**
    ii. Birth weight and/or length is less than two SD below the mean for gestational age; **AND**
    iii. Height remains less than two SD below the mean age and gender at two years of age; **AND**
    iv. Request is for Humatrope, Norditropin, or Zomacton; **AND**
        a. Treatment with Genotropin **AND** Omnitrope has been ineffective, contraindicated, or not tolerated.

Growth Hormone Therapy in Adults

Initial Evaluation

Genotropin and Omnitrope:

- There is no prior authorization required on these preferred agents, unless requesting over the allowed quantity limits noted above.

II. **Somatropin (Humatrope, Norditropin, Nutropin AQ, Saizen, or Zomacton) or somapacitan-beco (Sogroya)** may be considered medically necessary in **adults** when the following criteria below are met:

A. Medication is prescribed by, or in consultation with, an endocrinologist or gastroenterologist; **AND**

B. A diagnosis of one of the following:

1. **Short bowel syndrome; AND**
    i. Member is currently on specialized nutritional support that has been protein, calorie, and fluid intake-optimized for at least two weeks; **AND**
    ii. The request is for Zorbtive; **OR**
2. **HIV/AIDS associated wasting or cachexia; AND**
    i. Treatment with an appetite stimulant (dronabinol or megestrol) has been ineffective, contraindicated, or not tolerated; **AND**
    ii. The request is for Serostim; **OR**
3. **Adult Growth Hormone Deficiency (GHD); AND**
    i. Diagnosis of GHD that is one of the following:
        a. Adult onset from ONE of the following:
            i. genetic defects affecting the hypothalamic-pituitary axes;
            ii. hypothalamic-pituitary structural brain defects;
            iii. hypothalamic-pituitary disease with history of suprasellar mass with previous surgery and cranial radiation and evidence of multiple pituitary hormone deficiencies (≥3 pituitary hormone deficiencies [PHD]) and low-serum IGF-1 levels); **OR**
        b. Adult onset from ONE of the following:
            i. hypopituitarism due to pituitary disease;
            ii. traumatic brain injury;
            iii. hypothalamic-pituitary disease with history of suprasellar mass with previous surgery and cranial radiation and evidence of multiple pituitary hormone deficiencies (≤2 pituitary hormone deficiencies [PHD]) and low-serum IGF-1 levels; **AND**
                1. A subnormal response to any ONE of the following provocative growth hormone (GH) stimulation tests:
                    a. Clonidine
                    b. Glucagon

c. Insulin induced hypoglycemia
d. Propranolol; **OR**

c. Childhood-onset growth hormone deficiency; **AND**
i. Serum insulin-like growth factor-1 (IGF-1) concentration lower than the age- and gender appropriate reference range; **OR**

d. Idiopathic GH deficiency diagnosis; **AND**
i. Diagnosis been confirmed by BOTH of the following:
1. A subnormal response to any TWO of the following provocative growth hormone (GH) stimulation tests:
a. Clonidine
b. Glucagon
c. Insulin induced hypoglycemia
d. Propranolol; **AND**
2. Serum insulin-like growth factor-1 (IGF-1) concentration lower than the age- and gender appropriate reference range

ii. Treatment with Genotropin **AND** Omnitrope has been ineffective, contraindicated, or not tolerated.

II. Growth hormone is considered not medically necessary when used for all other conditions, including but not limited to:
A. Idiopathic (i.e. of unknown origin) short stature, also called non-growth hormone deficient short stature in children
B. Increased athletic performance in adults

III. Growth hormone is considered investigational when used for all other conditions, including but not limited to:
A. Growth hormone insensitivity (Laron Syndrome)
B. Constitutional growth delay
C. Children with growth failure caused by glucocorticoids
D. Children who are not growth hormone deficient but have short stature associated with chronic disease
E. Children with chromosomal and genetic disorders (except Turner's and Prader Willi Syndromes) or familial short stature
F. Russell Silver syndrome
G. Altered body habitus or lipodystrophy associated with antiviral therapy
H. Precocious puberty
I. Obesity
J. Cystic fibrosis
K. Idiopathic dilated cardiomyopathy
L. Juvenile idiopathic arthritis

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
III. A diagnosis of one of the following:
    A. **Children with Growth Hormone Deficiency**
        a. Member's epiphyses are not closed (as confirmed by radiograph of the wrist and hand); **AND**
        b. Member has not reached final height; **AND**
        c. Member has shown a response to growth hormone therapy (i.e., increase in height, increase in height velocity); **AND**
    B. **Children with short stature associated with Turner Syndrome, Prader-Willi Syndrome, Noonan Syndrome, SHOX Gene Deficiency, Chronic Renal Insufficiency, or Growth failure in children born small for gestational age (SGA); AND**
        a. Member's epiphyses are not closed (as confirmed by radiograph of the wrist and hand); **AND**
        b. Member has not reached final height; **AND**
        c. Member has shown a response to growth hormone therapy (i.e. increase in height, increase in height velocity); **AND**
    C. **HIV/AIDS associated wasting or cachexia; AND**
        a. Member has shown clinical benefits by an increase in muscle mass and weight from growth hormone replacement; **AND**
        b. Member has not received more than six months of therapy; **OR**
    D. **Adult Growth Hormone Deficiency; AND**
        a. Member has shown clinical benefits from growth hormone replacement as assessed by one of the following:
            i. Normalization of insulin-like growth factor I (IGF-I)
            ii. Improvement in body composition (i.e. bone density increase, lipolysis changes)
            iii. Clinical assessment of patient focusing on improvement in quality-of-life issues

Supporting Evidence

I. All recombinant human growth hormone (GH) products that are administered via daily injections are somatropin, and other than device and FDA approved indications, there is little to no differentiation between these products. Skytrofa (lonapegsomatropin) and Ngenla (somatrogon-ghla) are long-acting, pegylated prodrug of a human growth hormone (somatropin) indicated in pediatric patients, offering once weekly dosing. Sogroya (somapacitan), provides the option of weekly administration in both pediatrics and adults; however, the adult efficacy results were based on a single trial in which numerical values compared to open-label Norditropin showed lower results in adults. Sogroya (somapacitan) was evaluated statistically only against placebo in a space with several established treatment options

and patients in the trial were treatment naïve, thus place in therapy and clinical efficacy compared to other available agents is unknown in adults.

II. Sogroya (somapacitan) was evaluated for children and adolescents in a Phase 3, randomized, multinational, open-label, active-controlled parallel group (somatropin [Norditropin®]) 52-week trial (REAL4) in 200 children and adolescents with treatment naïve growth hormone deficiency. They groups were randomized 2:1 in respect to weekly somapacitan (n=132) and daily somatropin (n=68).

III. Its primary outcome, longitudinal treatment difference in growth in children assessed by annualized height velocity (HV – cm/y), found weekly somapacitan (Sogroya) to be non-inferior to the active-controlled daily GH (somatropin [Norditropin®]). Secondary endpoints include change from baseline to week 52 in HV SD score (HD SDS), height SDS (HSDS), and bone age (BA) versus calculated age (CA) ratio.

IV. A two-year extension was completed where patients who received daily somatropin (Norditropin) were switched to receive weekly somapacitan (Sogroya) 0.16mg/kg/wk, while current weekly somapacitan patients were continued on therapy. Both groups (somapacitan group and the switch group) continued to show comparable efficacy in height velocity at week 104 versus the new "baseline" at week 52. Long-term safety was comparable to the original 52-week trial and there were no new safety signals in the extension. Overall quality of evidence in pediatrics is moderate as it is non-inferior to daily GH and the clinical outcomes measures are consistent with comparable treatment options.

V. The agents listed above with weight based dosing quantity limits also have an alternative dosing regimen available (0.2mg/day, increasing by 0.1 to 0.2mg/daily every 1 to 2 months according to response); however, this dosing would still be approvable as it would fall below the maximum weight based dose.

VI. The 2019 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) updated guidance to adult GHD discussed diagnostic parameters. They recommend that certain adult populations do not require GH stimulation testing to confirm diagnosis. That population includes patients with genetic defects that affect the hypothalamic-pituitary axes, hypothalamic-pituitary structural brain defects, and hypothalamic-pituitary disease with history of suprasellar mass with previous surgery and cranial radiation and evidence of multiple pituitary hormone deficiencies (≥3 pituitary hormone deficiencies [PHD]) and low-serum IGF-1 levels as these populations predict adult GHD with high specificity. The guidelines are silent on the number of confirmatory GH stimulation tests that should be completed on initial diagnosis.

VII. The diagnosis of GH deficiency is confirmed by measurement of GH secretion, commonly following stimulation by a provocative agent. The 2019 guideline update provides new guidance on growth hormone response thresholds based on the stimulation test.

- insulin tolerance test (ITT) – less than 5 µg/L
- glucagon-stimulation test
    i. normal weight (BMI <25 kg/m^2) – 3 µg/L
    ii. overweight with high pretest probability (BMI 25 to 30 kg/m^2) – 3 µg/L
    iii. overweight with low pretest probability (BMI 25 to 30 kg/m^2) – 1 µg/L
    iv. obese (BMI >30 kg/m^2) – 1 µg/L
- macimorelin-stimulation test – 2.8 µg/L

- arginine and levodopa testing is no longer recommended due to the low sensitivity/specificity in adults and lack of evidence and validation.

VIII. Due to a lack of evidence that one GH product is more beneficial than other, AACE does not recommend a particular product. AACE provides no guidance regarding length of GH therapy, but states that treatment should continue so long as benefits are seen. Discontinuation of GH treatment should be considered when no apparent benefits are achieved after at least two years of treatment.

IX. Somatropin and somapacitan should not be used for growth promotion in pediatric patients with closed epiphyses.

X. Zorbtive is indicated for the treatment of SBS in patients receiving specialized nutritional support. Administration for more than 4 weeks has not been adequately studied.

XI. Payment consideration for growth hormone used to treat HIV/AIDS wasting syndrome or cachexia is reserved for members that have had an inadequate response to appetite stimulants. Per package insert, there is no safety or efficacy data available from controlled studies in which patients were treated with Serostim continuously for more than 48 weeks. There is also no safety or efficacy data available from trials in which patients with HIV wasting or cachexia were treated intermittently with Serostim. A search in the medical literature as of September 2020 revealed two prospective controlled trials which are the pivotal trials in the Serostim package insert. The search did not identify any clinical studies or reports evaluating the use of human GH longer than 48 weeks in this treatment setting.

XII. Guidelines for Use of Growth Hormone in Clinical Practice: Patients with childhood-onset GH deficiency previously treated with GH replacement in childhood should be retested after final height is achieved and GH therapy discontinued for at least 1 month to ascertain their GH status before considering restarting GH therapy. Exceptions include those with known mutations, those with embryopathic/congenital defects, those with irreversible hypothalamic-pituitary structural lesions, and those with evidence of panhypopituitarism (at least 3 pituitary hormone deficiencies) and serum IGF-I levels below the age- and sex-appropriate reference range off GH therapy.

- For childhood GH treatment of conditions other than GHD, such as Turner's syndrome and idiopathic short stature, there is no proven benefit to continuing GH treatment in adulthood; hence, there is no indication to retest these patients when final height is achieved.

XIII. The Endocrine Society's clinical guidelines now recommend GH for use in idiopathic adult GH deficiency although this diagnosis is rare. Significant false-positive error rates occur in response to a single GH stimulation test; therefore, use of two tests is recommended before making a diagnosis. The 2019 guidelines do also recommend two tests, but only if the suspicion of idiopathic adult GHD is low. The presence of a low I GF-I also increases the likelihood that this diagnosis is correct.

FDA Approved Indications for Growth Hormone Products

Brand	GHD		TS	ISS	SGA	PWS	CKD	NS	SHOX	HIV	SBS
	Ch	Ad									
Genotropin	x	x	x	x	x	x					
Humatrope	x	x	x	x	x				x		
Norditropin	x	x	x		x	xA		x			

Nutropin AQ	x	x	x	x			x				
Omnitrope	x	x	x	x	x	x					
Saizen	x	x									
Zomacton	x	x	x	x	x				x		
Skytrofa	x										
Sogroya	x	x									
Ngenla	x										
Serostim										x	
Zorbtive											x

GHD = Growth Hormone Deficiency (Ch = Children, Ad = Adult)
TS = Turner Syndrome
ISS = Idiopathic Short Stature
SGA = Growth failure in children born Small for Gestational Age
PWS = Prader-Willi Syndrome in children
CKD = Growth failure due to chronic kidney disease
NS = Noonan Syndrome
SHOX = Short stature homeobox-containing gene deficiency
HIV = HIV-associated Wasting or Cachexia
SBS = Short Bowel Syndrome

Investigational or Not Medically Necessary Uses

I. Idiopathic short stature
   A. Growth hormone therapy for certain conditions may not be approved when use is not expected to correct a significant functional deficit or when reduced growth is not due to an underlying medical condition. Idiopathic short stature is a term used to define height of children who are short, for unknown or hereditary reasons, compared to others in their age- and gender appropriate reference range. Idiopathic short stature is not associated with a definable physical functional impairment, is not due to growth hormone deficiency, and is not the result of accidental injury, disease, trauma, or treatment of a disease, and is not a congenital defect. Additionally, the efficacy of growth hormone therapy for idiopathic short stature is highly variable and those that respond may only have modest additional growth. Growth hormone therapy may be prescribed to circumvent psychosocial burden associated with idiopathic short stature; however, treatment has not been proven effective in producing those intended effects on health outcomes, such as morbidity and quality of life. The potential for modest improvement in growth and unknown impact to psychosocial burden should be balanced with safety concerns associated with treatment including increased risk of cancer, cerebrovascular disease, and metabolic side effects. Given highly variable response rate, modest potential height gain, lack of underlying medical condition, unproven impact on psychosocial burden, and risk for adverse effects, treatment with growth hormone therapy is not medically necessary.
II. Increased athletic performance in adults
   A. The AACE recommends that GH should only be prescribed to patients with clinical features suggestive of adult GHD. Administration of GH to patients for improvement of athletic performance or for any reason other than its approved medical uses is not recommended.
III. There is insufficient or inconclusive medical and scientific evidence to support the safety and efficacy of growth hormone therapy in the listed conditions:

A. Growth hormone insensitivity (Laron Syndrome)
B. Constitutional growth delay
C. Children with growth failure caused by glucocorticoids
D. Children who are not growth hormone deficient but have short stature associated with chronic disease
E. Children with chromosomal and genetic disorders (except Turner's and Prader Willi Syndromes) or familial short stature
F. Russell Silver syndrome
G. Altered body habitus or lipodystrophy associated with antiviral therapy
H. Precocious puberty
I. Obesity
J. Cystic fibrosis
K. Idiopathic dilated cardiomyopathy
L. Juvenile idiopathic arthritis

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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new indication for pediatric growth hormone deficiency for Sogroya and related supportive evidence. Updated criteria for adult growth hormone deficiency based on AACE/ACE 2019 guidelines and supportive evidence. Addition of Omnitrope as a preferred agent.	03/2024
Addition of somatrogon (Ngenla) to non-preferred position.	11/2023
Requirement of trial of lonapegsomatropin (Skytrofa) and Genotropin in pediatric growth hormone deficiency setting. Removal of confirmatory diagnostic criteria in setting of pediatric growth hormone deficiency setting. Update to not medically necessary supporting evidence for idiopathic short stature.	07/2022
Updated preferred product from Norditropin to Genotropin	01/2022
Addition of new product lonapegsomatropin in non-preferred position	08/2021
Addition of new product Sogroya in non-preferred position	02/2021
Added further supporting evidence to duration of therapy with Serostim in the setting of HIV/AIDS associated wasting or cachexia. Updated renewal section to require previous Omnitrope.	11/2020
Updated to policy format. Updated growth hormone stimulation requirements to align with guideline recommendations (Molitch 2011 and Grimberg 2016). Added requirement of treatment to be prescribed by specialist. Removed route for coverage in the setting of idiopathic short stature as growth hormone therapy for certain conditions may not be approved when growth hormone use is not expected to correct a significant functional deficit OR when reduced growth is not due to an underlying medical condition.	11/2019
Criteria update: updated criteria to new format, deleted question defining HIV wasting, added routing questions for growth failure in children born small for gestational age added clinical notes to questions.	03/2018
Criteria Created	08/2014

Policy Type: PA/SP Pharmacy Coverage Policy: UMP036

Description
The listed treatments for Hepatitis C are for orally administered Direct-Acting Antiviral (DAA) therapies.

Length of Authorization
- Initial: 8-16 weeks based on liver status*
- Renewal: none

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*
glecaprevir/pibrentasvir (Mavyret)	100 mg/40 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	84 tablets/28 days
	50mg/20mg oral pellets		140 packets/28 days
sofosbuvir (Sovaldi)	200 mg oral tablet	HCV Genotype 2 or 3 Treatment naïve or experienced	28 tablets/28 days
	400 mg oral tablet	HCV Genotype 1, 2, 3, 4 Treatment naïve or experienced	
ledipasvir/sofosbuvir (Harvoni)	45 mg /200 mg tablet	HCV Genotype 1, 4, 5, 6 Treatment naïve or experienced	28 tablets/28 days
	90 mg /400 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	
ledipasvir/sofosbuvir (authorized generic)	45 mg /200 mg tablet	HCV Genotype 1, 4, 5, 6 Treatment naïve or experienced	28 tablets/28 days
	90 mg /400 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	
velpatasvir/sofosbuvir (Epclusa)	50 mg / 200 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	56 tablets/28 days
	100 mg/ 400 mg tablet		28 tablets/28 days
	150mg/37.5mg oral pellets		28 packets/28 days
	200mg/50mg oral pellets		56 packets/28 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

velpatasvir/sofosbuvir (authorized generic)	100 mg/400 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	28 tablets/28 days
daclatasvir (Daklinza)	30 mg, 60 mg, 90 mg tablet	HCV Genotype 1, 3	28 tablets/28 days
elbasvir/grazoprevir (Zepatier)	50 mg /100 mg tablet	HCV Genotype 4	28 tablets/28 days
velpatasvir/sofosbuvir/ voxilaprevir (Vosevi)	100 mg/400 mg/ 100 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment experienced	28 tablets/28 days
simeprevir (Olysio)	150 mg capsule	HCV Genotype 1 Treatment naïve or experienced	28 capsules/28 days
ombitasvir/paritaprevir/ ritonavir/dasabuvir (Viekira Pak)	12.5/75/50 mg oral tablet and dasabuvir 250 mg tablet	HCV Genotype 1a, 1b Treatment naïve or experienced	1 box/ 28 days
ombitasvir/paritaprevir/ ritonavir/dasabuvir (Viekira XR)	12.5/75/50 mg oral tablet and dasabuvir 250 mg tablet	HCV Genotype 1a, 1b Treatment naïve or experienced	1 box/28 days
ombitasvir/paritaprevir/ ritonavir (Technivie)	12.5/75/50 mg tablet	HCV Genotype 4	1 box/28 days

*See appendix for specific treatment durations

Initial Evaluation

glecaprevir/pibrentasvir (Mavyret) is the preferred Direct-Acting Antiviral (DAA) therapy

- **Patients must have failed, have contraindication to, or intolerance of glecaprevir/pibrentasvir (Mavyret) prior to the consideration of any other Direct-Acting Antiviral (DAA) therapy.**
  - There is no prior authorization required for the preferred Direct-Acting Antiviral (DAA) therapy unless requesting above the quantity limit noted above.

I. **Non preferred Hepatitis C treatments** may be considered medically necessary when the following criteria are met:
   A. Patient has confirmed diagnosis of Hepatitis C and a quantifiable HCV RNA test >15 IU/mL within the last 12 months; **AND**
   B. Required documentation for confirmation of treatment duration, as confirmed by a clinical pharmacist, include:
      1. HCV Genotype; **AND**
      2. Current HCV RNA viral load less than 12 months old; **AND**
      3. Fibrosis staging test (e.g FibroScan or FibroSure) to determine liver fibrosis results LESS than 2 years old required to ensure the appropriate treatment regimen is

used (e.g. patients with cirrhosis and/or decompensation may require longer treatment and/or ribavirin); **AND**

4. If fibrosis level F4 (cirrhosis): Documentation decompensated or previous episodes of decompensated liver disease; **AND**
5. Documentation of treatment history including:
    i. Prior treatment regimen; **AND**
    ii. Duration of prior treatment; **AND**
    iii. Response to treatment; **AND**
    iv. Dates of prior treatment; **AND**
6. Documentation, if available, of the presence or absence of resistant mutations in treatment experienced patients; **AND**
7. Documented rationale why treatment with preferred product glecaprevir/pibrentasvir (Mavyret) is not appropriate; **AND**
8. If the request is for **Vosevi** the member meets one of the specific settings below:
    i. Member has previously failed treatment with elbasvir-grazoprevir (Zepatier) or glecaprevir/pibrentasvir (Mavyret); **OR**
    ii. Member has HCV genotype 3 and was previously treated with sofosbuvir

II. Treatment for Hepatitis C is considered <u>not medically necessary</u> when criteria above are not met and/or in members who:

A. Are taking medications that are contraindicated with, or that have a severe drug interaction with, the prescribed HCV treatment.
B. Are pregnant or planning on becoming pregnant
C. Have severe end organ disease and are not eligible for transplantation (e.g. heart, lung, kidney)
D. Have a clinically-significant illness or any other major medical disorder that may interfere with patients' ability to complete a course of treatment.
E. In the professional judgment of the primary treating clinician, those who would not achieve a long-term clinical benefit from HCV treatment (e.g. patients with multisystem organ failure, receiving palliative care, with significant pulmonary or cardiac disease, or with malignancy outside of the liver not meeting oncologic criteria for cure).
F. Have a MELD score <20 and one of the following:
    1. Cardiopulmonary disease that cannot be corrected and is a prohibitive risk for surgery
    2. Malignancy outside the liver not meeting oncologic criteria for cure
    3. Hepatocellular carcinoma with metastatic spread
    4. Intrahepatic cholangiocarcinoma
    5. Hemangiosarcoma
    6. Uncontrolled sepsis

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Policy Implementation/Update:

Action and Summary of Changes	Date
Removed PA edit of Mavyret and added box to state removal has been done; removed Mavyret specific criteria; added criteria requiring rationale why preferred product Mavyret is not appropriate	01/2022
Review of age expansion for Mavyret and Epclusa, no policy update needed	07/2021
Updated to include specific scenarios for Vosevi approval	06/2021
Appendix updated to follow Mavyret label update indicating an 8-week treatment duration in treatment naïve, compensated cirrhosis patients. Add newly available lower doses of Solvaldi and Harvoni.	10/2019
Updated to remove provider specialty and F0 requirements	06/10/2019
Updated preferred products to only include Mavyret, sofosbuvir/velpatasvir (authorized generic to Epclusa), and Vosevi.	04/01/2019
Previous reviews	04/2015 11/2014 11/2015 12/2015 04/2016 06/2016 08/2016 09/2016 06/2017 11/2017 02/2018
Policy created	02/2014

Appendix:

Please note, Mavyret is the preferred agent for Uniform Medical Plan.

Genotype	Regimen	Please select:
Genotype 1		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	

Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced^+ No cirrhosis	Mavyret x 16 weeks	
	Other:	
Treatment experienced^ + Cirrhosis	Mavyret x 16 weeks	
	Other:	
Treatment experienced‡ + No cirrhosis	Mavyret x 12 weeks	
	Other:	
Treatment experienced‡ + Cirrhosis	Mavyret x 12 weeks	
	Other:	
Treatment experienced❜ + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced❜ + Cirrhosis	Mavyret x 12 weeks	
	Other:	
Genotype 2		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced^ + No cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced^ + Cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced‡ + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced‡ + Cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced❜ + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced❜ + Cirrhosis	Mavyret x 12 weeks	
	Other:	
Genotype 3		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced^+ No cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced^ + cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced‡ + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	

	Other:	
Treatment experienced‡ + cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced❜ + No cirrhosis	Mavyret x 16 weeks	
	Other:	
Treatment experienced❜ + Cirrhosis	Mavyret x 16 weeks	
	Other:	
Genotype 4		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced^+ No cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced^ + cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced‡ + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced‡ + Cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced❜ + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced❜ + Cirrhosis	Mavyret x 12 weeks	
	Other:	
Genotype 5		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced^+ No cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced^ + cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced‡ + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced‡ + Cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced❜ + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced❜ + Cirrhosis	Mavyret x 12 weeks	
	Other:	

Genotype 6		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced^+ No cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced^ + cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced‡ + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced‡ + Cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced❗ + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced❗ + Cirrhosis	Mavyret x 12 weeks	
	Other:	

^Treatment experienced after only NS5A (ledipasvir, velpatasvir, daclatasvir, elbasvir, ombitasvir) containing regimen
‡Treatment experienced after only NS3/4A PI (simeprevir, boceprevir, telaprevir) containing regimen
❗Treatment experienced after peginterferon/ribavirin containing regimen with or without sofosbuvir
***Payment consideration for Daklinza with Sovaldi is reserved for no more than a 12 week course of treatment*

Policy Type: PA/SP Pharmacy Coverage Policy: UMP075

Description

C1 esterase inhibitors (Cinryze, Haegarda, Berinert, Ruconest) are injectable medications that regulate the activation of various systems that are thought to modulate the increased vascular permeability during HAE attacks by preventing the generation of bradykinin.

Lanadelumab (Takhzyro), icatibant (Firazyr), icatibant (Sajazir), and berotralstat (Orladeyo) are kallikrein inhibitors, the binding of these medications to plasma kallikrein results in the control of excess bradykinin generation in patients with HAE. Both lanadelumab (Takhzyro), icatibant (Firazyr), and icatibant (Sajazir) are injectable medications, and berotralstat (Orladeyo) is orally administered.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
C1 esterase inhibitor (Cinryze)	HAE prophylaxis	500 U single use vial for IV administration	20 vials/30 days
C1 esterase inhibitor (Haegarda)		2000 U single use vial for SQ administration	Weight based 60 IU/kg twice weekly, refer to chart below for quantity
		3000 U single use vial for SQ administration	
lanadelumab (Takhzyro)		300 mg/2 mL single dose vial for SQ administration	4 mL/28 days
		300 mg/2 mL prefilled syringe for SQ administration	2 syringes/28 day
		150 mg/mL prefilled syringe for SQ administration*	Ages 2 – 5: 1 syringe/28 day Ages 6 – 12: 2 syringes/28 day
berotralstat (Orladeyo)		110 mg capsules	28 capsules/28 days
		150 mg capsules	
C1 esterase inhibitor (Berinert)	Treatment of acute HAE attacks	500 U single use vial for IV administration	Weight based 20 IU/kg, refer to chart below
C1 esterase inhibitor (Ruconest)		2100 U single use vial for IV administration	16 vials/30 days
icatibant (Firazyr)		30 mg/3 mL SQ prefilled syringe	9 syringes (27 mL)/30 days
icatibant (generic Firazyr)		30 mg/3 mL SQ prefilled syringe	9 syringes (27 mL)/30 days
icatibant (Sajazir)		30 mg/3 mL SQ prefilled syringe	9 syringes (27 mL)/30 days

Initial Evaluation (All information must be supported by documentation and chart notes)

I. **Medications used for HAE** may be considered medically necessary when the following criteria below are met and supported by recent chart notes (within the past 12 months):
   A. Prescribed by, or in consultation with, one of the following specialists: allergist, immunologist, dermatologist, hematologist, pulmonologist, medical geneticist; **AND**
   B. A diagnosis of **hereditary angioedema** indicated by one of the following:
      1. **Type 1 HAE**: confirmed by documentation of the following laboratory values:
         i. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal; **AND**
         ii. C4 level below the lower limit of normal; **AND**
         iii. C1-INH functional level below the lower limit of normal; **AND**
         iv. Patient has a family history of HAE or a normal C1q level; **OR**
      2. **Type 2 HAE**: confirmed by documentation of the following laboratory values:
         i. Normal to elevated C1-INH antigenic level; **AND**
         ii. C4 level below the lower limit of normal; **AND**
         iii. C1-INH functional level below the lower limit of normal**; AND**
   C. The member has been evaluated for potentially treatable triggers of HAE attacks and is being managed to avoid triggers; **AND**
      1. **For prophylactic treatment of HAE**:
         i. Cinryze, Haegarda, Takhzyro, OR Orladeyo is requested; **AND**
            a. The member is NOT prescribed more than one agent FDA-approved for HAE prophylaxis (e.g., Cinryze, Haegarda, Takhzyro, Orladeyo); **AND**
            b. The member has a history of at least **one** of the following criteria for HAE prophylaxis:
               i. History of ≥ 2 severe HAE attacks per month (e.g., airway swelling, debilitating cutaneous or gastrointestinal complications) that required "on-demand" therapy (e.g., icatibant [Firazyr], icatibant [Sajazir], Berinert, Ruconest, Kalbitor)
               ii. The member is disabled ≥ 5 days per month by HAE
               iii. The member has a history of HAE laryngeal attacks; **AND**
            c. The member is ≥ 2 years to < 6 years of age; **AND**
               i. The request is for Takhzyro 150 mg/mL prefilled syringe; **OR**
            d. The member is ≥ 6 years of age; **AND**
               i. The request is for Cinryze; **OR**
               ii. The request is for Takhzyro; **OR**
               iii. The request is for Haegarda; **AND**
                  1. Member's current weight within the last six months has been documented to dose appropriately; **OR**
            e. The member is ≥ 12 years of age; **AND**
               i. The request is for Takhzyro, Orladeyo, or Cinryze; **OR**
               ii. The request is for Haegarda; **AND**

1. Member's current weight within the last six months has been documented to dose appropriately; **OR**

2. **For acute treatment of HAE attacks;**
   i. Icatibant (Firazyr), icatibant (Sajazir), Ruconest, OR Berinert is requested;**AND**
   ii. The member is NOT prescribed more than one agent FDA-approved for HAE acute treatment (e.g., icatibant [Firazyr], icatibant [Sajazir], Berinert, Ruconest, Kalbitor); **AND**
   iii. The member has a history of attacks that induce significant burden of disease or impact to activities of daily living due to HAE (e.g., impairment in work performance/productivity, facial swelling, painful distortion of the affected area, laryngeal attacks or airway swelling, severe gastrointestinal complications); **AND**
   iv. **For Berinert**: the member is ≥ 6 years of age; **AND**
      a. Documentation of current weight within the last six months, to dose appropriately; **OR**
   v. **For Ruconest**: the member is ≥ 13 years of age; **AND**
      a. Treatment with Berinert AND generic icatibant/icatibant (Sajazir), have been ineffective, contraindicated, or not tolerated; **OR**
   vi. **For icatibant (generic Firazyr):** the member is ≥ 18 years of age; **OR**
   vii. **For icatibant (Sajazir):** the member is ≥ 18 years of age; **AND**
      a. Generic icatibant has been ineffective, not tolerated, or contraindicated; **OR**
   viii. **For brand Firazyr**: the member is ≥ 18 years of age; **AND**
      a. Generic icatibant has been ineffective, not tolerated, or contraindicated; **AND**
      b. Icatibant (Sajazir) has been ineffective, not tolerated, or is contraindicated.

II. Medications used for HAE are considered investigational when used for all other conditions or scenarios, including but not limited to:
   A. Combination use of acute therapies (e.g., icatibant [Firazyr], Berinert, Ruconest, Kalbitor, icatibant [Sajazir])
   B. Combination use of prophylactic therapies (Cinryze, Haegarda, Takhzyro, Orladeyo)
   C. Angioedema due to other causes (e.g., type 3 HAE, medication induced, sepsis, cardiovascular comorbidities or conditions, allergic reaction, etc.)

Renewal Evaluation (All information must be supported by documentation and chart notes)

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. The member continues to be evaluated for potentially treatable triggers of HAE attacks and is being managed to avoid triggers; **AND**

IV. The member has been seen and evaluated for medication efficacy and safety in the past 12 months; **AND**

V. The quantity of medication prescribed does not exceed that needed to treat or prevent current average number of attacks or expected number of attacks; **AND**

VI. Documentation the member has experienced functional improvement AND improvement in the number, severity, or duration of attacks; **AND**

VII. **For prophylactic treatment of HAE**:

- A. The member has not been prescribed more than one medication FDA-approved for HAE prophylaxis (Cinryze, Haegarda, Takhzyro, Orladeyo), etc.; **AND**
- B. **For Haegarda**: documentation of current weight (within the last three months, to calculate appropriate dose); **OR**
- C. **For Takhzyro**: one of the following is met:
  - i. The member has been free of acute attacks for ≥ 6 months; **AND**
    - a. The dosing frequency for Takhzyro will be reduced to every 4 weeks (e.g., 150 mg/mL every 4 weeks, 300 mg/2 mL every 4 weeks) [Note: Dose reductions may not apply to members >2 years to <6 years of age]; **OR**
    - b. Documentation of medical necessity is provided for maintaining the dose at 'every two weeks' dosing interval; **OR**
- D. The request is for **Orladeyo** or **Cinryze**; **OR**

VIII. **For acute treatment of HAE attacks:**

- A. The member has not been prescribed more than one medication FDA approved for HAE treatment (e.g., icatibant [Firazyr], icatibant [Sajazir], Berinert, Ruconest, Kalbitor); **AND**
- B. **For brand Firazyr:** the member has tried and failed, not tolerated, or has contraindication to generic icatibant AND icatibant (Sajazir); **OR**
- C. **For icatibant (Sajazir):** the member has tried and failed, not tolerated, or has contraindication to generic icatibant
- D. **For Berinert**: documentation of current weight within the last three months, to calculate appropriate dose

Supporting Evidence

I. Hereditary angioedema (HAE) is a rare disease characterized by recurrent and sometimes severe episodes of angioedema without urticarial or pruritus. Skin and mucosal tissues in the upper respiratory and gastrointestinal tracks are often affected and may have airway involvement leading to asphyxiation if not treated appropriately. It should be noted that it is not uncommon for patients to have mild and/or self-limiting attacks that do not require treatment. Non-

pharmacologic and pharmacologic management of HAE is very complex and requires confirmatory tests and monitoring by, or in close consultation with, a specialist.

II. HAE is divided into two broad categories: HAE due to C1INH deficiency (HAE-C1INH) and HAE with normal C1INH (HAE-nl-C1INH). HAE-C1INH is further subdivided into type 1 and type 2, which appear to be clinically similar. HAE-nl-C1INH HAE was previously called type 3 HAE, however the "type 3" term has become obsolete. HAE-nl-C1INH HAE is further subdivided based on the underlying mutation or unknown in cases where the mutation has not been found. Clinical trials have only evaluated HAE therapies in patients with HAE-C1INH (types 1-2). Data on HAE therapies in the HAE-nl-C1INH setting are limited.

III. Normal C1-INH levels are generally 18-37 mg/dL, normal C4 levels are generally 10-40 mg/dL, normal functional level C1-INH is >67%, normal C1q levels are generally 5-8.6 mg/dL.

IV. Evaluation, documentation, and patient understanding of triggers is essential in the management of HAE and can reduce the number of disabling attacks and medication requirements. The most common triggers include stress, NSAIDS, ACE inhibitors, antibiotics, trauma, illness, dental work, hormonal fluctuations, and food sensitivities, although there are many other patient specific triggers. Furthermore, allergic/anaphylactic reactions and adverse effects related to foods and medications should be ruled out in light of an HAE diagnosis.

V. Hereditary angioedema treatment modalities include acute management and prophylactic methods. Acute therapies, also known as "on-demand" therapy, is essential in serious, debilitating, and laryngeal attacks, options include C1 esterase inhibitors (Berinert, Ruconest), bradykinin antagonist (icatibant [Firazyr], icatibant [Sajazir] – available generic), and kallikrein inhibitor (Kalbitor). Only one of these therapies should be prescribed and used at one time.

VI. Generic icatibant and icatibant (Sajazir) are both available AP rated (**therapeutically equivalent)** generics to icatibant (Firazyr).

VII. In addition to treating attacks of angioedema, patients with HAE may require prophylactic treatment. The goal of prophylactic treatment is either to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to precipitate an attack (short-term prophylaxis) or to decrease the overall number, severity, and burden of angioedema attacks.

VIII. Prophylactic therapy should be considered based on the number of attacks, severity of the attacks, comorbid conditions, emergency department visits, inadequate response or control using acute treatments, and/or where severe, debilitating, or laryngeal attacks are recurrent. Trauma or stress-related events, such as surgeries or dental procedures may entail the need for a short-term prophylaxis therapy. Current 2020 US HAEA Medical Advisory Board (HAEA MAB) guidelines recommend the use of a single dose of plasma derived C1 inhibitor (pdC1INH; e.g., Berinert) as the preferred agent for short-term prophylaxis or a course of anabolic androgen (e.g., danazol) when access to Berinert is limited.

IX. For long-term HAE prophylaxis, current guidelines recommend the use of IV or SQ replacement of pdC1INH as the first-line agents (e.g, Cinryze, Haegarda) along with kallikrein inhibitors (e.g., Takhzyro, Orladeyo). Before the advent of current HAE prophylactic agents, androgens (danazol), antifibrinolytics (aminocaproic acid, tranexamic acid) were used in practice for HAE prophylaxis based on their mechanisms of action and limited clinical trials (1970s and 1980s) indicating symptomatic benefits. However, the current HAEA MAB guidelines recommend these agents as second-line therapies. Use of the second-line prophylactic agents should be reserved for when first-line therapies are not available. Lack of strong clinical data coupled with significant risks of long-term adverse reactions, and lack of FDA approval in the setting of HAE prophylaxis has driven this change in practice in recent years. It should be noted that only danazol is approved in the US for HAE prophylaxis. However, dose-related side effects,

considerations on populations to avoid use in (age <16, pregnant and breastfeeding women), and tolerability concerns limit its widespread use

X. Patients with HAE may also require short-term prophylactic treatment to reduce the likelihood of swelling in a patient before an invasive medical, surgical or dental procedure that is likely to precipitate in an attack. Either plasma-derived C1-inhibitor (pdC1INH) or a course of anabolic androgen is administered for short-term prophylaxis of HAE. The medications in this policy are not specifically FDA-approved for use in short-term prophylaxis at this time.

XI. Both on-demand and prophylactic HAE therapies have FDA-approvals for various age groups; therefore, the ages outlined in this policy are based on FDA-approval. Of note, pediatric populations are underrepresented in clinical trials; however, FDA-approval is often based on clinical experience from a few pediatric patients coupled with several years of safety data in other age populations with limited available treatment options for a potentially life-threatening condition.

XII. Lanadelumab (Takhzyro) was evaluated in two phase 3 studies in patients aged 12 years and older with HAE.

- Study DX2930-03 was a phase 3, multicenter, randomized, double-blind, placebo-controlled parallel-group study. The 26-week study included 125 patients 12 years of age and older with HAE-I or HAE-II who experienced at least one investigator-confirmed attack per 4 weeks during the run-in period. During the study run-in period, attack rates of ≥3 attacks/month were observed in 52% of patients. The primary endpoint was mean monthly attack rate from day 0 to 182, those in the Takhzyro 150 mg every 4 weeks arm had 0.48 mean monthly attack rate, those in the Takhzyro 300 mg every 4 weeks arm had 0.53 mean monthly attack rate and 0.26 mean monthly attack rate was observed in those who received Takhzyro 300 mg ever 2 weeks, while those in the placebo arm had a 1.97 mean monthly attack rate ($p<0.001$). This secondary endpoint of the study was mean number of monthly attacks requiring acute treatment from day 0 to 182. Clinically meaningful and statistically significant outcomes were observed across all Takhzyro arms. Participants in the placebo arm had a mean of 1.64 monthly attacks requiring acute treatment, compared to 0.31 (150 mg every 4 weeks), 0.42 (300 mg every 4 weeks) and 0.21 (300 mg every 2 weeks) [$p<0.001$] as observed across all Takhzyro arms.
- The open-label phase 3 extension study DX2930-04 evaluated the long-term safety of lanadelumab 300 mg Q2W in Types I and II HAE patients. The study consisted of rollover subjects who completed the double-blind treatment period of Trial DX2930-03 and non-rollover subjects who enrolled directly into the OLE study. A secondary objective of the study was to characterize the outer bounds of dosing frequency in the rollover subjects. The primary objective of the study was to provide long-term safety data which include adverse events/serious adverse events, clinical labs (hematology, chemistry, LFTs, UA, coagulation, pregnancy), ECG, vital signs, physical exam, and ADA testing.
- An open-label, single-arm, phase 3 trial (SPRING) measured safety, pharmacokinetics and pharmacodynamics (PK/PD) of lanadelumab (Takhzyro) in patients ≥ 2 years to 12 years of age (N=21) consisting of 17 participants in the 6 years to 12 years age group (group A) and 4 participants aged 2 years to 6 years of age (group B). At 52 weeks of treatment exposure, lanadelumab (Takhzyro) exhibited comparable PK/PD characteristics in pediatric patients (group A) to those for systemic drug exposure in adult patients. For group B patients (<6 years of age), the minimum steady-state plasma drug levels were 50% to 60% lower than those for

adult patients (reported from previous clinical data), however were reported to produce a treatment response. During the SPRING trial, 76% (n=16) participants remained HAE attack-free during full treatment period and the rate of HAE attacks per month reduced by 94% versus baseline (1.84 attacks per month to 0.08 attacks). Although robust conclusions may not be drawn from this data due to open-label study design, limited sample size and lack of comparator, this data provides support to previously reported efficacy of lanadelumab (Takhzyro) in patients >12 years of age. Additionally, no additional safety signals were reported during SPRING trial. 33% participants reported injection site reactions as the common AE, which did not lead to treatment interruptions, discontinuations or hospitalizations.

XIII. Berotralstat (Orladeyo) was evaluated in a three-part phase 3 study, and the approval was based on data submitted from part 1 (24 weeks). Parts 2 and 3 of this study are still ongoing to evaluate the long-term efficacy and safety or berotralstat (Orladyo), additional data on laboratory tests of interest from part 1 (such as LFT elevations) and HAE attack data.

- APeX-2 was a double-blind, randomized, placebo-controlled trial in 121 patients with type I or type II HAE. The primary efficacy outcome of part 1 was the rate of investigator confirmed HAE attacks per month at week 24, which was 1.31 ($p< 0.001$) for the berotralstat 150 mg arm, 1.65 ($p=0.024$) for the berotralstat 110 mg arm and 2.35 for placebo. Although berotralstat (Orladyeo) met its primary efficacy endpoint, the study failed to meet statistical significance in its secondary endpoint, which was the change from baseline of AE-QOL total scores at 24 weeks. The long-term efficacy and safety of this product is currently unknown due to the lack of published long-term data. The distribution of on-demand medication use during the study across all study arms was not provided; therefore, there is a risk the concomitant therapies confounded the outcome results.

XIV. There are no direct head-to-head studies comparing lanadelumab (Takhyzro) and berotralstat (Orladeyo) to establish superior safety or efficacy of one product over the other; however, lanadelumab (Takhzyro) has a more established safety profile, and favorable quality of evidence for efficacy.

Investigational or Not Medically Necessary Uses

I. Use of two or more therapies for the same indication (e.g., acute or prophylactic) has not been evaluated for safety and efficacy.
II. The medications listed in this policy have not been sufficiently evaluated for safety and efficacy outside of hereditary angioedema.

Appendix

Weight-based dosing for Haegarda and Berinert

Medication	Body Weight (kg)	Vial Configuration	Vials per Dose	Number of Vials per 30 days
Haegarda	Up to 33 kg	2000 unit	1	8
	34-50	3000 unit	1	8
	51-67	2000 unit	2	16
	68-100	3000 unit	2	16
	101-133	2000 unit	4	32

	134-150	3000 unit	3	32
Berinert	Up to 25	500 unit	1	4
	25 - 50		2	8
	50 - 75		3	12
	75 - 100		4	16
	100-125		5	20
	125-150		6	24

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Related Policies

Currently there are no related policies

Policy Implementation/Update:

Action and Summary of Changes	Date
Added expanded indication for Takhzyro (>2 years of age); In the prophylaxis setting, removed requirement of trial with danazol, aminocaproic acid, and tranexamic acid following updated guideline recommendations; updated supporting evidence. Removed requirement of specialist prescribing upon renewal. Increased initial approval duration from 3 months to 6 months.	04/2023
Addition of icatibant (Sajazir) to policy, requiring use of generic icatibant prior to use of Sajazir and allowing brand Firazyr coverage only if medical necessity established for brand over generic (generic icatibant and Sajazir)	10/2021
Added Orladeyo criteria for prophylactic treatment of HAE for P&T, added renewal criteria requiring initial policy criteria needs to be met, no continuation based on samples and must have had prior approval by plan.	02/2021
Age for Haegarda expanded down to six years of age (from previous 12)	10/2020
Added age restriction to Takhzyro of ≥ 12 years of age	03/2020
Policy created and criteria added to initial and renewal portions. Takhzyro combined with other agents. Specification on inappropriateness of dual therapy use, medical necessity of therapy, and addition of generic icatibant to the policy and use required prior to brand payment consideration.	10/2019
Takhzyro criteria created for P&T.	10/2018
Criteria updated to include Cinryze prophylactic therapy for patients six years of age and older, a new FDA approved age range.	01/2018
HAE indication review completed, agents included in policy were updated and questions added to align with clinical appropriateness and medical criteria.	11/2017
Criteria created	10/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP127

Description

Human chorionic gonadotropin (hCG) stimulates production of gonadal steroid hormones by causing production of androgen by the testes and the development of secondary sex characteristics in males. In females, hCG acts as a substitute for luteinizing hormone (LH) to stimulate ovulation.

Length of Authorization

- Initial: 12 months (for hypogonadotropic hypogonadism); six months (for cryptorchidism)
- Renewal: 12 months (for hypogonadotropic hypogonadism)*
  * Other indications are not eligible for renewal

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
human chorionic gonadotropin (human chorionic gonadotropin)	10,000 unit vial	Hypogonadotropic hypogonadism Ovulation induction* Prepubertal cryptorchidism	5 vials/30 days
human chorionic gonadotropin (Novarel)	5,000 unit vial		10 vials/30 days
human chorionic gonadotropin (Pregnyl)	10,000 unit vial		5 vials/30 days

**Drugs used in the treatment of fertility are excluded from coverage. Please refer to the member handbook/certificate of coverage for further information.*

Initial Evaluation

I. Human chorionic gonadotropin (Novarel; Pregnyl) may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      1. **Hypogonadotropic hypogonadism; AND**
         i. Two sub-normal testosterone concentration levels taken on two separate mornings while fasting; **AND**
         ii. Treatment with **all** of the following has been ineffective, contraindicated, or not tolerated:
            a. Generic injectable testosterone (i.e. testosterone cypionate, testosterone enanthate); **AND**
            b. Generic topical testosterone (i.e. generic testosterone 1% gel); **OR**
      2. **Prepubertal cryptorchidism; AND**
         i. Not due to anatomical obstruction

II. Human chorionic gonadotropin (Novarel; Pregnyl) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Men with low testosterone concentration and without clinical symptoms and signs consistent with testosterone deficiency. The routine assessment of testosterone level in the absence of hypogonadal symptoms is not advised.
   B. Men with a single, sub-normal testosterone concentration that is not repeatable per the U.S. Endocrine Society.
   C. Men with symptoms of hypogonadism; however, current testosterone level is within normal range.

III. Human chorionic gonadotropin (Novarel; Pregnyl) is considered investigational when used for all other conditions including but not limited to:
   A. Age-related hypogonadism
   B. Men with type 2 diabetes mellitus with low testosterone for the purpose of improving glycemic control
   C. Obesity

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. A diagnosis of **hypogonadotropic hypogonadism; AND**
IV. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

I. Human chorionic gonadotropin (Novarel; Pregnyl) is FDA approved for the treatment of hypogonadotropic hypogonadism, prepubertal cryptorchidism, and ovulation induction. Coverage of medications used in the treatment of fertility is an excluded benefit; thus, criteria for coverage in the setting of ovulation induction is unrepresented within this policy.
II. There are several dosing regimen options in the setting of prepubertal cryptorchidism; however the label only supports a six week course with the potential of another series given one month later if the initial course was not successful.
III. Per the 2018 AUA guidelines, diagnosis of hypogonadism should be confirmed prior to initiating testosterone replacement therapy. Testosterone levels should be drawn ideally between 8 and 10 AM while fasting due to the diurnal fluctuation of testosterone and its sensitivity to glucose ingestion. A separate, confirmatory measurement is recommended.
IV. Thirty percent of men with an initial testosterone concentration in the hypogonadal range can have a measurement within the normal range on repeat measurement.
V. The Endocrine Society strongly advises against “trial periods” of testosterone in men with a single sub-normal testosterone concentration and vague symptoms of deficiency.

VI. In patients within normal range, or have low testosterone concentration due to age, obesity or otherwise, the benefit of increased testosterone has not been shown. Rather, in this patient population with low testosterone and an intact gonadal system, increasing testosterone is associated with an increase of certain health risks, including cardiovascular disease. Because of this, the FDA has required manufacturers to label testosterone products warning of the increased risk for heart attack and stroke.

Investigational or Not Medically Necessary Uses

I. All of the aforementioned conditions listed in the not medically necessary section are considered to be excluded from coverage.
II. In the conditions listed, there is insufficient information, or, information reports inconclusive evidence, to support the safety and efficacy of using human chorionic gonadotropin (Novarel; Pregnyl).

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Policy Implementation/Update:

Date Created	December 2019
Date Effective	December 2019
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date

Policy Type: PA/SP Pharmacy Coverage Policy: UMP212

Description

Hydrocortisone (Alkindi Sprinkle) is a an orally administered corticosteroid.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
hydrocortisone (Alkindi Sprinkle)	0.5mg capsules	Adrenocortical insufficiency	10 mg/m^2/day*
	1mg capsules		
	2mg capsules		
	5mg capsules		

*limited to three capsules a day

Initial Evaluation

I. **Hydrocortisone (Alkindi Sprinkle)** may be considered medically necessary when the following criteria below are met:
   A. The member is 17 years of age or younger; **AND**
   B. The medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. A diagnosis of an **Adrenocortical insufficiency** (e.g. primary adrenal insufficiency, Addison's Disease, secondary adrenal insufficiency) and the following are met:
      1. The request is for hydrocortisone (Alkindi Sprinkle) 0.5 mg, 1 mg, or 2 mg capsules; **AND**
         i. Each individual dose is less than 5 mg (of note, when a 5 mg dose is reached, member is required to transition to generic hydrocortisone oral tablets, unless contraindicated); **AND**
         ii. Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated; **OR**
      2. The request is for hydrocortisone (Alkindi Sprinkle) 5 mg capsules;
         i. Treatment with generic hydrocortisone oral tablet is contraindicated (documentation must be attached); **AND**
         ii. Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated

II. Hydrocortisone (Alkindi Sprinkle) is considered not medically necessary when the following are met:

A. Total daily dose requirement for hydrocortisone may be met using hydrocortisone (Cortef) oral tablets (5 mg, 10 mg, or 20 mg) or hydrocortisone compound (solution or suspension)
B. Treatment requiring hydrocortisone (Alkindi Sprinkle) 5 mg capsules

III. Hydrocortisone (Alkindi Sprinkle) is considered investigational when used for all other conditions, including but not limited to:

A. Treatment of members 18 years of age or older, requiring hydrocortisone therapy
B. Chemotherapy induced nausea and vomiting

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The request is for hydrocortisone (Alkindi Sprinkle) 0.5 mg, 1 mg, or 2 mg capsules; **AND**
    - Each individual dose is less than 5 mg (of note, when a 5 mg dose is reached, member is required to transition to generic hydrocortisone oral tablets, unless contraindicated); **AND**
    - Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated; **OR**
IV. The request is for hydrocortisone (Alkindi Sprinkle) 5 mg capsules;
    - Treatment with generic hydrocortisone oral tablet is contraindicated (documentation must be attached); **AND**
    - Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated
V. Provider attests that the member remains ineligible to transition to generic hydrocortisone tablets and compounded hydrocortisone products (solution or suspension); **AND**
VI. Member has exhibited improvement or stability of disease symptoms (e.g. improved cortisol levels over baseline, improvement in symptoms such as hypotension, hyponatremia)

Supporting Evidence

I. Hydrocortisone (Alkindi Sprinkles) is a corticosteroid, indicated as a replacement therapy in pediatric patients (less than 17 years of age) with adrenocortical insufficiency. Alkindi Sprinkle is a granular formulation of hydrocortisone, which was designed to overcome the barrier of inaccuracy of dosing (when using currently available hydrocortisone formulations) for younger patients.
II. Pediatric patients (neonate to <17 years old) usually require less than 5 mg of total daily dose of hydrocortisone. The daily dose of hydrocortisone is usually divided into two to three doses with initial dose of 8mg/m^2 to 10mg/m^2 per day. Hydrocortisone (Alkindi Sprinkle) is supplied in a pack size of 50 capsules to be stored in the original bottle (unbreakable package). Quantity limit

for hydrocortisone (Alkindi Sprinkles) is based on total daily dose divided into two to three individualized doses and should be rounded up to the nearest pack size.

III. Currently there are no published clinical trial or treatment regimens for children with Primary Adrenal Insufficiency (PAI). The Journal of Endocrinology and Metabolism guideline recommends that treatment in children is aimed at managing and controlling symptoms of adrenal insufficiency with optimal doses that allow for growth and pubertal development. Because PAI is a complex disease state, management and treatment monitoring of PAI in pediatric patients must be in consultation with an endocrinologist or a healthcare provider with endocrine expertise.

IV. Differential diagnose of PAI requires confirmation with the Corticotropin simulation test, which is considered the gold standard due to its higher degree of specificity and sensitivity. A confirmed diagnosis of PAI is determined by low morning serum cortisol concentrations (≤ 140 *n*Mol/L) and high adrenocorticotropic hormone (ACTH) levels (≥ 66 *p*mol/L).

V. While glucocorticoid monotherapy is a typical initial treatment approach, many patients also require a mineralocorticoid as an add-on agent. The Journal of Endocrinology and Metabolism guideline recommends use of 100 µg per day of fludrocortisone. Mineralocorticoids are essential in maintaining water and electrolyte homeostasis; however, use in PAI has not been studied systematically. The rationale is to dose fludrocortisone in the mornings to mimic aldosterone levels, which are generally high in the morning due to circadian rhythms.

VI. Patients with PAI are at high risk of developing Adrenal crisis, an acute etiology that develops due to inability of the adrenal gland to produce enough cortisol in response to an increased need. Clinical features of adrenal crisis consist of volume depletion and hypotension. In such cases, parenteral injections (50mg/m^2) of hydrocortisone may be required.

VII. Hydrocortisone (Alkindi Sprinkle) received FDA approval for pediatric patients (<17 years of age) based on the ease of dosing and proposed accuracy of dosing as it is available in smaller doses (0.5 mg, 1 mg, 2 mg, and 5 mg). Hydrocortisone (Alkindi Sprinkle) was granted FDA-approval as a new dosage form of hydrocortisone and was limited to the indication of adrenocortical insufficiency. There are no independent prospective clinical trials to support efficacy and safety of hydrocortisone (Alkindi Sprinkle) for any other conditions. As such, until now, patients requiring a daily dose of hydrocortisone > 5 mg per day have been managed using hydrocortisone (Cortef) oral tablets (intact or crushed and mixed with liquid), or compounded formulations of hydrocortisone (oral solution or suspension). Notably, the compounded formulations of hydrocortisone have been successfully used in pediatric populations to fulfill the need for optimum daily doses less than 5 mg. These formulations provide accuracy of dosing as well as ease of administration. Although hydrocortisone (Alkindi Sprinkle) is a new formulation that provides administrative convenience, use of this formulation is cost-prohibitive. Given the long-standing efficacy, safety, accuracy of dosing, cost, and clinical experience, compounded formulations of hydrocortisone are considered standard and practical high-value treatment options in this space and should be preferred over hydrocortisone (Alkindi Sprinkle).

Investigational or Not Medically Necessary Uses

I. There are no direct head-to-head clinical trials comparing efficacy and safety of glucocorticoid drugs used in in long term treatment of PAI in children. The Endocrine Societal Guidelines recommend children should be treated with hydrocortisone because of its optimal pharmacokinetic profile, and short half-life, furthermore overtreatment should be avoided.

Doses of ≥ 5mg daily are considered not medically necessary for children aged less than 17 years of age due to risk of growth retardation. Therefore, close monitoring of glucocorticoid dosing is advised in children with increasing body surface area.

II. Hydrocortisone (Alkindi Sprinkle) is not considered medically necessary in any other disease state other than adrenocortical insufficiency. Epidemiology in this setting largely involves pediatric population. Based on the scope of FDA-approval, hydrocortisone (Alkindi Sprinkle) is deemed medically necessary only for pediatric patients diagnosed with adrenocortical insufficiency, for whom, the total daily dose requirement may not be met using generic hydrocortisone tablets or compounded hydrocortisone formulations.

III. Use of hydrocortisone has been widely recommended in many inflammatory conditions including chemotherapy induced nausea, prostate cancer, chronic lung disease and gout. However, it should be noted that typical daily dose requirement of hydrocortisone in the treatment of these conditions is higher than 5 mg per day. As such, use of hydrocortisone (Alkindi Sprinkle) in these settings over traditionally used hydrocortisone formulations (e.g. generic Cortef oral tablet) is not practical and FDA-approved, given the lack of the clinical superiority data for the former, as well as, higher cost of therapy.

IV. Efficacy and Safety of hydrocortisones (Alkindi Sprinkle) for treatment of conditions other than adrenocortical insufficiency have not been studied and remain unknown.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	12/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP175

Description

Hydroxyprogesterone caproate is an injectable synthetic progestin.

Length of Authorization

- Initial:
  - i. Endogenous estrogen measurement, diagnosis: 2 months
  - ii. All other indications: 12 months
- Renewal:
  - i. Endogenous estrogen measurement, diagnosis: No renewal allowed
  - ii. All other indications: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
hydroxyprogesterone caproate*	1250 mg/5mL (250mg/mL)	Advanced adenocarcinoma of the uterus Amenorrhea Endometrial disorder Endogenous estrogen measurement, diagnosis	1 vial/28 days

**As of April 6, 2023, there is only one NDC of hydroxyprogesterone caproate FDA-approved for interstate commerce (67457-0886-05). All other NDCs have been discontinued by the FDA.*

Initial Evaluation

I. **Hydroxyprogesterone caproate** may be considered medically necessary when the following criteria are met:
   A. Member is age 18 years or older; **AND**
   B. Member is NOT currently pregnant; **AND**
   C. A diagnosis of one of the following:
      1. Advanced adenocarcinoma of the uterus (stage III or IV); **OR**
      2. Amenorrhea; **OR**
      3. Endometrial disorder (production of secretory endometrium and desquamation); **OR**
      4. Endogenous estrogen measurement test

II. Hydroxyprogesterone caproate (Makena) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Reducing the risk of recurrent preterm birth

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has a diagnosis of one of the following:
    a. Advanced adenocarcinoma of the uterus (stage III or IV); **AND**
        i. Member has exhibited disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
    b. Amenorrhea; **OR**
    c. Endometrial disorder (production of secretory endometrium and desquamation); **AND**
        i. Member has exhibited improvement or stability of disease symptoms [e.g., normal menstrual bleeding]

Supporting Evidence

I. Hydroxyprogesterone caproate was initially approved under the ANDA pathway as a therapeutic equivalent to the reference listed drug (RLD) Delalutin in 2015. The labeled indications approved are in non-pregnant adult women: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV), in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer, as a test for endogenous estrogen production and for the production of secretory endometrium and desquamation.
II. It should be noted that the RLD Delalutin has been discontinued and removed from the U.S. market in 2010. The U.S. Food and Drug Administration (FDA) noted in their approval letter for the generic equivalent that because the RLD Delalutin as not withdrawn from sale for reasons of safety or effectiveness, it allowed the agency to continue to approve applications that refer to Delalutin. The FDA concluded that adequate information had been presented to demonstrate hydroxyprogesterone caproate is safe and effective for use as recommended in the submitted labeling (noted above) and was subsequently approved.
III. As of June 2023, there is only one hydroxyprogesterone caproate generic that is marketed in the U.S.; this product is manufactured by McGuff Pharmaceuticals for Mylan Institutional Inc.

Not Medically Necessary Uses

I. Hydroxyprogesterone caproate has not demonstrated sufficient safety and efficacy for the conditions or settings listed below:
    A. Reducing the risk of recurrent preterm birth

i. As of April 6, 2023, the FDA announced their final decision to withdraw approval of Makena from the U.S. market, indicating that Makena and its generics (hydroxyprogesterone caproate) are no longer approved and cannot lawfully be distributed in interstate commerce. This decision was issued jointly by the FDA Commissioner and Chief Scientist after finding that there is an insufficient demonstration of effectiveness to balance any level of risk.
ii. Hydroxyprogesterone caproate (Makena) was initially approved via the accelerated approval pathway based on the data from the NICHD-MFMU Network trial. The NICHD-MFMU Network trial was acquired by a pharmaceutical company (Adeza, Sunnyvale, CA) and submitted as part of a new drug application (NDA) to the Food and Drug Administration (FDA) in April 2006. In August 2006, an FDA Advisory Committee voted unanimously that an additional confirmatory clinical trial was required to further assess safety and efficacy.
iii. Based on the FDA ruling, the NDA sponsor initiated the confirmatory clinical trial (PROLONG), enrolling 5% of the overall subjects prior to FDA approval. The study was designed to have the power to show a direct clinical benefit (i.e., a reduction in a prespecified neonatal morbidity and mortality index).
iv. PROLONG is a Phase 3B, randomized double-blind parallel group study with a 2:1 ratio of active drug: vehicle, assigned randomly by a global telephone-based interactive registration system. Key inclusion criteria: at least 18 years of age, pregnant with a singleton gestation, documented history (chart notations from previous pregnancy and not just oral history) of singleton spontaneous preterm birth (PTB) between 200/7 and 366/7 weeks, after spontaneous PTB, or premature rupture of membranes. The primary safety outcome was fetal/early infant death defined as any of the following: spontaneous abortion/miscarriage (delivery from 160/7–196/7 weeks of gestation), stillbirth delivering after 200/7 weeks through term, or early infant death. The results of the PROLONG trial: fetal/early infant death rates were lower than expected and not different between treatment groups (17-OHPC 1.7% vs. placebo 1.9%; RR 0.87 [95% CI: 0.4–1.81]). No statistically significant difference in the frequency of stillbirth (17-OHPC 1.1% vs placebo 0.5%; RR 2.07 [95% CI 0.59–7.29])
v. On October 5, 2020, The Center for Drug Evaluation and Research (CDER) proposed withdrawing accelerated approval of Makena (hydroxyprogesterone caproate) on the grounds that the confirmatory study failed to verify clinical benefit of the drug and the evidence does not establish that the drug is effective under its conditions of use. A hearing took place in October 2022 where the advisory committee discussed and voted on whether the findings from PROLONG verify the clinical benefit of Makena and if the available evidence demonstrates that Makena is effective for its approved indication. The advisory committee voted unanimously that the PROLONG trial does not verify the clinical benefit of Makena, and 13 advisory committee members voted that the available evidence does not demonstrate that Makena is effective for its approved indication, with one member voting 'yes' and one member 'abstained'. Finally, 14 advisory committee members voted that Makena should not remain on the market while

an appropriate confirmatory study is designed and conducted, while one member voted 'yes'. Most advisory committee members agreed during discussion that there was not sufficient evidence that Makena is effective in any population.

vi. Given the lack of efficacy for reducing the risk of preterm birth and the subsequent decision by the FDA to withdraw the indication, treatment with hydroxyprogesterone caproate for risk reduction in recurrent preterm birth is not medically necessary.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria for medical necessity of hydroxyprogesterone caproate (Makena) removed; use of hydroxyprogesterone caproate (Makena) for reducing risk of recurrent preterm birth moved to not medically necessary section; criteria added for medical necessity of hydroxyprogesterone caproate (therapeutic equivalent of Delalutin); supporting evidence updated	06/2023
Policy created	02/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP269

Description

ibrexafungerp (Brexafemme) is an orally administered triterpenoid antifungal.

Length of Authorization

- Initial:
  - i. Acute vulvovaginal candidiasis (VVC): one month
  - ii. Recurrent vulvovaginal candidiasis (RVVC): 6 months
- Renewal: Cannot be renewed

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
ibrexafungerp (Brexafemme)	Treatment of vulvovaginal candidiasis (VVC)	150mg tablet	4 tablets/1 day
	Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC)		

Initial Evaluation

I. **Ibrexafungerp (Brexafemme)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Member has experienced menarche; **AND**
   C. A diagnosis of one of the following:
      1. **Acute vulvovaginal candidiasis (VVC)**; **AND**
         i. Treatment with fluconazole 150mg (Diflucan) has been ineffective, contraindicated, or not tolerated; **OR**
      2. Recurrent vulvovaginal candidiasis (RVVC); AND
         i. Member has a history of three or more acute vulvovaginal candidiasis (VVC) episodes within the last 12 months; **AND**
         ii. Member is currently experiencing signs and symptoms consistent with an acute episode of VVC (e.g., vulvovaginal pain, pruritis or irritation, abnormal vaginal discharge, etc.); **AND**
         iii. Diagnosis of acute VVC has been confirmed by positive KOH or culture; **AND**
         iv. Member has been treated with weekly oral fluconazole for a period of 6 months; **OR**
            a. Treatment with fluconazole is not tolerated or contraindicated; **OR**

b. Antifungal susceptibility testing has been conducted and confirms fluconazole resistance; **OR**
c. Member has experienced a recurrence during or following maintenance therapy with fluconazole

II. Ibrexafungerp (Brexafemme) is considered investigational when used for all other conditions, including but not limited to:
   A. Allergic bronchopulmonary aspergillosis
   B. Blastomycosis
   C. Coccidioidomycosis
   D. Histoplasmosis
   E. Invasive candidiasis
   F. Invasive and/or chronic pulmonary aspergillosis
   G. Mucocutaneous candidiasis

Renewal Evaluation

I. Please see initial evaluation

Supporting Evidence

I. Ibrexafungerp (Brexafemme) was initially approved by the FDA in 2021 for the treatment of acute vulvovaginal candidiasis (VVC) in adult and post-menarche pediatric females. In 2022, the FDA granted approval for a second indication, reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC).

II. **Acute Vulvovaginal Candidiasis**
   - In the setting of acute VVC, ibrexafungerp (Brexafemme) was studied in two identically designed randomized, double-blind, placebo-controlled, Phase 3 trials in 558 total post-menarche females aged 12 years and older (VANISH-303 and VANISH-306). The primary efficacy outcome was clinical cure (defined as complete resolution of signs and symptoms) at day 10 test-of-cure (TOC) visit. The key secondary outcomes included mycological eradication (negative culture for growth of yeast [candida species]) at TOC and clinical cure at follow-up visit (day 25). Ibrexafungerp (Brexafemme) was statistically significant compared to placebo for all primary and key secondary endpoints in both the VANISH-303 and VANISH-306 trials.
   - Ibrexafungerp (Brexafemme) was also studied against fluconazole in a Phase 2b, multicenter, randomized, double-blind, double-dummy, active-controlled, dose-finding study (DOVE) in 186 patients with moderate-to-severe acute VVC. The primary endpoint was percentage of patients with clinical cure at the TOC (day 10), which was 53% for ibrexafungerp (Brexafemem) and 58% for fluconazole. This study was not statistically powered; thus, the clinical significance of these results cannot be determined.

III. **Recurrent Vulvovaginal Candidiasis**

- In the setting of RVVC, ibrexafungerp (Brexafemme) was studied in one randomized, double-blind, placebo-controlled trial (CANDLE) of 260 post-menarche females aged 12 years and older who had a diagnosis of RVVC, defined as at least three prior episodes of acute VVC in the past 12 months. The trial consisted of an acute phase and a maintenance phase. All patients received fluconazole 150mg on days 1, 4, and 7 during the acute phase to treat their current infection. Patients who responded to fluconazole therapy with significant resolution of their vulvovaginal signs and symptoms, defined as total composite score of ≤ 2 on the VSS Scale) then entered the maintenance phase. Patients in the maintenance phase were randomized to receive ibrexafungerp (Brexafemme) or placebo once monthly for 6 months.
- The primary endpoint was percentage of patients with clinical success (defined as no mycologically proven, presumed, or suspected recurrence of VVC) up to the test-of-cure (TOC) visit at week 24 post-dose. The secondary endpoint was percentage of patients with no mycologically proven recurrence (defined as an episode of VVC with total composite VSS Score of ≥3 and a culture positive for Candida spp. That required antifungal treatment), also at TOC (24 weeks). For the primary endpoint, 65.4% of patients in the ibrexafungerp (Brexafemme) group met the primary endpoint compared to 53.1% of patients in the placebo group (p=0.02); this was sustained over the three-month follow-up period (p=0.034). For the secondary endpoint, 70.8% of patients in the ibrexafungerp (Brexafemme) group met the secondary endpoint compared to 58.5% of patients in the placebo group (p=0.019), which was also sustained over the follow-up period (p=0.029).

IV. Patients enrolled in the trial were aged 12 years and older who had already experienced menarche (i.e., first menstrual cycle). The safety and/or efficacy of ibrexafungerp (Brexafemme) in pediatric patients who are either under the age of 12 years or have not experienced menarche has not been evaluated.

V. The safety profile for ibrexafungerp (Brexafemme) was consistent between the acute VVC and RVVC trials. The most commonly reported side effects include diarrhea (~15%), nausea (~11%), abdominal pain (~11%), headache (~17%), and dizziness (~2%). Although ibrexafungerp (Brexafemme) carries a contraindication for use during pregnancy due to risk of embryo-fetal toxicity, women of childbearing age were included in the clinical trial and were advised to not become pregnant during the trial duration. FDA label recommends verifying pregnancy status prior to initiating therapy with ibrexafungerp (Brexafemme), and prior to each dose when using for RVVC.

VI. Clinical guidelines, including those published by the Centers for Disease Control and Prevention (CDC) and Infectious Disease Society of America (IDSA), indicate that diagnosis of VVC can typically be made via the presentation of infection signs/symptoms: pruritis, irritation, vaginal soreness, external dysuria, and dyspareunia accompanied by signs of vulvar edema, erythema, excoriation, fissures and white, thick, curd-like vaginal discharge. For complicated VVC and RVVC, diagnosis should be confirmed with a wet-mount preparation with use of saline and 10% potassium hydroxide (KOH). If KOH is negative, a culture for *Candida* should be obtained.

VII. For the treatment of acute VVC, IDSA and CDC guidelines carry a strong recommendation for topical (intravaginal) antifungals or oral fluconazole 150mg for acute, uncomplicated VVC. The

same medications can be used for complicated and/or recurrent VVC, but at extended treatment durations of 10 – 14 days. Topical antifungals, such as miconazole and clotrimazole, are available in multiple over the counter (OTC) formulations, while oral fluconazole remains prescription only.

VIII. RVVC is usually defined as having at least three episodes of acute VVC within one year and are typically caused by azole-susceptible *C. albicans*. Clinical guidelines recommend beginning treatment with induction therapy with a 10-to-14-day course of a topical azole or oral fluconazole, followed by maintenance therapy with fluconazole 150mg once weekly for six months. If oral fluconazole is not feasible, topical clotrimazole (200mg cream twice weekly or 500mg vaginal suppository once weekly) or other intermittent oral or topical antifungal treatment is recommended. After cessation of maintenance therapy, IDSA approximates a 40-50% recurrence rate. Ibrexafungerp (Brexafemme) may be considered medically necessary if oral fluconazole has been not tolerated, is contraindicated, fluconazole resistance is confirmed, or if members experience recurrence of acute VVC symptoms anytime during or after maintenance therapy with fluconazole.

IX. According to results of the CANDLE trial, nearly 70% of participants who completed the maintenance regimen with ibrexafungerp (Brexafemme) did not experience a recurrent episode for up to 36 weeks (approximately nine months). However, rates of recurrence beyond nine months or safety and efficacy of retreatment with ibrexafungerp (Brexafemme) has not been established. Due to lack of adequate safety and efficacy data to establish an appropriate timeline for retreatment, renewal requests will be evaluated against initial policy criteria.

Investigational or Not Medically Necessary Uses

I. Ibrexafungerp (Brexafemme) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Allergic bronchopulmonary aspergillosis
   B. Blastomycosis
   C. Coccidioidomycosis
   D. Histoplasmosis
   E. Invasive candidiasis
   F. Invasive and/or chronic pulmonary aspergillosis
   G. Mucocutaneous candidiasis

References

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2. Pappas PG, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2016;62(4):e1-50.
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6. Cadet R, et al. A Phase 2b, dose-finding study evaluating oral ibrexafungerp vs fluconazole in vulvovaginal candidiasis (DOVE). Obstet Gynecol. 2019;133 (suppl):113S–114S.
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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
oteseconazole (Vivjoa™)	Recurrent vulvovaginal candidiasis (RVVC)

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	03/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP037

Split Fill Management*

Description

Ibrutinib (Imbruvica) is an orally administered Bruton's tyrosine kinase (BTK) inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
ibrutinib (Imbruvica)	Chronic Graft versus Host Disease (refractory); Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; Waldenström Macroglobulinemia Chronic Graft versus Host Disease (refractory)	420 mg tablets	28 tablets/28 days
		70mg/mL suspension	216mL/35 days**
	Dose modification	280 mg tablets	56 tablets/28 days
	Dose modification	140 mg tablets	112 tablets/28 days
	Dose modification	140 mg capsules	120 capsules/30 days
	Dose modification	70 mg capsules	30 capsules/30 days

***Body surface area (BSA) dosing under 12 years of age: 240 mg/m^{2}once daily; maximum dose: 420 mg/dose. Due to the unbreakable packaging, 216mL/35 days is the maximum dosing. Those 12 and older should use 420mg tablets.*

Initial Evaluation

I. **Ibrutinib (Imbruvica)** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. If the request is for the 140 mg tablets or 280 mg tablets, there is documentation that the member has tried and failed or has a contraindication to the 140 mg capsules; **OR**
      1. If the request is for the 70mg/mL suspension, the patient is under 12 years of age; **AND**
   C. Member has not experienced disease progression while on a BTK inhibitor [e.g., zanubrutinib (Brukinsa), acalabrutinib (Calquence)]; **AND**
   D. A diagnosis of one of the following:
      1. **Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL); AND**
         i. Member is 18 years of age or older; **AND**

ii. The member does not have a 17p deletion or TP53 mutation confirmed by testing; **AND**
a. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
i. The request is for use in combination with bendamustine and rituximab in the relapsed/refractory setting; **OR**
iii. The member has a 17p deletion or TP53 mutation confirmed by testing; **AND**
a. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**

2. **Waldenström Macroglobulinemia (WM); AND**
i. Member is 18 years of age or older; **AND**
ii. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
iii. Ibrutinib (Imbruvica) will be used with rituximab; **OR**
3. **Chronic Graft versus Host Disease (cGVHD); AND**
i. Member is one year of age or older; **AND**
ii. Member has failed one or more lines of systemic therapy (e.g., corticosteroids, mycophenolate mofetil, calcineurin inhibitors, sirolimus)

II. Ibrutinib (Imbruvica) is considered not medically necessary when criteria above are not met and/or when used for:
A. Chronic lymphocytic leukemia/small lymphocytic lymphoma in combination with rituximab only
B. Mantle cell lymphoma (new to therapy)
C. Marginal zone lymphoma (new to therapy)

III. Ibrutinib (Imbruvica) is considered investigational when used for all other conditions, including but not limited to:
A. Chronic lymphocytic leukemia/small lymphocytic lymphoma in the first line setting in combination with obinutuzumab
B. Relapsed/refractory Hodgkin lymphoma
C. Diffuse large B cell lymphoma
D. Relapsed/refractory multiple myeloma
E. Hairy cell leukemia
F. Primary CNS lymphoma
G. Esophagogastric carcinoma
H. Glioblastoma
I. Non-small-cell lung carcinoma
J. T-cell lymphoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Treatment is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
IV. If the request is for the 140 mg tablets or 280 mg tablets, the member has tried and failed or has a contraindication to the 140 mg capsules; **OR**
    - If the request is for the 70mg/mL suspension, the member under the age of 12 years; **AND**
V. The member has exhibited improvement of their condition defined as:
    - **For GVHD:** The member has exhibited improvement or stability of symptoms [e.g., manifestations of disease to the skin, oral cavity, musculoskeletal system]; **OR**
    - **For oncology indications:** The member has not experienced disease progression while on ibrutinib (Imbruvica); **OR**
VI. Documentation of compelling clinical evidence of benefit is provided if therapy is to be continued after disease progression.

Supporting Evidence

I. NCCN guidelines note that acquired resistance to ibrutinib (Imbruvica) is mediated by BTK mutations, which have also been described in patients receiving other BTK inhibitors (e.g., acalabrutinib [Calquence], zanubrutinib [Brukinsa]).
II. The safety and efficacy of ibrutinib (Imbruvica) in patients with CLL/SLL were demonstrated in one uncontrolled trial and four randomized, controlled trials.
    - The RESONATE study, was a randomized, multicenter, open-label, phase 3 study of ibrutinib (Imbruvica) versus ofatumumab in patients with relapsed or refractory CLL/SLL. With an overall follow-up of 63 months, the median PFS was 44.1 months [95% CI (38.5, 56.9)] in the ibrutinib (Imbruvica) arm and 8.1 months [95% CI (7.8, 8.3)] in the ofatumumab arm, respectively. RESONATE included 127 patients with del17p CLL/SLL, PFS at 63 months was 40.6 months [95% CI (25.4, 44.6)] in the ibrutinib (Imbruvica) arm and 6.2 months [95% CI (4.6, 8.1)] in the ofatumumab arm.
    - The RESONATE-2 study, a randomized, multicenter, open-label, phase 3 study versus chlorambucil in patients 65 years or older with treatment-naive CLL/SLL (n=269) reported an overall survival analysis in the intention to treat patient population which resulted in a statistically significant HR of 0.44 [95% CI (0.21, 0.92)] and 2-year survival rate estimates of 94.7% [95% CI (89.1, 97.4)] and 84.3% [95% CI (76.7, 89.6)] in the ibrutinib (Imbruvica) and chlorambucil arms, respectively.
    - The HELIOS study was a randomized, double-blind, placebo-controlled, Phase 3 trial of ibrutinib (Imbruvica) in combination with bendamustine and rituximab in 578 patients with relapsed or refractory CLL/SLL. Patients with del17p were excluded. The primary efficacy endpoint was PFS. Ibrutinib (Imbruvica) in combination with bendamustine and rituximab had a median PFS that was not evaluable compared to 13.3 months for ibrutinib (Imbruvica) in combination with placebo. The HR was 0.20 (95% CI 0.15, 0.28) for PFS.

- NCCN CLL/SLL guidelines recommend ibrutinib (Imbruvica) monotherapy as a Category 1 recommendation in in the relapsed/refractory setting in patients with or without 17p deletion/TP53 mutation. In the first-line setting monotherapy also carries a Category 1 recommendation in patients without 17p deletion/TP53 mutation, with a 2A recommendation in those with the deletion/mutation. NCCN guidelines do not list combination ibrutinib (Imbruvica) with rituximab, ibrutinib (Imbruvica) with rituximab and bendamustine, or ibrutinib (Imbruvica) with obinutuzumab in members with 17p deletion/TP53 mutation as a treatment option.

III. The safety and efficacy of ibrutinib (Imbruvica) in patients with WM were demonstrated in two single-arm trials and one randomized, controlled trial. Study 1118, an open-label, multi-center, single-arm trial of 63 previously treated patients reported a response rate of 61.9%. The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received single-agent ibrutinib (Imbruvica). The response rate observed in the INNOVATE monotherapy arm was 71%, with a median follow-up time on study of 34 months. The INNOVATE study, a randomized, double-blind, placebo-controlled, phase 3 study of ibrutinib (Imbruvica) or placebo in combination with rituximab in subjects with treatment naïve or previously treated WM. The primary endpoint of progression-free survival (PFS) was 82% with ibrutinib–rituximab versus 28% with placebo–rituximab (hazard ratio for progression or death, 0.20; P<0.001).

IV. The safety and efficacy of ibrutinib (Imbruvica) in cGVHD was shown in two clinical trials. One being the confirmatory FDA approval trial for adults and the second was a safety trial for an age expansion in pediatrics.

- Ibrutinib (Imbruvica) was studied in an open-label, multi-center, single-arm trial of 42 adult (18 and over) patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy; patients received 420mg of ibrutinib daily. Therapy with ibrutinib (Imbruvica) resulted in an ORR of 67%. Corticosteroids are the mainstay of initial systemic treatment for patients with cGVHD. Alternatives to, or add-on therapy to, corticosteroids include, but are not limited to, mycophenolate mofetil, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), and sirolimus.
- In 2022, ibrutinib (Imbruvica) was studied in an open-label, multi-center, single arm trial in pediatric patients aged between 1 year and 22 years with moderate to severe cGVHD. The trial enrolled 47 patients who required additional therapy after failure of one or more prior lines of systemic therapy (e.g. cyclosporine, tacrolimus). Patients 12 and older were treated with 420mg once daily and those 1 year to under 12 were treated with 240mg/m^2 once daily, with a maximum dose of 420mg. The ORR through week 25 was 60%. Additionally, there were no new safety signals compared to the adult confirmatory trial.

V. For several indications and trials, the rate of discontinuation/dose reduction/dose interruption was greater than 20% of the population studied. The high rate of discontinuation meets the requirements for split-fill criteria.

Investigational or Not Medically Necessary Uses

I. Ibrutinib (Imbruvica) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below.

Not Medically Necessary Uses

A. Chronic lymphocytic leukemia/small lymphocytic leukemia, in combination with rituximab
   i. In the E1912 trial, ibrutinib (Imbruvica) in combination with rituximab, showed significant improvements in PFS compared to fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy. The primary endpoint was PFS, and the HR for disease progression was 0.34 (95% CI 0.22, 0.52). The results of the Phase 3 Alliance North American Intergroup Study (A041202) comparing ibrutinib (Imbruvica) monotherapy to ibrutinib (Imbruvica) + rituximab found the estimate 2-year PFS rates were 87% and 88% (p=0.49), respectively. NCCN guidelines note that the addition of rituximab to ibrutinib has not yet demonstrated improvement in clinical outcomes compared to ibrutinib monotherapy in a randomized clinical trial. The consensus was that the longer PFS in combination trials was more the result of continuous and indefinite treatment with ibrutinib, rather than due to the contribution of rituximab. There is a consideration that improved outcomes with the addition of anti-CD20 monoclonal antibodies may more likely be seen with fixed-duration treatment with these regimens.

B. Mantle cell lymphoma (MCL)
   i. Ibrutinib (Imbruvica) was previously FDA-approved under the accelerated approval pathway for the treatment of adult patients with MCL who have received at least one prior therapy. This indication approval was based on overall response rate and continued approval was contingent upon verification and description of clinical benefit in confirmatory trials. The confirmatory phase 3 trial (SHINE) met the primary endpoint of progression-free survival but failed to show significant overall survival benefit in patients treated with combination of ibrutinib (Imbruvica), bendamustine, and rituximab compared to patients treated with combination of placebo, bendamustine, and rituximab. Overall survival at 7 years was 55% in the ibrutinib (Imbruvica) group and 56.8% in the placebo group. Moreover, the addition of ibrutinib (Imbruvica) to chemotherapy was associated with increased adverse reactions compared to placebo-controlled group. After discussion of the results with the FDA, AbbVie voluntarily withdrew the U.S. accelerated approval for patients with MCL as the confirmatory study was insufficient to support conversion to full approval. Requests for initiation of ibrutinib (Imbruvica) for the treatment of MCL are considered not medically necessary due to a failed confirmatory Phase 3 trial and lack of continued FDA approval. Patients currently receiving ibrutinib (Imbruvica) and experiencing benefit from therapy are eligible for renewal and continued use for the treatment of MCL.

ii. Ibrutinib (Imbruvica) was also studied against temsirolimus in one randomized, open-label, multi-center, Phase 3 trial in patients with relapsed or refractory MCL. Data is available for three years of follow up. Median progression free survival (PFS) was significantly longer for ibrutinib (Imbruvica) than temsirolimus (15.6 vs 6.2 months; HR 0.45 [95% CI 0.35–0.60]; P < 0.0001). Overall survival (OS) data was not statistically significant but favored ibrutinib (Imbruvica) numerically (30.3 vs 23.5 months, respectively; HR 0.74 [95% CI 0.54–1.02]; P = 0.0621).

<u>Ongoing studies of ibrutinib (Imbruvica) for the treatment of MCL:</u>

iii. Mantle cell lymphoma, frontline
    1. Ibrutinib (Imbruvica) is being investigated as a first-line treatment in patients up to 65 years of age in the European TRINANGLE trial (NCT02858258). The study evaluates the addition of ibrutinib (Imbruvica) in the induction phase and as maintenance, as well as if autologous stem cell transplant may be omitted. Three-year results have been reported at the 2022 American Society of Hematology Annual meeting, however, longer follow up is needed to confirm benefit.
    2. Ibrutinib (Imbruvica) is being investigated as a first line treatment in a Phase 2/3 trial (ENRICH) in patients over 60 years of age with MCL. The trial is comparing ibrutinib combined with rituximab, followed by rituximab maintenance against rituximab combined with chemotherapy, followed by rituximab maintenance. ENRICH is fully enrolled but there are no data available yet.

iv. Mantle cell lymphoma, combination therapy.
    1. Ibrutinib (Imbruvica) was studied in an open-label, single-arm, Phase 2 trial in combination with rituximab in patients with relapsed or refractory MCL and in patients over 65 years of age with newly-diagnosed, untreated MCL. At a median follow-up of 16.5 months, 44 (88%, 95% CI 75.7-95.5) patients achieved an objective response. Additional studies are needed to further evaluate and support this combination use.
    2. Combination of ibrutinib (Imbruvica), lenalidomide, and rituximab was studied in one open-label, single-arm, Phase 2 trial in patients with relapsed or refractory MCL who had previously been treated with at least one rituximab-containing regimen. The primary endpoint, ORR at 17.8 months was achieved in 38 (76%, 95% CI 63-86) patients. Additional studies are needed to further evaluate and support this combination use.
    3. A Phase 2 study of ibrutinib (Imbruvica) plus venetoclax in relapsed or refractory MCL patients (n=23), found the primary endpoint of complete response rate at week 16 was 42%, which was higher than the historical control of 9% at this time point with ibrutinib (Imbruvica) monotherapy (P<0.001). Additional studies are needed to further evaluate and support this combination use.

C. Marginal zone lymphoma (MZL)
    i. In the setting of MZL, ibrutinib (Imbruvica) was FDA-approved under accelerated approval pathway based on an open-label, multi-center, single-arm trial (PCYC-

1121) of 63 adult patients who received at least one prior therapy, including one anti-CD20-directed regimen. The confirmatory phase 3 study (SELENE; NCT01974440) in patients with relapsed/refractory follicular lymphoma or MZL did not meet its primary endpoint of progression-free survival in patients with R/R FL or MZL. The SELENE study results will be presented at a future scientific forum. After discussion of the results with the FDA, AbbVie voluntarily withdrew the U.S. accelerated approval for patients with MZL as the confirmatory study was insufficient to support conversion to full approval. Requests for initiation of ibrutinib (Imbruvica) for the treatment of MZL are considered not medically necessary due to a failed confirmatory Phase 3 trial and lack of continued FDA approval. Patients currently receiving ibrutinib (Imbruvica) and experiencing benefit from therapy are eligible for renewal and continued use for the treatment of MZL.

Ongoing studies of ibrutinib (Imbruvica) for the treatment of MZL:

i. Marginal zone lymphoma, frontline
    1. Ibrutinib (Imbruvica) has not been sufficiently studied in treatment naïve patients with MZL. A Phase 3, double-blind, placebo-controlled study evaluating ibrutinib (Imbruvica) in combination with rituximab in treatment naïve patients is currently underway with estimated completion date of June 30, 2024 (NCT04212013). Additionally, a Phase 2, single-arm, open-label trial (MALIBU) evaluating ibrutinib (Imbruvica) in combination with rituximab is also underway with expected completion date of June 15, 2024 (NCT03697512).

Investigational

A. Chronic lymphocytic leukemia/small lymphocytic lymphoma in the first line setting in combination with obinutuzumab
    ii. The iLLUMINATE study was a randomized, open-label, active-controlled, multicenter, Phase 3 trial of ibrutinib (Imbruvica) in combination with obinutuzumab studied against chlorambucil in combination with obinutuzumab in 229 patients with treatment naïve CLL/SLL. Patients were either aged 65 years or older or younger than 65 years with coexisting conditions. The primary efficacy outcome was PFS. Ibrutinib (Imbruvica) in combination with obinutuzumab, had a median PFS that was not evaluable, compared to 19 months for chlorambucil in combination with obinutuzumab. The HR was 0.23 (95% CI 0.13, 0.37) for PFS. There have been no direct comparisons between ibrutinib (Imbruvica) monotherapy and ibrutinib (Imbruvica) in combination with obinutuzumab, therefore, it is not known if combination of the two agents will provide superior efficacy outcomes than ibrutinib (Imbruvica) monotherapy. Additionally, NCCN guidelines state that longer PFS may be the result of continuous and indefinite treatment with ibrutinib, rather than due to contribution of an anti-CD20 mAb during the first six months of treatment. There is a consideration that improved

outcomes with the addition of anti-CD20 monoclonal antibodies may more likely be seen with fixed-duration treatment with these regimens.
NCCN guidelines recommend ibrutinib (Imbruvica) + obinutuzumab (for frail patients with significant comorbidities and patients aged ≥65 years and younger patients with significant comorbidities) and ibrutinib + rituximab (for patients <65 years without significant comorbidities) as a 2B (other recommended regimens) recommendation.

B. Relapsed/refractory Hodgkin lymphoma
    iii. Subject of current ongoing trials.
C. Diffuse large B cell lymphoma
    iv. Ibrutinib (Imbruvica) was studied in a phase 1/2 clinical trial that involved 80 subjects with relapsed or refractory DLBCL, ibrutinib (Imbruvica) produced complete or partial responses in 37% (14/38) of those with activated B cell–like (ABC) DLBCL, but in only 5% (1/20) of subjects with germinal center B cell–like (GCB) DLBCL (P = 0.0106). Additional studies are need and are currently underway, as ibrutinib (Imbruvica) is the subject of several ongoing phase 2 trials in the relapsed/refractory setting.
    v. The addition of ibrutinib (Imbruivca) to standard R-CHOP chemotherapy regimen in the DLBCL first-line setting failed to meet its primary endpoint of improving event-free survival (EFS) when compared to R-CHOP alone in the phase III PHOENIX (NCT01855750) study.
D. Relapsed/refractory multiple myeloma
    vi. Ibrutinib (Imbruvica) was studied in a phase 2 study that examined various doses of ibrutinib (Imbruvica) ± low-dose dexamethasone in patients who received ≥2 prior lines of therapy, including an immunomodulatory agent. The primary objective of clinical benefit rate (CBR; ≥minimal response) was the highest (CBR 28%) in Cohort 4 which consisted of ibrutinib (Imbruvica) + dexamethasone (n=43). Further evaluation is needed to support use of ibrutinib (Imbruvica) in this setting.
E. Hairy cell leukemia
    vii. Ibrutinib (Imbruvica) was subject of a single arm phase two study (n=28) in patients with hairy cell leukemia stage 1. The primary overall of objective response rate, was seen in 46%, with objective responses more commonly seen in those patients with classical hairy cell leukemia (c-HCL). Additional studies are needed to further evaluate and support this use.
F. Primary CNS lymphoma
    viii. Ibrutinib (Imbruvica) was subject of a phase 1 trial in patients (n=13) with relapsed or refractory CNS lymphoma. Additional studies are needed to further evaluate and support this use.
G. Esophagogastric carcinoma
    ix. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.
H. Glioblastoma
    x. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.
I. Non-small-cell lung carcinoma

xi. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

J. T-cell lymphoma

xii. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

Related Policies

Policy Name	Disease state
ruxolitinib (Jakafi®)	Chronic Graft versus Host Disease
belumosudil (Rezurock™)	
acalabrutinib (Calquence ®)	Mantle cell lymphoma; CLL; SLL
lenalidomide (Revlimid®); pomalidomide (Pomalyst®); thalidomide (Thalomid®)	Mantle cell lymphoma; marginal zone lymphoma
zanubrutinib (Brukinsa™)	Mantle cell lymphoma; Waldenstrom's macroglobulinemia; marginal zone lymphoma' CLL, SLL

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated QL table to allow coverage of suspension in all indications	02/2024
Following withdrawal of FDA approval: removed mantle cell lymphoma (MCL) from covered indications, added MCL in the not medically necessary uses section, removed marginal zone lymphoma (MZL) from experimental and investigational uses section, added marginal zone lymphoma (MZL) in the not medically necessary uses section, updated renewal section with standard policy renewal language requirements, updated supporting evidence, changed quantity limits for 140 mg tablets and capsules and 280 mg tablets to allow for MCL and MZL dosing, removed MCL and MZL from quantity limits table, removed 560 mg tablet formulation, changed initial authorization length from three to six months.	04/2023
Updated cGVHD for the age expansion for those aged 1 year or older. Added criteria for the new formulation approved (70mg/ml suspension) for use in pediatric patients. Added in related policy table.	10/2022
Removed initial criteria and moved MZL indication to investigational or not medically necessary uses section. Added supporting evidence for MCL indication and updated MCL investigational or not medically necessary uses section. Moved ibrutinib (Imbruvica) in combination with obinutuzumab in the setting of treatment naïve CLL/SLL to investigational or not medically necessary uses section.	01/2022
Addition of split-fill requirement. Included requirement the member has not progressed on a previous BTK inhibitor. Updated policy based on new indication in combination with rituximab for CLL/SLL as not medically necessary. Criteria for CLL/SLL updated to focus on diagnosis and mutation status over use in combination with other agents. Updated criteria for MCL and MZL to only be used as monotherapy. Removed toxicity renewal requirement and added disease stability renewal examples for GVHD patients.	06/2020
Updated criteria to policy format, specified combination therapy in CLL/SLL patients to be used in members without 17p deletion/TP53 mutation, addition of trial and failure of 140mg capsules prior to use of 140 mg or 280 mg tablets. In MCL, marginal zone lymphoma, and graft versus host disease, added more detail on type of prior therapy required. For Waldenström macroglobulinemia added use to be as monotherapy or with rituximab.	03/2019
Updated formatting, extended initial approval from 3 months to 6 months.	01/2018
Previous updates	08/2014 02/2015 04/2015 08/2017
Criteria created	02/2014

Policy Type: PA/SP Pharmacy Coverage Policy: UMP168

Description

Idelalisib (Zydelig) is an orally administered PI3Kδ kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
idelalisib (Zydelig)	100 mg tablets	Relapsed Chronic Lymphocytic Leukemia	60 tablets/30 days
	150 mg tablets		

Initial Evaluation

I. Idelalisib (Zydelig) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. A diagnosis of one of the following:
      1. Relapsed Chronic Lymphocytic Leukemia (CLL); AND
         i. Documentation of use of at least one prior therapy; **AND**
         ii. Use is in combination with rituximab; **AND**
         iii. Will not be used with any other oncology therapy

II. Idelalisib (Zydelig) is considered investigational when used for all other conditions, including but not limited to:
   A. Relapsed Small Lymphocytic Lymphoma (SLL)
   B. Relapsed Follicular B-cell non-Hodgkin Lymphoma (FL)
   C. Idelalisib as monotherapy for the treatment of relapsed or refractory CLL/SLL
   D. Use as treatment naïve or first line therapy for any indication
   E. In combination with other medications for any indication outside of dual therapy with rituximab for the indication of relapsed CLL
   F. Marginal zone lymphoma
   G. Lymphoplasmacytic lymphoma with or without Waldenstrom's macroglobulinemia
   H. Immunoglobulin M (IgM) associated primary amyloidosis
   I. Hodgkin Lymphoma
   J. Acute Lymphoblastic Leukemia
   K. Non-Small Cell Lung Cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Member has a diagnosis of one of the following:
    A. **Relapsed Chronic Lymphocytic Leukemia (CLL)**; **AND**
        1. Use is in combination with rituximab

Supporting Evidence

I. Safety and efficacy of idelalisib (Zydelig) has not been studied or established in the pediatric population.
II. Treatment for CLL is a difficult to treat condition requiring consultation with an oncologist or hematologist.
III. Idelalisib (Zydelig) was studied in a Phase III, randomized, double blind placebo controlled clinical trial in combination with rituximab in patients with relapsed chronic lymphocytic leukemia (CLL). Patients were given idelalisib (Zydelig) 150mg twice daily until disease progression or unacceptable toxicity. Nearly all patients had prior treatment with anti-CD20 monoclonal antibodies, and most patients also had prior treatment with bendamustine/rituximab, fludarabine/cyclophosphamide/rituximab, or rituximab monotherapy. Primary outcome was progression free survival and overall response rate with the median duration of response not reached.

Investigational or Not Medically Necessary Uses

I. Relapsed Small Lymphocytic Lymphoma (SLL)
    A. FDA accelerated approval was previously granted to idelalisib (Zydelig) for the treatment of SLL and FL based on results from a phase 2 clinical trial of patients with indolent Hodgkin lymphoma. Approval was contingent upon a positive confirmatory study, and this was not achieved. As the treatment landscape for FL and SLL has evolved, enrollment into the confirmatory study was an ongoing challenge. As a result, Gilead Sciences, Inc. notified the FDA of its decision to voluntarily withdraw these indications from the U.S. market.
    B. Idelalisib (Zydelig) was studied in a Phase II, open label, single group clinical trial including patients with small lymphocytic leukemia (SLL) who had relapsed within six months following rituximab and an alkylating agent and had at least two prior treatments. The most common prior treatments included rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, fludarabine/cyclophosphamide/rituximab, and bendamustine/rituximab. Primary outcome was overall response rate with the median duration of response of 11.9 months.
II. Relapsed Follicular B-cell non-Hodgkin Lymphoma (FL)

A. FDA accelerated approval was previously granted to idelalisib (Zydelig) for the treatment of SLL and FL based on results from a phase 2 clinical trial of patients with indolent Hodgkin lymphoma. Approval was contingent upon a positive confirmatory study, and this was not achieved. As the treatment landscape for FL and SLL has evolved, enrollment into the confirmatory study was an ongoing challenge. As a result, Gilead Sciences, Inc. notified the FDA of its decision to voluntarily withdraw these indications from the U.S. market.
B. Idelalisib (Zydelig) was studied in a single-arm study including patients with follicular B-cell non-Hodgkins lymphoma who had relapsed within 6 months following treatment with rituximab and an alkylating agent and had at least two prior treatments. Patients were given idelalisib (Zydelig) 150mg twice daily until disease progression or toxicity. The most common prior treatments included rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, rituximab/cyclophosphamide/vincristine/prednisone, and bendamustine/rituximab. Primary outcome was overall response rate with the median duration of response being not evaluable.

III. Idelalisib as monotherapy for the treatment of relapsed or refractory CLL
A. Idelalisib (Zydelig) was not found to be beneficial as monotherapy or as first line in patients with CLL. Label does not support use as monotherapy.

IV. Idelalisib (Zydelig) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
A. Use as treatment naïve or first line therapy for any indication
B. In combination with other medications for any indication outside of dual therapy with rituximab for the indication of relapsed CLL.
C. Marginal zone lymphoma
D. Lymphoplasmacytic lymphoma with or without Waldenstrom's macroglobulinemia
E. Immunoglobulin M (IgM) associated primary amyloidosis
F. Hodgkin Lymphoma
G. Acute Lymphoblastic Leukemia
H. Non-Small Cell Lung Cancer

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Policy Implementation/Update:

Action and Summary of Changes	Date
Moved FL and SLL to E/I section following voluntary withdraw of these indications by the manufacturer.	03/2022
Policy updated to require use of one prior therapy for CLL; removed history of toxic epidermal necrolysis	02/2020

Previous reviews	11/2014

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Policy Type: PA/SP Pharmacy Coverage Policy: UMP123

Split Fill Management* (applies to olutasidenib [Rezlidhia] and ivosidenib [Tibsovo] only)

Description
Ivosidenib (Tibsovo) and olutasidenib (Rezlidhia) inhibit the isocitrate dehydrogenase 1 (IDH-1) enzyme. It limits the proliferation of the 2-HG oncometabolite, a competitive inhibitor of the normal metabolite, and promotes cell differentiation. Enasidenib (Idhifa) inhibits isocitrate dehydrogenase 2 (IDH-2). It specifically targets IDH-2 variants mutant R140Q, R172S, and R172K to decrease 2-hydroxyglutarate (2-HG) levels and induce myeloid differentiation; thereby, reducing blast counts and increasing mature myeloid cell percentage.

Length of Authorization
- Initial: Six months; first three months split fill for ivosidenib (Tibsovo) and olutasidenib (Rezlidhia)
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
enasidenib (Idhifa)	Acute myeloid leukemia, relapsed/refractory	50 mg tablets	30 tablets/30 days
		100 mg tablets	
ivosidenib (Tibsovo)	Acute myeloid leukemia, relapsed/refractory Acute myeloid leukemia, newly diagnosed Cholangiocarcinoma, advanced/ metastatic Myelodysplastic syndromes, relapsed/refractory	250 mg capsule	60 capsules/ 30 days
olutasidenib (Rezlidhia)	Acute myeloid leukemia, relapsed/refractory	150 mg capsule	60 capsules/ 30 days

Initial Evaluation

I. **Enasidenib (Idhifa)**, **ivosidenib (Tibsovo),** and **olutasidenib (Rezlidhia)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**

B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
C. The member has not previously progressed on or after an IDH inhibitor [e.g., ivosidenib (Tibsovo), olutasidenib (Rezlidhia), enasidenib (Idhifa)]; **AND**
D. A diagnosis of one of the following:
    1. **Relapsed or refractory acute myeloid leukemia (AML); AND**
        a. Medication will not be used in combination with other oncologic agents (i.e., as monotherapy); **AND**
        b. Treatment with <u>one</u> of the following has been ineffective, or not tolerated unless both are contraindicated:
            i. Systemic chemotherapy**; OR**
            ii. Allogenic hematopoietic stem cell transplant; **AND**
        c. Presence of IDH-1 mutation as detected by an FDA-approved test is documented; **AND**
            i. Request is for ivosidenib (Tibsovo) or olutasidenib (Rezlidhia); **OR**
        d. Presence of IDH-2 mutation as detected by an FDA-approved test is documented; **AND**
            i. Request is for enasidenib (Idhifa); **OR**
    2. **<u>Newly</u> diagnosed AML**; **AND**
        i. Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
        ii. Member is 75 years of age or older; **OR**
        iii. Provider attests that the member has comorbidities that preclude intensive induction chemotherapy (e.g., baseline Eastern Cooperative Oncology Group performance status of ≥ 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, or creatine clearance <45 mL/min); **AND**
        iv. Request is for ivosidenib (Tibsovo); **AND**
            a. Treatment will <u>not</u> be used in combination with other oncologic agents (i.e., as monotherapy); **OR**
            b. Treatment will be used in combination with injectable azacitidine; **OR**
    3. **Locally advanced or metastatic cholangiocarcinoma; AND**
        a. Request is for ivosidenib (Tibsovo); **AND**
        b. Ivosidenib (Tibsovo) will not be used in combination with other oncologic agents (i.e., as monotherapy); **AND**
        c. Provider attests that the member is not a candidate for surgery (i.e., unresectable cholangiocarcinoma); **AND**
        d. Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
        e. Member has had disease progression on, or after, at least one systemic therapy (e.g., gemcitabine, or 5-fluorouracil)
    4. Relapsed or refractory myelodysplastic syndromes (MDS); AND
        i. Request is for ivosidenib (Tibsovo); **AND**
        ii. Ivosidenib (Tibsovo) will not be used in combination with other oncologic agents (i.e., as monotherapy); **AND**

iii. Documentation of IDH-1 mutation as detected by an FDA-approved test; **AND**
iv. Member has had disease progression on, or after, at least one systemic therapy (e.g., azacitidine, decitabine, cedazuridine, lenalidomide); **AND**
v. Attestation member is not eligible for currently enrolling clinical trials

II. Enasidenib (Idhifa), ivosidenib (Tibsovo), and/or olutasidenib (Rezlidhia) are considered investigational when used for all other conditions, including but not limited to:
A. Enasidenib (Idhifa), ivosidenib (Tibsovo), or olutasidenib (Rezlidhia) used in combination with oncology therapies not specifically detailed above
B. Advanced cholangiocarcinoma without IDH-1 mutation
C. Chondrosarcomas
D. Enasidenib (Idhifa) and olutasidenib (Rezlidhia) for the treatment of Myelodysplastic Syndrome (MDS)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., became independent of red blood cell and platelet transfusion, or exhibited tumor response).

Supporting Evidence

I. Efficacy and safety of enasidenib (Idhifa), olutasidenib (Rezlidhia), and Ivosidenib (Tibsovo) has not been studied in the pediatric population. Current FDA approvals for these agents are limited to adult members.
II. Diagnosis and management of acute myeloid leukemia, myelodysplastic syndromes, and cholangiocarcinoma require detailed clinical examination in combination with advanced testing such as MRI, EEG, and genetic screening (e.g., IDH-1 mutation). Given the complexities of diagnosis and treatment of these conditions, supervision of treatment by a hematologist or an oncologist is required.

Enasidenib (Idhifa):

I. Enasidenib (Idhifa) was studied in a Phase I/II open-label, single-arm, multicenter, two-cohort clinical trial in patients who have a diagnosis of relapsed/refractory acute myeloid leukemia (AML) and IDH2 mutation. The study was conducted in 3 parts: (1) Phase 1 dose escalation, (2) Phase 1 expansion, and (3) Phase 2 expansion. Cohort 1 (dose-escalation): patients receiving enasidenib (Idhifa) 50mg to 650mg. Cohort 2 (Phase 1 & phase 2 expansion): patients receiving enasidenib (Idhifa) 100mg daily. The primary outcome measure of the study was to determine the safety and maximum tolerated dose (MTD) of enasidenib (Idhifa). In the phase I/II study, enasidenib (Idhifa) demonstrated that the MTD was not reached at doses of up to 650mg daily and 26.1% of all patients in the study had treatment-related serious adverse events.

II. In the most recent Phase 2 expansion data, the secondary outcome measures were reported for patients who were taking enasidenib (Idhifa) 100mg daily, which included: a complete response (CR) of 20.1%, a median time to CR of 3.7 months, and the median duration of response for patients who achieved CR was 8.8 months.

III. NCCN Guidelines preferred therapies for the treatment of recurrent/relapse AML include the following: clinical trial, systemic chemotherapy, or allogenic hematopoietic stem cell transplant.

Ivosidenib (Tibsovo):

I. Ivosidenib (Tibsovo) was studied in an open-label, single-arm, multicenter clinical trial in 174 adult patients with relapsed or refractory AML with an IDH-1 mutation. In this trial, the primary objectives were to assess the safety, maximum tolerated dose, and the recommended phase 2 dose of ivosidenib (Tibsovo) in patients with secondary, or later, relapse. Patients included in the trial had a relapse after stem-cell transplantation, had disease that was refractory to induction or reinduction chemotherapy, or had a relapse less than 12 months after initial therapy. Ivosidenib (Tibsovo) was approved in the setting of relapsed and refractory AML based on the following results: the rate of complete remission or complete remission with partial hematologic recovery was 30.4% (95% confidence interval [CI], 22.5 to 39.3), the rate of complete remission was 21.6% (95% CI, 14.7 to 29.8), and the overall response rate was 41.6% (95% CI, 32.9 to 50.8). Of note, 12% of the patients went on to stem cell transplantation following ivosidenib (Tibsovo) treatment and 15.1% of the patients died due to disease progression and complication of underlying disease (e.g., infection, respiratory failure, hemorrhage).
    - Ivosidenib (Tibsovo) was studied in an open-label, single-arm, multicenter clinical trial in 28 adult patients with newly diagnosed AML that have an IDH-1 mutation. In this trial, the eligible population included patients who were age 75 years or older or who had comorbidities that precluded the use of intensive induction chemotherapy (ECOG performance ≥2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, or CrCL <45 mL/min). In this trial, the efficacy was determined by the rate of complete remission (CR) or complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. Ivosidenib (Tibsovo) was granted FDA-approval as first-line therapy for AML patients with IDH-1 mutation, aged 75 years or above, or whose present comorbidities preclude the use of intensive induction chemotherapy. This approval was based on the following results: CR + CRh rate was 42.4% (95% confidence interval [CI], 25.5-60.8%) and 41.2% became independent of red blood cell (RBC) and platelet transfusion during any 56-day post-baseline period. Of note, 7% of the patients went on to stem cell transplantation following ivosidenib (Tibsovo) treatment.

II. Efficacy and safety of combination ivosidenib (Tibsovo) and azacitidine was studied in a double-blind, randomized, placebo controlled, phase 3 (AGILE) clinical trial. Adult participants (N=146) with newly diagnosed AML, confirmed IDH-1 mutations who were age 75 years or older or who had comorbidities that precluded the use of intensive induction chemotherapy were included in the study population. Patients were randomized 1:1 to ivosidenib (Tibsovo) plus azacitidine or placebo plus azacitidine. The trial ended early per an observation of the difference in number of deaths favoring ivosidenib (Tibsovo) and azacitidine arm – concluding the trial prior to enrolling the number needed for its power calculation. The primary outcome measure was progression event-survival reported as a hazard ratio of 0.33 (95% confidence interval [CI], 0.16 to 0.69; p=

0.002]. Median event-free survival was 0.03 months in both the treatment and placebo arms as more than half the patients in each arm did not have complete remission by week 24. Secondary endpoints included the rate of complete remission (CR) or complete remission with partial hematologic recovery (CRh) was 53% (95% CI, 41 to 65) in the treatment arm compared to 18% (95% CI, 10 to 28) in the placebo arm. CR was 47% (95% CI, 35 to 59) to 15% (95% CI, 8 to 25) respectively and the objective response rate was 62% (95% CI, 50 to 74) to 19% (95% CI, 11 to 30; p< 0.001). Median overall survival on the basis of 74 deaths was 24 months in the treatment arm (95% CI, 11.3 to 34.1) compared to 7.9 months (95% CI, 4.1 to 11.3) in the placebo arm HR 0.44; 95% CI, 0.27 to 0.73; P = 0.001). Together the combination ivosidenib (Tibsovo) + azacitidine provided a significantly better CR rate as compared to placebo + azacitidine. Additionally, combination therapy provided a favorable risk reduction in both PFS and OS indicating efficacy in the newly diagnosed AML population.

- Though the AGILE study did not compare ivosidenib (Tibsovo) monotherapy to combination therapy with azacitidine indirect comparisons between ivosidenib (Tibsovo) monotherapy and ivosidenib (Tibsovo) + azacitidine combination therapy can be made. Combination therapy showed an increase in CR rates between the two trials [28.6% to 47% respectively]. CR is the first goal of AML induction chemotherapy**.** With a noted increase in reported CR rates in combination and monotherapy trials it can be assumed with moderate confidence that combination ivosidenib (Tibsovo) + azacitidine provides a clinically meaningful benefit as compared to monotherapy alone.

III. Efficacy and safety of ivosidenib (Tibsovo) for the treatment of cholangiocarcinoma was evaluated in a double-blind, placebo-controlled, phase 3 (ClarIDHy) clinical trial. Adult participants (N=185), who had advanced or metastatic unresectable cholangiocarcinoma with documented IDH-1 mutation, and who had progressed on or after at least one systemic therapy consisting of gemcitabine or 5-fluorouracil were included. This trial included a one-way crossover allowing the patients randomized to placebo arm to crossover to receive ivosidenib (Tibsovo) upon progression. Although the crossover population was included for the calculation of overall survival (OS) data, primary outcome (progression-free survival (PFS)) only included initially randomized population (ITT analysis). After a median follow-up of 6.9 months, ivosidenib (Tibsovo) exhibited statistically significant improvement in PFS: 2.7 months versus 1.4 months for placebo arm (HR 0.37; 95% CI 0.25 to 0.54; p<0.0001). Additionally median OS at data cut-off was 10.8 months (7.7, 17.6) with ivodesinib (Tibsovo) as compared to 9.7 months (4.8, 12.1) with placebo (HR 0.69; 95% CI 0.44, 1.10; p 0.06). Although not statistically significant, in presence of significant primary outcome (PFS), the OS data provided indication of survival benefit with ivosidenib (Tibsovo). Additionally, treatment with ivosidenib (Tibsovo) also indicated improvement in quality of life parameters (QoL) upon comparing the patient answered questionnaires at cycle 2 of treatment versus cycle.

- During ClarIDHy clinical trial, 30% patients, who were on ivosidenib (Tibsovo), reported serious (≥ grade 3) adverse reactions, which included hyperbilirubinaemia, jaundice cholestatic, ECG QT prolonged, and pleural effusion. No additional concerning safety signals were noted during this clinical trial when compared to previous trials for AML. Treatment related dose reduction rates were 3%, treatment discontinuation rate 6%, and dose interruption rate 29%, respectively. Among the 78 deaths (49 in the treatment arm) reported during the trial, none were ascribed as treatment-emergent.

- NCCN Guideline preferred first-line systemic therapies for the treatment of hepatobiliary cancer include: surgical resection followed by adjuvant chemotherapy (e.g., capecitabine, 5-fluorouracil (5FU), cisplatin). For non-resectable metastatic biliary tract cancer, first-line gemcitabine in combination with cisplatin is preferred regimen (category 1). 5FU, FOLFOX, FOLFIRI may serve as subsequent-line therapies.

IV. Ivosidenib (Tibsovo) was studied in an ongoing Phase 1, open-label, single-arm, multicenter clinical trial of 18 adult patients with relapsed or refractory MDS with a susceptible IDH-1 mutation as detected by an FDA-approved test. Patients had a median age of 74 (range 61-84) and were treatment experienced, with chemotherapy (17% intensive chemotherapy vs 83% non-intensive chemotherapy). At the data cutoff, a CR of 38.9% was achieved with a median time to CR of 1.9 months (1.0 to 5.6 months). The median follow-up was 27.1 months (3.7 to 88.7 months) and median duration of exposure to ivosidenib (Tibsovo) was 8.3 months (3.3 to 78.8 months). Of the nine patients who were dependent on transfusions prior to initiation of therapy 6 (67%) became independent to RBC and platelet transfusions during the 56 days post-baseline.

- Fourteen patients (74%) were exposed to ivosidenib (Tibsovo for at least 6 months and 8 patients (42%) were exposed for at least 1 year. Serious adverse reactions in ≥ 5% included differentiation syndrome (11%), fatigue (5%), and rash (5%).
- NCCN guidelines currently recommend allo-HSCT, HMA-based therapies, high intensity chemo (induction), and clinical trial as standard therapies for MDS dependent on a patients IPSS-R score. For those who are progress or fail to respond Tibsovo (ivosidenib) is guideline recommended as a treatment option (Category 2A) for those with *IDH1* mutation.

Olutasidenib (Rezlidhia):

I. The clinical program for olutasidenib (Rezlidhia) studied this agent as a monotherapy for the treatment of R/R AML. Participants in the clinical trial did not have previous treatment exposure to another IDH1 inhibitor (e.g., ivosidenib (Tibsovo)). At this time, the efficacy of olutasidenib (Rezlidhia) for patients, who have progressed on or after ivosidenib (Tibsovo) is unknown.

II. FDA approval of olutasidenib (Rezlidhia) was based on an ongoing open-label, single-arm, phase 1/ 2 clinical trial (Study 2102-HEM-101). Subjects (N= 147) with R/R AML and confirmed IDH1 mutation were given olutasidenib (Rezlidhia) 150 mg twice daily. The majority of patients had intermediate to poor cytogenetic risk and were experiencing first or second relapse with 31% patients being primary refractory. Twelve percent of patients had a history of HSCT. The efficacy of olutasidenib (Rezlidhia) was assessed based on the rate of complete remission (CR), complete remission with partial hematological recovery (CRh), and the duration of CR+CRh after a median follow-up duration of 10.2 months. Thirty-fice percent of trial participants reported a combined CR + CRh with 32% achieving CR at the end of treatment exposure. Median duration of combined response was reported to be 25.9 months.

III. Additionally, among the 86 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 29 (34%) became independent of RBC and platelet transfusions during any time in the 56-day post-baseline period. Of the 61 patients who were transfusion independent at baseline, 39 (64%) remained transfusion independent during any 56-day post-baseline period. Given the exchange between transfusion dependence and independence, the direct effect upon conversion to transfusion independence as a result of olutasidenib (Rezlidhia) remains uncertain.

IV. Limitations of the clinical trial for olutasidenib (Rezlidhia) include the lack of a comparator, open-label study design, and lack of clinically meaningful outcomes. Although CR is an objective measure and can indicate an effective response to therapy, it remains shy of accurately predicting long-term prognosis and survival outcomes in AML. For newly diagnosed AML, CR following induction therapy has been associated with overall survival (OS) benefits. However, in the setting of R/R AML, morphologic and hematologic thresholds that define CR may be only indirect predictors of adequate response depth. CR remains an imperfect proxy for key long-term mortality outcomes. The quality of evidence is considered low due to the observational nature of the trial. Additionally, the efficacy of olutasidenib (Rezlidhia) in comparison with, or after, progression on ivosidenib (Tibsovo), remains unknown.

V. During clinical trial, serious adverse events (AE) occurred in 25% of patients on therapy, which included differentiation syndrome (9%) and transaminitis (6%). The most common (≥20%) AE included nausea (38%), fatigue (36%), edema (18%), arthralgia (28%), and leukocytosis (25%). Olutasidenib (Rezlidhia) therapy led to 32% dose interruptions due to AE, 11% dose reductions, and 8% permanent discontinuation of the therapy. Differentiation syndrome is a unique adverse effect of IDH inhibitors, which affected 16% of trial subjects within day one or 18 months of therapy and accounted for one death. The prescribing information for olutasidenib (Rezlidhia) includes boxed warnings regarding the risk of fatal differentiation syndrome and additional warning of hepatotoxicity. At this time, the real-world safety profile of olutasidenib (Rezlidhia) remains largely unknown.

VI. The NCCN guidelines for the treatment of AML recommend olutasidenib (Rezlidhia) for the treatment of R/R AML (Category 2A recommendation). Olutasidenib (Rezlidhia) may be considered an alternative to ivosidenib (Tibsovo). The current clinical data for olutasidenib (Rezlidhia) does not provide evidence of the superiority of this drug as compared to ivosidenib (Tibsovo). At this time, weighing in the evidence of efficacy, safety, cost and net health benefits, ivosidenib (Tibsovo) and olutasidenib (Rezlidhia) may be considered comparable treatment options for R/R AML.

Investigational or Not Medically Necessary Uses

I. Enasidenib (Idhifa), ivosidenib (Tibsovo), or olutasidenib (Rezlidhia) used in combination with oncology therapies not specifically detailed above
   A. Current clinical trial data leading to FDA approval are in the monotherapy setting [with the exception of ivosidenib (Tibsovo) in combination with azacitidine]. Safety and efficacy have not been established for specific combination regimens.
   B. Olutasidenib (Rezlidhia) is currently being investigated in ongoing clinical trials in the settings of newly diagnosed AML, for the treatment of R/R AML in combination with hypomethylating agents (e.g., azacitidine), and for the treatment of myelodysplastic syndrome (MDS). However, clinical data from these trials are not available as of February 2023, and robust conclusions cannot be drawn with respect to potential of olutasidenib (Rezlidhia) as a treatment for these conditions.

II. Advanced cholangiocarcinoma without IDH-1 mutation
   A. Ivosidenib (Tibsovo) has received FDA approval in the setting of advanced cholangiocarcinoma with IDH-1 mutations. Efficacy and safety of this drug has not been established in the absence of IDH-1 mutations. Additionally, enasidenib (Idhifa) has not

been sufficiently studied and is not FDA-approved for the treatment of cholangiocarcinoma.

III. Chondrosarcomas
   A. Clinical trials currently ongoing and limited to proof-of-concept.

IV. Enasidenib (Idhifa) and olutasidenib (Rezlidhia) for the treatment of Myelodysplastic Syndrome (MDS)
   A. Current clinical trials are being conducted in patients with myelodysplastic syndrome (MDS). There is currently insufficient evidence to support the safety and efficacy of enasidenib (Idhifa) and olutasidenib (Rezlidhia) for the treatment of MDS.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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12. National Comprehensive Cancer Network. Myelodysplastic Syndromes. NCCN. V 3.2023; November 10, 2023. Accessed December 8,2023. https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
venetoclax (Venclexta®)	Newly diagnosed acute myeloid leukemia (AML)
azacitidine (Onureg®)	Acute Myeloid Leukemia (AML), maintenance treatment after first complete remission

glasdegib (DAURISMO®)	Newly diagnosed acute myeloid leukemia (AML)
decitabine/cedazuridine (Inqovi™)	Myelodysplastic Syndrome (MDS)
	Chronic myelomonocytic leukemia (CMML)
lenalidomide (Revlimid®), pomalidomide (Pomalyst®), thalidomide (Thalomid®)	Follicular lymphoma
	Marginal zone lymphoma
	Multiple myeloma
	Myelodysplastic syndromes
	Mantle cell lymphoma
	Erythema Nodosum Leprosum

Policy Implementation/Update:

Action and Summary of Changes	Date
Update to include expanded indication for ivosidenib (Tibsovo) in R/R MDS and updated formatting of supporting evidence.	03/2024
Removed the requirement of contraindication/intolerance to Tibsovo prior to coverage of Rezlidhia for R/R AML. Current evidence of efficacy, safety, cost, and net health benefits indicates Tibsovo and Rezlidhia may be considered comparable treatment options for R/R AML.	03/2023
Update to include olutasidenib (Rezlidhia) for the new indication of R/R AML;	02/2023
Update to include expanded indication for ivosidenib (Tibsovo) plus azacitidine in newly diagnosed AML; updated supporting evidence; added related policies table.	11/2022
Update to include expanded indication for ivosidenib (Tibsovo) for cholangiocarcinoma; updated supporting evidence; added split fill requirement for Tibsovo.	10/2021
Criteria update: To improve the clinical flow of the policy, the indication of relapse/refractory AML was separated from newly diagnosed AML. For clinical appropriateness and standard of practice, the requirement for both chemotherapy “AND” allogenic stem cell transplant for relapsed or refractory AML, was changed to an “OR;” therefore, either one prior regimen would satisfy that requirement. For the newly diagnosed AML diagnosis, additional information around comorbidities has been included in the policy to help better determine the comorbidities that may preclude newly diagnosed AML patients from intensive induction chemotherapy. Based on current clinical trials that are being conducted, myelodysplastic syndrome (MDS) has been added to the investigation/experimental section of this policy and supporting evidence has been updated to reflect the rationale for the addition. The supporting evidence in this whole policy has been updated to reflect the pivotal trials. The references section has been updated to include the pivotal trials and NCCN guideline for AML.	02/2020
Policy created. Tibsovo and Idhifa was combined into one policy.	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP128

Description

Imatinib (Gleevec) is an orally administered protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase to suppress proliferation and promote apoptosis of cancer cells.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
imatinib	100 mg tablet	Chronic eosinophilic leukemia; Dermatofibrosarcoma protuberans, unresectable, recurrent, and/or metastatic; Gastrointestinal stromal tumor, Kit (CD117)-positive, adjuvant treatment; Gastrointestinal stromal tumor, Kit (CD117)-positive, unresectable or metastatic disease; Hypereosinophilic syndrome; Myelodysplastic syndrome, PDGFR gene rearrangement; Myelodysplastic syndrome, chronic, PDGFR gene rearrangement; Philadelphia chromosome-positive acute lymphoblastic leukemia, newly diagnosed, in combination with chemotherapy; Philadelphia chromosome-positive acute lymphoblastic leukemia, relapsed/refractory; Philadelphia chromosome positive chronic myelogenous leukemia, accelerated phase or blast crisis;	90 tablets/ 30 days
	400 mg tablet		30 tablets/ 30 days
imatinib (Gleevec)	100 mg tablet		90 tablets/ 30 days
	400 mg tablet		30 tablets/ 30 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

		Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, after failure of interferon-alpha therapy; Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, newly diagnosed; Systemic mast cell disease, aggressive, D816V c-Kit mutation negative or unknown	

Initial Evaluation

I. Imatinib may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older for all indications except the following;
      1. Philadelphia chromosome-positive acute lymphoblastic leukemia, newly diagnosed, in combination with chemotherapy
      2. Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, newly diagnosed;
      AND
   B. Medication is prescribed by, or in consultation with, an oncologist **AND**
   C. Not used in combination with other oral oncolytic therapies (e.g., sunitinib [Sutent], regorafenib [Strivarga], bosutinib [Bosulif], nilotinib [Tasigna]); **AND**
   D. Generic imatinib is prescribed, unless generic has been tried and failed, is not tolerated or contraindicated [documentation required] (note: imatinib is the interchangeable AB-rated generic of Gleevec); **AND**
   E. A diagnosis of one of the following:
      1. **Chronic eosinophilic leukemia**
      2. **Dermatofibrosarcoma protuberans, unresectable, recurrent, and/or metastatic**
      3. **Gastrointestinal stromal tumor, Kit (CD117)-positive, adjuvant treatment**
      4. **Gastrointestinal stromal tumor, Kit (CD117)-positive, unresectable or metastatic disease**
      5. **Hypereosinophilic syndrome**
      6. **Myelodysplastic syndrome, PDGFR gene rearrangement**
      7. **Myelodysplastic syndrome, chronic, PDGFR gene rearrangement**
      8. **Philadelphia chromosome-positive acute lymphoblastic leukemia, newly diagnosed, in combination with chemotherapy**
      9. **Philadelphia chromosome-positive acute lymphoblastic leukemia, relapsed/refractory**
      10. **Philadelphia chromosome positive chronic myelogenous leukemia, accelerated phase or blast crisis**
      11. **Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, after failure of interferon-alpha therapy**
      12. **Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, newly diagnosed**

13. Systemic mast cell disease, aggressive, D816V c-Kit mutation negative or unknown

II. Imatinib (Gleevec) is considered investigational when used for all other conditions, including but not limited to:
   A. Breast cancer
   B. Cervical cancer
   C. Graft-versus-host disease
   D. Malaria
   E. Melanoma
   F. Mesothelioma
   G. Multifocal leukoencephalopathy
   H. Multiple sclerosis
   I. Neurofibromas
   J. Non-Hodgkin's lymphoma
   K. Ovarian or peritoneal cancers
   L. Pancreatic cancer
   M. Renal cancers
   N. Sickle cell anemia
   O. Thyroid cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescribed by, or in consultation with, an oncologist; **AND**
IV. Member has exhibited improvement or stability of disease with lack of disease progression; **AND**
V. For imatinib (Gleevec) brand: generic imatinib has been tried and failed, not tolerated, or is contraindicated [documentation required] (note: imatinib is the interchangeable AB-rated generic of Gleevec).

Supporting Evidence

I. Imatinib (Gleevec) is a tyrosine kinase inhibitor, indicated in a variety of disease states in adults, and two indications have been evaluated with treatment of imatinib (Gleevec) in pediatric patients. Dosing is indication specific, but ranges from 100 mg to 800 mg per day, with standard dosing ranging from 400 mg to 800 mg per day.. Dose adjustments may be warranted in the setting of toxicity or organ dysfunction/impairment. Imatinib (Gleevec) may be used as

monotherapy or in addition to chemotherapy for certain indications. Use with other oral tyrosine kinase oncolytic therapies has not been evaluated for safety and/or efficacy to date.

II. Overarching indications include chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), gastrointestinal stromal tumor (GIST), eosinophilic leukemia and syndromes, dermatofibrosarcoma protuberans, myelodysplastic syndromes, and systemic mast cell disease. An extensive number of clinical trials have been completed for imatinib (Gleevec).

III. Generic imatinib is available and is recognized as the AB-rated interchangeable generic to Gleevec. It provides better value and is a cost effective option compared to brand Gleevec with no known safety or efficacy differences at this time. Payment consideration for brand is reserved for those that have had inefficacy, intolerance, or contraindication to generic imatinib. Occurrence of toxicities known to be in the adverse event profile of imatinib (Gleevec), does not meet medical necessity for brand over generic exception. If toxicity occurs, consistent with the imatinib (Gleevec) adverse event profile, dose reduction or discontinuation may be appropriate.

Investigational or Not Medically Necessary Uses

I. Imatinib (Gleevec) has not been sufficiently evaluated for safety and/or efficacy and/or is in clinical trials for the following indications:
   A. Breast cancer
   B. Cervical cancer
   C. Graft-versus-host disease
   D. Malaria
   E. Melanoma
   F. Mesothelioma
   G. Multifocal leukoencephalopathy
   H. Multiple sclerosis
   I. Neurofibromas
   J. Non-Hodgkin's lymphoma
   K. Ovarian or peritoneal cancers
   L. Pancreatic cancer
   M. Renal cancers
   N. Sickle cell anemia
   O. Thyroid cancer

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Policy Implementation/Update:

Date Created	August 2008
Date Effective	August 2008
Last Updated	November 2019
Last Reviewed	02/2016, 03/2016, 05/2017, 11/2018, 11/2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format, new indications added/specified, age edit added, addition of specialist provider, and limitation of dual oral therapy.	11/2019
Generic imatinib preferred therapy indicated for initial and continuation of therapy, unless medical necessity for brand met.	11/2018
Criteria questions rearranged and clarified.	08/2017
Criteria updated to prefer generic imatinib for initial approval.	05/2017
Criteria updated for new disease states.	02/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP241

Description

Infigratinib (Truseltiq) is a selective inhibitor of fibroblast growth factor receptor 1-4 (FGFR).

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
infigratinib (Truseltiq)	50 mg dose: 25 mg capsules (1 blister card)	Previously treated adults with unresectable, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement	42 capsules/28 days
	75 mg dose: 25 mg capsules (2 blister cards)		63 capsules/28 days
	100 mg dose: 100 mg capsules (1 blister card)		21 capsules/28 days
	125 mg dose: 25 mg/100 mg capsules (1 blister pack)		42 capsules/28 days

Initial Evaluation

I. **Infigratinib (Truseltiq)** is considered investigational when used for all conditions, including but not limited to unresectable, locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or other rearrangement.

Renewal Evaluation

I. N/A

Supporting Evidence

I. Infigratinib (Truseltiq) is a selective inhibitor of fibroblast growth factor receptor 1-4 (FGFR), FDA-approved for previously treated adults with unresectable, locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement. It was approved under the accelerated approval pathway based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

II. Cholangiocarcinoma (CCA) is rare group of cancers originating in the bile duct. Depending on the tumor location, CCA is classified as intrahepatic (iCCA), or extrahepatic (eCCA) with perihilar

(pCCA) and distal (dCCA) subtypes. CCA commonly presents in the seventh decade of life but can occur at any age.

III. The current recommendations for the treatment of unresectable, locally advanced metastatic CCA are detailed in the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of hepatobiliary cancers.
    A. As of August 2021, the preferred regimens for primary treatment are chemotherapy, specifically, gemcitabine and cisplatin (Category 1 recommendation). Other preferred primary regimens include combination of various chemotherapy agents including 5-flourouracil, capecitabine, oxaliplatin, and albumin-bound paclitaxel.
    B. Preferred regimens for subsequent line therapy include FOLFOX (leucovorin, fluorouracil, oxaliplatin). Other recommended regimens for subsequent line therapy include FOLFIRI (leucovorin, fluorouracil, irinotecan) (Category 2B recommendation), and regorafenib (Stivarga) (Category 2B recommendation). Guidelines also note agents used in certain circumstances, such as in various mutations. For FGFR2 fusions or rearrangements, pemigatinib (Pemazyre) and infigratinib (Truseltiq) are recommended (Category 2A recommendation). Additionally, nivolumab (Opdivo) (Category 2B recommendation) and lenvitinib (Lenvima) and pembrolizumab (Keytruda) (Category 2B recommendation) are also listed.

IV. Infigratinib (Truseltiq) joins pemigatinib as the second FGFR inhibitor on the market indicated in previously treated patients with unresectable, advanced, or metastatic disease. The expected place in therapy is a second-line treatment option refractory to chemotherapy. Currently, both drugs are considered experimental and investigational by the health plan as there is lack of robust efficacy evidence and potential safety concerns associated with their use. When available, participation in a clinical trial remains the most favorable treatment option for patients with unresectable, advanced or metastatic CCA refractory to chemotherapy treatment. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment with close safety monitoring and follow-up.

V. Infigratinib (Truseltiq) was studied in one open-label, single-arm, multi-cohort trial in 108 patients with advanced or metastatic CCA who had received at least one prior regimen containing gemcitabine with or without cisplatin. The median patient age was 53 years (range: 23 to 81 years), 62% were female, 72% were White, 3.7% were Black or African American, 10% were Asian, 99% had stage IV disease, 63% had two or more metastatic sites, and 54% had two or more previous lines of therapy. The FDA approval was based on Cohort 1; study involving Cohorts 2 and 3 is still ongoing and includes patients with other FGFR mutations and patients previously treated with other FGFR inhibitors.

VI. The primary endpoints studied in Cohort 1 were objective response rate (ORR), which was 23.1% (95% CI 15.6-32.2) and median duration of response (DOR), which was 5 months (95% CI 3.7-9.3) at the time of the data cutoff on March 31, 2020. Progression-free survival (PFS) was a median of 7.3 months (95% CI 5.6-7.6) and median overall survival (OS) was 12.2 months (10.7-14.9). At the time of data cut off for OS analysis, 65% of patients had died and patients without death recorded were censored at the last known date to be alive.

VII. The most common treatment related adverse events (TRAEs) were hyperphosphatemia (74%), stomatitis (51%), fatigue (29%), alopecia (32%), dry eye (31%), palmar-plantar erythrodysaesthesia syndrome (31%), and arthralgia (29%). Serious adverse events occurred in 34 patients (31%), most frequent being anemia, pyrexia, hypercalcemia, and sepsis. One death was reported due to sepsis. Warnings and precautions include retinal pigment epithelial detachment (RPED), dry eye,

hyperphosphatemia and soft tissue mineralization, and embryo-fetal toxicity. There are no black box warnings. At the time of data cutoff, 89% of patients had discontinued the drug. Discontinuation rate due to adverse events (AEs) in the overall population was 15%, dose interruption and dose reduction rate due to AEs was 64% and 60%, respectively.

VIII. True medication safety and efficacy of infigratinib (Truseltiq) remain unknown given the observational nature of the trial (i.e., lack of comparator arm and open-label study design). Efficacy endpoints utilized in the clinical trial such as ORR, DOR, and PFS are surrogate markers and do not have a confirmed relationship with clinical meaningful outcomes such as improvement in OS, symptoms, or quality of life. OS data presented in this trial remains an exploratory outcome due to observational study design and requires confirmation in a randomized controlled trial.

Investigational or Not Medically Necessary Uses

I. Infigratinib (Truseltiq) has not been sufficiently studied for safety and efficacy for any condition to date.

References

1. Truseltiq [Prescribing Information]. QED Therapeutics: Brisbane, CA. May 2021.
2. NCCN Guidelines for the treatment of Hepatobiliary Cancers. V.3.2021. Updated June 15, 2021.
3. Javle M, Roychowdhury S, Kelley RK, et al. Infigratinib (BGJ398) in previously treated patients with advanced or metastatic cholangiocarcinoma with FGFR2 fusions or rearrangements: mature results from a multicentre, open-label, single-arm, phase 2 study [published online ahead of print, 2021 Aug 3]. Lancet Gastroenterol Hepatol. 2021;S2468-1253(21)00196-5. doi:10.1016/S2468-1253(21)00196-5.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP207

Description

inotersen (Tegsedi) is a subcutaneously administered antisense oligonucleotide inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

inotersen (Tegsedi)	Indication	Quantity Limit	*DDID*
284 mg/1.5 mL syringe	hereditary transthyretin-mediated amyloidosis	6 mL/28 days	204500

Initial Evaluation

I. inotersen (Tegsedi) may be considered medically necessary when the following criteria are met:
   A. Prescribed by or in consultation with a neurologist or cardiologist; **AND**
   B. A diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) when the following are met:
      1. Age 18 years and older; **AND**
      2. Documented transthyretin variant (TTR mutation) by genotyping (e.g., V30M); **AND**
      3. Documented amyloid deposit by biopsy; **AND**
      4. Patient has a platelet count > 100 × 109/L; **AND**
      5. Documentation of one of the following:
         i. Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb
         ii. Patient has a baseline FAP Stage 1 or 2
         iii. Patient has a baseline neuropathy impairment (NIS) score ≥ 10 and ≤ 130

         AND
      6. Presence of clinical signs and symptoms of the disease (e.g., peripheral sensorimotor polyneuropathy, autonomic neuropathy, motor disability, etc.); **AND**
      7. No prior liver transplant or anticipated liver transplant; **AND**
      8. New York Heart Association (NYHA) functional classification of <3; **AND**
      9. Does not have presence of known type 1 or type 2 diabetes mellitus; **AND**
      10. Does not have renal insufficiency (defined as CrCl <60 mL/min); **AND**
      11. Patient has tried and failed or has a contraindication to patisiran (Onpattro); **AND**
      12. Inotersen (Tegsedi) will not be used in combination with patisiran (Onpattro) or tafamidis meglumine (Vyndaqel)

II. inotersen (Tegsedi) is considered investigational when used for all other conditions, including but not limited to:
    A. Cardiac amyloidosis due to wild-type or mutant TTR

Renewal Evaluation

I. Patient has previously received treatment with inotersen (Tegsedi); **AND**
II. Documentation of one of the following:
    A. Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb; **OR**
    B. Patient has a baseline FAP Stage 1 or 2; **OR**
    C. Patient has a baseline neuropathy impairment (NIS) score ≥ 10 and ≤ 130

    AND
III. Documentation that the patient has experienced a positive clinical response to inotersen (Tegsedi) (e.g., improved neurologic impairment, motor function, quality of life, slowing of disease progression, etc.); **AND**
IV. Inotersen (Tegsedi) will not be used in combination with patisiran (Onpattro) or tafamidis meglumine (Vyndaqel); **AND**
V. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. In the pivotal NEURO-TTR trial leading to approval, inotersen (Tegsedi) was studied in adults with stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) hereditary transthyretin amyloidosis with polyneuropathy.
II. Diagnosis of the hereditary form of ATTR requires demonstration of a TTR gene mutation. Although mass spectrometry can demonstrate a mass difference between wild-type and TTR protein variants in serum, it does not specify the site and kind of amino acid substitution in a number of disease-related *TTR* gene mutations; thus, DNA sequencing is usually required.
III. Use of inotersen (Tegsedi) is contraindicated in patients with platelet count less than 100 x 109/L, history of acute glomerulonephritis caused by inotersen (Tegsedi), or history of hypersensitivity reaction to inotersen (Tegsedi).
IV. Patients with a PND score greater than IIIb (i.e. PND of IV) are confined to a wheelchair or bedridden. Patients with FAP stage 1 have unimpaired ambulation, stage 2 require assistance with ambulation, and FAP stage 3 patients are wheelchair bound or bedridden. As mentioned above, all patients included in the study were ambulatory. Patents included also had a baseline NIS score ≥ 10 and ≤ 130.
V. Additional exclusion criteria in the NEURO-TTR trial consisted of prior liver transplant or anticipated liver transplant, New York Heart Association (NYHA) functional classification of <3, presence of known type 1 or type 2 diabetes mellitus, and renal insufficiency (defined as CrCl <60 mL/min).
VI. Inotersen (Tegsedi) carries two black box warnings related to potential for life-threatening thrombocytopenia and glomerulonephritis that may require immunosuppressive treatment and may result in dialysis. Tegsedi is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) program because of these risks. Patisiran (Onpattro) is also indicated and FDA approved for the polyneuropathy of hATTR in adults and provides a more favorable safety profile. Onpattro efficacy was evaluated in a randomized, double-blind,

placebo-controlled trial in adults with polyneuropathy caused by hATTR amyloidosis. Onpattro met its primary endpoint of change from baseline to Month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7).

VII. Use of inotersen (Tegsedi) in combination with other therapies for hATTR (e.g., patisiran (Onpattro) or tafamidis meglumine (Vyndaqel) has not been studied.

Investigational or Not Medically Necessary Uses

I. Cardiac amyloidosis due to wild-type or mutant TTR
   A. Pivotal trials leading to FDA approval were specifically in the hereditary transthyretin-mediated amyloidosis setting. Wild-type TTR is not considered hereditary. Inotersen (Tegsedi) in this setting is under investigation, trials have not yet started recruiting.

References

1. Tegsedi [Prescribing Information]. Carlsbad, CA: Ionis Therapeutics, Inc., 2018.
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Policy Implementation/Update:

Date Created	January 2019
Date Effective	February 2019
Last Updated	January 2019
Last Reviewed	01/2019

Action and Summary of Changes	Date
Criteria created	01/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP238

Description

Interferon Gamma-1B (Actimmune®) is a subcutaneously administered medication which works through an unknown mechanism of action after binding to the cell's surface. The three major groups of interferons (alpha, beta, gamma) all have overlapping properties. Interferon gamma binds to a different surface receptor than alpha and beta and is considered a Type 2 interferon. Specific effects from using interferon gamma include activation of natural killer (NK) cells, enhancement of the oxidative metabolism of macrophages, and antibody dependent cellular cytotoxicity (ADCC).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Interferon Gamma-1B (Actimmune®)	100mcg (2 million IU)/0.5ml vial	Severe Malignant Osteopetrosis (SMO); Chronic Granulomatous Disease (CGD)	BSA* **over** 0.5 m^2: 50mcg/m^2 Three times weekly
			BSA* **equal to or less than** 0.5m^2: 1.5mg/kg/dose Three times weekly

**maximum dose: 50mcg/m^2 Body surface area (BSA*

Initial Evaluation

I. **Interferon Gamma-1B (Actimmune)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a specialist (e.g., endocrinologist, immunologist, geneticist); **AND**
   B. Member will not use this medication in combination with another biologic or other non-biologic specialty medication; **AND**
   C. A diagnosis of one of the following:
      1. **Chronic granulomatous disease (CGD)**; **AND**
         i. Attestation the member has a confirmed molecular genetic test and/or by neutrophil-functioning test confirming diagnosis; **AND**
         ii. Member is on continuous daily antibiotic therapy (e.g., sulfamethoxazole-trimethoprim) and antifungal therapy (e.g., itraconazole) for infection prophylaxis; **OR**
      2. **Severe Malignant Osteopetrosis (SMO)**; **AND**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

i. Member has confirmed genetic testing identifying a mutation linked to severe, infantile, malignant osteopetrosis; **AND**
ii. Member has had a radiographic (x-ray) image confirming skeletal features related to osteopetrosis

II. **Interferon Gamma-1B (Actimmune)** is considered investigational when used for all other conditions, including but not limited to:
A. Atopic Dermatitis
B. Renal Cell Carcinoma
C. Mycosis Fungoides/Sezary Syndrome
D. Friedreich's Ataxia
E. Noninfantile osteopetrosis (conditions outside of severe, infantile (SMO))

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in primary infections, stabilization of platelet or hemoglobin counts, decrease/stabilization in optic atrophy]

Supporting Evidence

I. Chronic granulomatous disease (CGD) is a rare and inherited primary immune deficiency disorder affecting white blood cells and the body's ability to resist infections caused by certain types of bacterial and fungal species. Overtime, this causes the body to develop chronic inflammation of the tissues, known as granulomas, which can be widely distributed over the body and have the potential to develop into life-threatening infections of the skin, lungs, and bones.
II. In CGD, there is a genetic mutation in one of five genes that cause a defect in an enzyme called phagocyte NADPH oxidase; this enzyme is used by certain white blood cells in the cell killing process of certain bacteria and fungi. Usually this is routinely done in children with a family history of CGD or will be performed in children who have symptoms that match the symptom profile. The first testing done is either the DHR (dihydrorhodamine) (flow cytometry test) or the NBT (nitroblue tetrazolium) test. Both work in a similar manner and check to see if the patient's blood cells are producing the enzyme NADPH oxidase. The DHR test will change the fluorescein of dihydrorhodamine and that can be detected by the flow cytometer; the NBT test will change the color of the cell itself and this can be then seen under a microscope. Once a positive result is found on either test, genetic testing is done to assess which mutation the patient has, as the type of mutation can impact how the disease might present and when it might present (i.e. later in life in certain carriers; more autoimmune manifestations like Raynaud's, oral ulcers) and this genetic testing is important for carriers to know the genetic potential of passing to any children they might have.

III. As CGD is a genetic disease, the first symptoms are usually noticed during infancy or childhood, though cases have been reported not diagnosed until the early teens or even adulthood. Standard of care consists of continuous antibiotic therapy to help prevent infections, such as trimethoprim/sulfamethoxazole to prevent bacterial infections and itraconazole for anti-fungal protection. Corticosteroids are also helpful for treating granulomatous complications and to bring down inflammation. The only potential cure for CGD is a bone marrow transplant which has been successful in some patients. Interferon gamma-1B has been shown in vitro and in vivo to correct parts of the damage to the oxidative metabolic system of the cells and therefore, help improvement their microbe killing potential (ability to kills bacteria, fungi, and viruses).

IV. Actimmune was approved by the FDA for use in CGD following a randomized, double blind, placebo-controlled trial to determine if Actimmune used subcutaneously (SQ) three times a week could decrease the incidence of serious infectious episodes and improve existing infectious and inflammatory conditions of those enrolled in the study with CGD. A hundred and twenty-eight patients were enrolled, of those enrolled all had different methods of genetic inheritance and most patients were on prophylactic antibiotics. Patients had a median age of 14.6 years but ranged from 1-44 years. The study itself ended early following demonstration of a highly statistically significant benefit of Actimmune compared to placebo, (p=0.0036) for the primary endpoint of the study, time to a serious infection. There was a 67% reduction in relative risk of serious infections in those receiving Actimmune to place (N=63 to N=65, respectively) and additional evidence for the treatment benefit of Actimmune showed a twofold reduction in the number of primary infections (30, placebo and 14, Actimmune; p=0.002).

V. Osteopetrosis is a genetic disease marked by increased bone density from a defect in the bone being reabsorbed into the cells by osteoclasts. This leads to bone being made up/built of a defective structure causing them to be brittle and likely to fracture; this often leads to misclassification under a type of bone fragility. Three types of osteopetrosis exist and are differentiated based on the genetic mutation. The autosomal recessive form, severe malignant osteopetrosis (SMO) [sometimes referred to as malignant infantile osteoporosis (MIOP)], is apparent soon after birth and shortens life expectancy, usually leading to death within the first decade of life, affecting about 1 in 250,000 people. Genetic testing is recommended once an x-ray diagnosis is established because it can separate the different forms of osteopetrosis and provide meaningful effect on management strategies.

VI. Additional types of osteopetrosis are Autosomal Dominant (aka Albers-Schonberg disease or ADO), Intermediate Autosomal (IAO), and Adult Delayed-Onset. ADO is the most common and usually has an onset in adolescence or adulthood with long bone involvement leading to fractures along these bones such as the femur and ulnar. Other common symptoms include hip osteoarthritis, scoliosis, osteomyelitis of the jawbone, and infection within the bone itself. IAO onsets in childhood and can cause skeletal changes as well as visual impairment from optic nerve compression but does not change life expectancy. Adult Delayed-Onset is a milder type of ADO with normal bone structure at birth and people tend to remain asymptomatic. In this later state, bone mass will increase with age, and usually osteomyelitis of the jaw is first symptom, followed by bone pain, fractures, back pain (along vertebra), and degenerative arthritis.

VII. The only established cure for SMO is a hematopoietic stem cell transplant (HSCT) which allows restoration of bone resorption by the donor osteoclasts. Certain genetic mutations within SMO will not benefit from the transplant (those with the *RANKL* gene) and a large number of patients

develop some sort of progression neurodegeneration which is not helped with a HSCT. For patients where an HSCT is not appropriate, corticosteroids may be considered, but there is not strong evidence to support their routine use. Interferon Gamma-1B was approved to help delay disease progression along with dietary and nutrition support. Interferon Gamma-1B is not indicated for the other types of osteopetrosis as ADO, IAO, or Adult-Delayed; as they can all be managed by things such as calcitriol, to help stimulate osteoclasts, erythropoietin, or corticosteroids.

VIII. Actimmune received FDA approval for SMO following a randomized, controlled trial in patients with SMO who received doses of Actimmune (three times weekly) + calcitriol or just calcitriol alone. The study only enrolled 16 patients with n=11 receiving study regime and n=5 receiving the controller alone; patients were a mean age of 1.5 years (1month-8 years). The study evaluated time to disease progression and treatment failure was considered to be disease progression based on four outcomes: 1. Death; 2. Significant reductions in hemoglobin or platelet counts; 3. Serious bacterial infections requiring antibiotics; or 4. A 50dB decrease in hearing or progressive optic atrophy. The median time to disease progression was significantly delayed in the study arm versus control arm. However, this was based on the observed data as time to progression in the treatment arm was at least 165 days versus 65 days in the calcitriol alone arm.

IX. Actimmune has a similar safety profile as the other interferons. The most common adverse reactions include fever, headache, chills, myalgia, or fatigue. It is recommended to have baseline hematology, blood chemistries, and urinalysis prior to starting and at 3-month intervals once using the medication. It is further recommended for severe reactions, to dose reduce by 50% or discontinue the therapy until the ADE resolves. Examples of these serious adverse reactions are neutropenia, thrombocytopenia, elevations of AST/ALT, decreased mental status, and gait disturbances.

X. As each of these FDA label indications are an involved genetic disorder, the request should be coming from a specialist with understanding of the disease state.

Investigational or Not Medically Necessary Uses

I. Interferon Gamma-1B (Actimmune) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Atopic Dermatitis (AD)
      i. In 2000, a randomized, placebo-controlled study looked at the therapeutic effect of two different dosages of interferon gamma for AD for therapeutic efficacy. Fifty-one patients with severe recalcitrant AD were treated with interferon gamma (20 patients at low dose and 21 patients at high dose) SQ 3 x weekly for 12 weeks. Both groups reached treatment goals compared to placebo with statistical significance ($p<0.05$) and the higher dose showed more rapid improvement. The conclusion of the study was that interferon gamma was safe and effective for AD. Since then, there have been 6 other clinical trials, with largest enrolling 51 patients and the longest lasting 24 weeks, all noting improvement. Currently, this indication is considered experimental and investigational due to the lack of larger scale clinical trials or head-to-head clinical trials; coupled with the approval of the

gold standard biologics such as Dupixent, for treatment of AD which occurred after the 2016 review article was published.

B. Renal Cell Carcinoma
    i. A multicenter, randomized, placebo-controlled, double-blind trial for metastatic renal cell carcinoma was completed in 1999/2000. This trial enrolled 197 patients to receive either placebo or recombinant interferon gamma-1b (60 mcg/m2) SQ every 7 days until disease progression. There was no statistical significance (p=0.75) for the 95% confidence interval of overall response rate of interferon gamma-1b of 4% (1.4-11.5) to placebo of 6% (2.5-13.2). The study concluded with a statement that the lack of efficacy in this trial shows the importance of continued research in this field.

C. Mycosis Fungoides/Sezary Syndrome
    i. Support for this experimental use is supported by the National Comprehensive Cancer Network (NCCN) guidelines for Primary Cutaneous Lymphomas as level of evidence 2a. The trial used in the supporting evidence is from the late 1980s/early 1990s; the phase II trial had a total of 16 patients enrolled with various stages of cutaneous T-cell lymphomas (CTCL). Five patients had partial response with a median response of 10 months, and 6 others showed minor or mixed response. The trial suggested that interferon gamma has efficacy in the treatment of CTCL refractory to use interferon alpha (as being on another interferon was allowed by study design). The quality of this evidence is considered low at this time given the open label trial design, small sample size, and lack of comparator arm.

D. Friederichs's Ataxia
    i. In 2016, Horizon Pharma launched a phase 3 trial, STEADFAST, to evaluate Actimmune for the treatment of Friederichs's Ataxia (FA). The study's primary endpoint was a change from baseline in the modified Friedreich's Ataxia Rating Scale at 26 weeks versus treatment with placebo. The scale is an exam-based rating scale that measuring progression using parameters such as speech, ability to swallow, upper and lower limb coordination, gait, and posture. The trial did not meet statistically significant to this end point or the secondary end points and was stopped prior to original end date due to this finding.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	10/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP084

Description

Istradefylline (Nourianz) is an orally administered adenosine receptor antagonist.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
istradefylline (Nourianz)	20 mg tablets	Parkinson's disease	30 tablets/30 days	207954
	40 mg tablets		30 tablets/30 days	207955

Initial Evaluation

I. Istradefylline (Nourianz) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years or older; **AND**
   B. Prescribed by or in consultation with a neurologist; **AND**
   C. A diagnosis of **Parkinson's Disease** when the following are met:
      1. Treatment with one the following has been ineffective, contraindicated or not tolerated:
         i. Carbidopa/levodopa IR up to five times a day; **OR**
         ii. Carbidopa/levodopa XR/CR/ER; **AND**
      2. Current or previous treatment with at least TWO of the following agents used as adjunctive treatment to levodopa/carbidopa has been ineffective, contraindicated, or not tolerated:
         i. Dopamine agonist (e.g., ropinirole, pramipexole)
         ii. COMT inhibitor (e.g,. entacapone, tolcapone)
         iii. MAO-B inhibitor (e.g., rasagiline, safinamide, selegiline); **AND**
      3. Provider attests that the member is experiencing OFF time after trial of first line Parkinson's medications (i.e., Carbidopa/levodopa at four times a day, add on therapy of dopamine agonist); **AND**
      4. Prescriber attests that member will be using istradefylline (Nourianz) in combination with carbidopa/levodopa

II. Istradefylline (Nourianz) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Parkinson's disease WITHOUT documentation of motor fluctuations, "wearing off"

B. Restless Leg Syndrome
C. Promotion of Breathing Plasticity in Amyotrophic Lateral Sclerosis (ALS)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescriber attests that member will be using istradefylline (Nourianz) in combination with carbidopa/levodopa; **AND**
IV. Documentation that member has a reduction in wearing off period from baseline.

Supporting Evidence

I. Due to the complexity around the diagnosis of Parkinson's disease (PD) and the treatment options, therapy should be prescribed by, or in consultation with, a neurologist.
II. There is a lack of safety and efficacy data in the use of istradefylline (Nourianz) in those under the age of 18.
III. Motor symptoms in PD affect as many as 77% of patients; these include physical, visible signs of PD: resting tremor, muscular rigidity, postural instability. These advance into falls, axial postural deformities, dysphagia, and in advanced disease, these pharyngeal dysfunctions have an increase aspiration risk and lead to higher numbers of upper respiratory tract infections and pneumonia. Pharmacotherapies for managing the symptoms of PD show the greatest efficacy early in the course of the disease. As symptoms become refractory to standard therapies, levodopa, patients begin experiencing fluctuations in symptoms (OFF periods) within two years of beginning therapy.
IV. Levodopa, administered in oral carbidopa/levodopa formulations, is the mainstay and most effective medication for management of PD motor symptom management. Currently, motor fluctuations are managed by increasing the patient's levodopa dose, reducing intake of dietary protein with levodopa administration, using longer acting carbidopa/levodopa formulations, and adding other agents that can be clinically useful in extending "on" time (e.g., dopamine agonists, COMT inhibitors, and MAO-B inhibitors).
V. The efficacy of istradefylline (Nourianz) as adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes was shown in four 12-week placebo-controlled trials that included a total of 1,143 patients. In these pivotal clinical trials, patients were experiencing at least two hours of daily OFF time and were receiving the following concomitant therapies: dopamine agonists (85%), COMT inhibitors (38%), MAO-B inhibitors (40%), anticholinergics (13%), and/or amantadine (33%). The primary efficacy endpoint was the change from baseline in the daily awake percentage of "off" time, or the change from baseline in daily "off" time. In all four studies, patients treated with istradefylline (Nourianz) experienced a statistically significant decrease compared to patients receiving a placebo.
VI. The 2018 International Parkinson and Movement Disorder Society Evidence-Based Medicine Review reported istradefylline (Nourianz) to be "likely efficacious" and "possibly useful" for

clinical practice due to conflicting evidence but generally positive outcomes. Guidelines do not recommend one adjunctive therapy approach over another. The 2019 update did not give other guidance on motor therapies.

Investigational or Not Medically Necessary Uses

I. Parkinson's disease WITHOUT documentation of motor fluctuations, "wearing off"
   A. Istradefylline (Nourianz) has not been studied in patients with Parkinson's disease who aren't experiencing motor fluctuations; therefore, it would be considered investigational when requested in this setting.
II. Restless Leg Syndrome
III. Promotion of Breathing Plasticity in Amyotrophic Lateral Sclerosis (ALS)

References

1. Nourianz [Prescribing Information]. Kyowa Kirin Inc.: Bedminster, NJ. August 2019.
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8. Stacy M, Silver D, Mendis T, et al. A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. Neurology 2008;70:2233-2240.
9. Pourcher E, Fernandez HH, Stacy M, Mori A, Ballerini R, Chaikin P. Istradefylline for Parkinson's disease patients experiencing motor fluctuations: results of the KW-6002-US-018 study. Parkinsonism Relat Disord 2012;18:178-184.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
pimavanserin (Nuplazid)	Parkinson's Disease
levodopa_Inbrija	
apomorphine_Apokyn_Kynmobi	

Policy Implementation/Update:

Action and Summary of Changes	Date
Annual updates; changes to initial requirements were made with removal of duration of OFF time requirement, addition of age, and reformatting of criteria requirements.	11/2023
Policy Created	9/2019

Policy Type: PA Pharmacy Coverage Policy: UMP040

Description

Ivabradine (Corlanor) is an orally administered direct and selective inhibitor of the hyperpolarization-activated cyclic nucleotide-gated (HCN-gated) channels, or the f-channels that are located in the cardiac sinoatrial node which results in a lowering of the heart rate.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
ivabradine (Corlanor)	5 mg tablets	Heart Failure in Adult Patients; Heart Failure in Pediatric Patients; Inappropriate Sinus Tachycardia	60 tablets/30 days
	7.5 mg tablets		60 tablets/30 days
	5 mg/5 mL solution		450 mL/30 days

Initial Evaluation

I. Ivabradine (Corlanor) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by or in consultation with a cardiologist; **AND**
   B. A diagnosis of one of the following:
      1. **Heart Failure in Adult Patients**; **AND**
         i. Prescribed by or in consultation with a cardiologist; **AND**
         ii. The member have stable, symptomatic chronic heart failure; **AND**
         iii. The member have left ventricular ejection fraction ≤ 35%; **AND**
         iv. The member is in sinus rhythm with resting heart rate ≥ 70 beats per minute; **AND**
         v. Treatment with maximally tolerated beta-blockers have been ineffective, contraindicated, or not tolerated; **AND**
         vi. The member does not have any of the following contraindications:
            a. Acute decompensated heart failure
            b. Blood pressure less than 90/50 mmHg
            c. Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
            d. Resting heart rate less than 60 bpm prior to treatment
            e. Severe hepatic impairment
            f. Pacemaker dependence

g. Concomitant use of strong cytochrome CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors);

OR

2. **Heart Failure in Pediatric Patients; AND**
   i. Member is ≥ 6 months years of age; **AND**
   ii. The member has stable symptomatic heart failure due to dilated cardiomyopathy; **AND**
   iii. The member is in sinus rhythm with elevated heart rate; **AND**
   iv. The member does not have any of the following contraindications:
      a. Acute decompensated heart failure
      b. Blood pressure less than 90/50 mmHg
      c. Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
      d. Resting heart rate less than 60 bpm prior to treatment
      e. Severe hepatic impairment
      f. Pacemaker dependence
      g. Concomitant use of strong cytochrome CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors);

OR

3. **Inappropriate Sinus Tachycardia**; **AND**
   i. The member has inappropriate sinus tachycardia; **AND**
   ii. The member does not have any of the following contraindications:
      a. Acute decompensated heart failure
      b. Blood pressure less than 90/50 mmHg
      c. Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
      d. Resting heart rate less than 60 bpm prior to treatment
      e. Severe hepatic impairment
      f. Pacemaker dependence
      g. Concomitant use of strong cytochrome CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors)

II. Ivabradine (Corlanor) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Coronary artery disease with or without heart failure

III. Ivabradine (Corlanor) is considered investigational when used for all other conditions, including but not limited to:
   A. Non-stable, asymptomatic chronic heart failure
   B. Pediatric heart failure not due to dilated cardiomyopathy

Renewal Evaluation

I. **Heart Failure in adults, heart failure in pediatrics, inappropriate sinus tachycardia**; **AND**
   A. Member has previously received treatment with ivabradine (Corlanor); **AND**
   B. Continues to meet criteria identified in section I of the initial Evaluation; **AND**
   C. Provider attest to stabilization of disease (e.g. heart rate reduction, reduction in hospitalization due to worsening heart failure); **AND**
   D. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. Ivabradine (Corlanor) is indicated to reduce the risk of hospitalization for worsening heart failure in adult patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use.
II. ACC/AHA 2015 guideline recommends the use of ivabradine (Corlanor) [moderate evidence] over the historical standard treatment of beta-blockers [weak evidence] for the treatment of inappropriate sinus tachycardia.

Investigational or Not Medically Necessary Uses

I. Coronary artery disease
   A. In the BEAUTIFUL and SIGNIFY trials, no benefits were found in patients with stable coronary artery disease with or without stable heart failure, who were given ivabradine (Corlanor).
II. Non-stable, asymptomatic chronic heart failure
   A. Ivabradine (Corlanor) has not been studied in patients with non-stable, asymptomatic chronic heart failure; therefore, it would be considered investigational when Corlanor is requested in that setting.
III. Pediatric heart failure not due to dilated cardiomyopathy
   A. Ivabradine (Corlanor) has not been studied in pediatric patients with heart failure that is not due to dilated cardiomyopathy; therefore, it would be considered investigational when Corlanor is requested in that setting.

References

1. Corlanor [Prescribing Information]. Thousand Oaks, CA: Amgen, Inc. April 2019.
2. Fox K, Ford I, Steg G, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Sep 6;372(9641):807-16. doi: 10.1016/S0140-6736(08)61170-8.
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Policy Implementation/Update:

Date Created	May 2015
Date Effective	May 2015
Last Updated	August 2015
Last Reviewed	06/2019

Action and Summary of Changes	Date
Transitioned criteria to policy. In this transition, the following updates were made: added new indication for pediatric heart failure due to dilated cardiomyopathy, incorporated the approvable off-label indication of inappropriate sinus tachycardia, and added renewal criteria.	06/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP129

Description

Ixazomib (Ninlaro) is an orally administered reversible proteasome inhibitor that binds and inhibits chymotrypsin-like activity of the beta 5 subunit of the 20s proteasome.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
ixazomib (Ninlaro)	2.3 mg capsule	Previously treated multiple myeloma, in combination with lenalidomide and dexamethasone	3 capsules/28 days
	3 mg capsule		
	4 mg capsule		

Initial Evaluation

I. Ixazomib (Ninlaro) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND**
   C. A diagnosis of **Previously treated multiple myeloma** when the following are met:
      1. The member has relapsed or refractory disease; **AND**
      2. The member has progressed on at least one prior therapy (e.g., melphalan, thalidomide, bortezomib, stem cell transplant, etc.); **AND**
      3. The member has **not** previously progressed on or after lenalidomide (Revlimid); **AND**
      4. Ixazomib (Ninlaro) will be used in combination with lenalidomide (Revlimid) AND dexamethasone; **AND**
      5. Ixazomib (Ninlaro) will be **not** be used with any other oncolytic medication other than those noted above.

II. Ixazomib (Ninlaro) is considered investigational when used for all other conditions, including but not limited to:
   A. Graft-Versus-Host Disease
   B. AL Amyloidosis
   C. Non-Hodgkin lymphoma
   D. Follicular lymphoma

E. Breast cancer
F. Mantle cell lymphoma
G. Sarcoma
H. Kidney cancer
I. Central nervous system cancers

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Ixazomib (Ninlaro) is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
IV. Clinical documentation of response to treatment such as stabilization or improvement in disease or symptoms; **AND**
V. Will be used in combination with lenalidomide (Revlimid) AND dexamethasone; **AND**
VI. Will **not** be used in combination with any other oncolytic medication other than lenalidomide (Revlimid).

Supporting Evidence

I. The safety and efficacy of ixazomib (Ninlaro) was evaluated in a randomized, double-blind, placebo controlled trial.
    - Ixazomib (Ninlaro) was evaluated in combination with lenalidomide (Revlimid) and dexamethasone for multiple myeloma in adults. Subjects were relapsed or refractory to at least one prior therapy, with those who were refractory to lenalidomide (Revlimid) excluded from the trial. The label indicates 69% of participants in each group had previously progressed on bortezomib (Velcade), 44-47% had progressed on thalidomide (Thalomid), 80-81% had progressed on melphalan therapy, and 55-59% had previous stem cell transplantation.
    - A total of 722 subjects were randomized and treated until disease progression or unacceptable toxicity with ixazomib (Ninlaro)on days one, eight, and 15 of the 28-day cycles.
    - The primary endpoint was progression-free survival (PFS) according to the 2011 International Myeloma Working Group (IMWG) Consensus Uniform Response Criteria, assessed by a blinded independent review committee. The PFS for ixazomib (Ninlaro) was 20.6 months (17, NE) versus 14.7 months (12.9, 17.6) [HR 0.74 (0.59-0.94), p<0.012].
    - A statistically significant survival benefit has not been demonstrated with ixazomib (Ninlaro).

II. National Comprehensive Cancer Network guidelines indicate that treatment with a three drug regimen is standard of care; however, for those that have low performance status, initiation with a two-drug regimen may be appropriate until performance improves.

III. Clinical resources indicate ixazomib (Ninlaro) is approved for multiple myeloma maintenance therapy for newly diagnosed disease; however, the label does not indicate this use. A clinical trial for maintenance therapy after hematopoietic stem cell transplant shows preliminary results for PFS; however, clinically relevant data, such as overall survival, are unknown at this time.

Investigational or Not Medically Necessary Uses

I. Ixazomib (Ninlaro) has not been sufficiently studied for safety and efficacy, and/or are is currently being evaluated in clinical trials for the following indications:
   A. Graft-Versus-Host Disease
   B. AL Amyloidosis
   C. Non-Hodgkin lymphoma
   D. Follicular lymphoma
   E. Breast cancer
   F. Mantle cell lymphoma
   G. Sarcoma
   H. Kidney cancer
   I. Central nervous system cancers

References

1. Ninlaro [Package Insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc. November 2016.
2. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. Version 2.2019 [Updated October 9, 2019]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
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4. Dimopolulos MA., Gay F., Schjesvold F., et al. Oral ixazomib maintenance following autologous stem cell transplant (TOURMALINE-MM3): a double-blind, randomized, placebo-controlled phase 3 trial. *Lancet*. 2019; 393(10168):253-264.

Policy Implementation/Update:

Date Created	December 2015
Date Effective	February, 2016
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Age requirement added, as well as clarification on place in therapy and appropriate combination therapy. Renewal requirements changed to include specialist prescriber, and appropriate place in therapy and combination therapy.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP076

Description

Lapatinib (Tykerb) is an orally administered tyrosine kinase inhibitor against epidermal growth factor receptors HER1 and HER2.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
lapatinib (Tykerb)	250 mg tablets	Breast cancer, HER2 overexpression, advanced or metastatic in combination with capecitabine after prior therapy	105 tablets/21 days
		Breast cancer, HR-positive, HER2 overexpression, in postmenopausal women, in combination with letrozole	168 tablets/28 days

Initial Evaluation

I. **Lapatinib (Tykerb)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Lapatinib (Tykerb) will not be used in combination with any other oncolytic medication with the exception of, capecitabine (Xeloda), letrozole, or trastuzumab (Herceptin, Trazimera, Kanjinti, etc.); **AND**
   D. A diagnosis of **breast cancer** when the following are met:
      1. The tumor is positive for HER2(+) gene expression; **AND**
      2. The breast cancer is advanced (stage III) or metastatic (stage IV); **AND**
      3. The medication will be used in one of the following settings:
         i. Progression following ALL of the following therapies: anthracycline therapy (e.g., doxorubicin), taxane therapy (e.g., paclitaxel, docetaxel), trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.); **AND**
            a. Will be used in combination with capecitabine; **AND**
            b. Request is for generic lapatinib; **OR**
               i. Member has an intolerance or contraindication to generic labatinib; **OR**
         ii. Initial therapy in the metastatic setting; **AND**

a. The member is a postmenopausal female (natural or pharmacotherapy induced [e.g., GnRH therapy used concomitantly [e.g., Lupron]); **AND**
b. The disease is hormone receptor (HR)-positive; **AND**
c. Will be used in combination with letrozole or trastuzumab (Herceptin, Trazimera, Kanjinti, etc.); **AND**
d. Request is for generic lapatinib; **OR**
    i. Member has an intolerance or contraindication to generic labatinib

II. Lapatinib (Tykerb) is considered investigational when used for all other conditions, including but not limited to:
    A. HER2(–) breast cancer
    B. Concurrent use with therapies outside of those listed above
    C. Ovarian, uterine, endometrial cancer
    D. Peritoneal cancer
    E. Pancreatic cancer
    F. Melanoma
    G. Central nervous system cancers
    H. Head and neck cancer
    I. Gastrointestinal cancer
    J. Bladder, urothelial, renal cancer

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member has received a previous prior authorization approval for this agent; **AND**
III. The medication is prescribed by or in consultation with, an oncologist; **AND**
IV. Lapatinib (Tykerb) will not be used in combination with any other oncolytic medication with the exception of an letrozole, capecitabine or trastuzumab; **AND**
III. Documentation is provided indicating disease response to therapy, as defined by stabilization of disease, decrease in the size of the tumor, or tumor spread; **AND**
    A. Request is for generic lapatinib; **OR**
        1. Member has an intolerance or contraindication to generic labatinib

Supporting Evidence

I. Lapatinib (Tykerb) was evaluated in in combination with capecitablne for HER2(+), metastatic breast cancer. The trial was a Phase 3, randomized study versus capecitabine monotherapy in subjects that had previous exposure to anthracyclines, taxanes, and trastuzumab. The primary

endpoint was time to progression and the results were statistically significant in favor of lapatinib (Tykerb).

II. Overall survival data was not mature at time of assessment, and future results are likely to be confounded as subjects on placebo were allowed to cross over to active therapy during the trial.

III. In two randomized trials, lapatinib (Tykerb) showed to be less effective than trastuzumab-based chemotherapy regimens. The package label indicates subjects should have disease progression on trastuzumab prior to initiation of lapatinib (Tykerb) when used in combination with capecitabline for those with advanced or metastatic, HER2(+) disease.

IV. Lapainib (Tykerb) in combination with letrozole was evaluated in a double-blind, placebo-controlled study. The trial included women with HR+, HER2(+), metastatic breast cancer who had not received prior therapy for metastatic disease. The primary outcome was progression-free survival (PFS) which was statistically significant in favor of lapatinib (Tykerb).

V. Another trial evaluated lapatinib (Tykerb) in combination with an aromatase inhibitor, again evaluating in HR+, HER2(+), metastatic disease. These subjects had progressed after trastuzumab chemotherapy and endocrine therapies. The treatment arms included lapatinib (Tykerb) + trastuzumab + AI, trastuzumab + AI, or lapatinib (Tykerb) + AI. The results were statistically significant in PFS for the triple therapy, followed by lapatinib (Tykerb) + AI, then trastuzumab + AI. Additionally, lapatinib (Tykerb) has demonstrated a statistically significant improvement in PFS in HER2(+) breast cancer when added to trastuzumab compared to lapatinib (Tykerb) alone.

Investigational or Not Medically Necessary Uses

I. Lapatinib (Tykerb) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. HER2(–) breast cancer
   B. Concurrent use with therapies outside of those listed above
   C. Ovarian, uterine, endometrial cancer
   D. Peritoneal cancer
   E. Pancreatic cancer
   F. Melanoma
   G. Central nervous system cancers
   H. Head and neck cancer
   I. Gastrointestinal cancer
   J. Bladder, urothelial, renal cancer

References

1. Tykerb [Prescribing Information[. East Hanover, NJ. Novartis Pharmaceuticals Corporation. December 2018.
2. Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(6):732-742.
3. Pivot X, Manikhas A, Żurawski B, et al. CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2015;33(14):1564-73.

4. Johnston S, Pippen J, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol. 2009;27(33):5538-46.
5. NCCN Clinical Practice Guideline in Oncology: Breast Cancer. Version 3.2019. National Comprehensive Cancer Network. Available at https://www.nccn.org/professionals/ physician_gls/pdf/breast.pdf. Updated September 6, 2019.
6. Geyer C, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-2743

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria to prefer generic lapatinib over brand Tykerb unless contraindicated or not tolerated	06/2021
Criteria transitioned to policy. Policy updated to include the following requirement: specialist prescriber, age, concurrent therapies, specified place in therapy.	10/2019
Previous Reviews	09/2013 08/2013 08/2011 10/2008
Policy Created	09/2008

Policy Type: PA/SP Pharmacy Coverage Policy: UMP042

Split Fill Management*

Description

Larotrectinib (Vitrakvi) is an orally administered tropomyosin receptor kinase (TRK) inhibitor; specifically TRKA, TRKB, and TRKC.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
larotrectinib (Vitrakvi)	25 mg capsule	Neuotrophic receptor tyrosine kinase gene fusion positive solid tumor, metastatic	180 tablets/30 days
	100 mg capsule		60 tablets/30 days
	20 mg/1 mL solution		Quantity calculated to 100 mg/m2 of body surface area

Initial Evaluation

I. Larotrectinib (Vitrakvi) may be considered medically necessary when the following criteria are met:
   A. Prescribed by, or in consultation with, an oncologist; **AND**
   B. Medication will **not** be used in combination with any other oncolytic medication; **AND**
   C. The member has **not** previously progressed on other NTRK gene fusion medications (e.g., entrectinib [Rozlytrek]); **AND**
   D. A diagnosis of solid tumor with confirmed **NTRK gene fusion; AND**
   E. Member has metastatic disease, or surgical resection is likely to result in severe morbidity (i.e., tumor is unresectable); **AND**
   F. The member does **not** have an acquired resistance mutation (resistant mutations include, but may not be limited to: G595R, G623R, G696A, F617L); **AND**
   G. **All** alternative therapies for diagnosis and stage of cancer have been exhausted, as defined by:
      1. Progression following all appropriate treatments; **OR**
      2. Nonresponse to all available therapies; **OR**
      3. All available therapies are contraindicated or not tolerated; **OR**
      4. No standard or satisfactory treatments exist; **AND**
   H. The member has intolerance to or contraindication to entrectinib (Rozlytrek); **OR**

1. Member is less than 12 years of age

II. Larotrectinib (Vitrakvi) is considered not medically necessary when criteria above are not met and/or when used for the following:
   A. When used for a resistance mutation (resistant mutations include, but may not be limited to G595R, G623R, G696A, F617L)

III. Larotrectinib (Vitrakvi) is considered investigational when used for all other conditions, including but not limited to:
   A. Oncolytic indications as an adjunct therapy
   B. Non-small cell lung cancer without NTRK fusion gene rearrangements
   C. Solid tumors that do not harbor NTRK gene fusions
   D. Leukemias or lymphomas

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescribed by, or in consultation with, an oncologist; **AND**
IV. Medication will **not** be used in combination with any other oncolytic medication; **AND**
V. Response to therapy as indicated by stabilization of disease or decrease in tumor size or spread; **AND**
VI. Member does **not** have unacceptable medication toxicity (e.g., hepatotoxicity, severe delirium or gait disturbances, etc.); **AND**
VII. Documentation of absence of acquired resistance

Supporting Evidence

I. Per the landmark trials LOXO-TRK-14001 (SCOUT and NAVIGATE): All subjects were diagnosed with measurable or evaluable metastatic or locally advanced solid tumors, had progressed beyond all effective and available therapies per the National Comprehensive Cancer Network (NCCN), had no therapies available for the diagnosis per NCCN guidelines, or surgical resection would result in significant morbidity.
II. Subjects were without acquired resistance mutations to NTRK-inhibitors, without active cardiovascular disease or history of myocardial infarction within the prior six months, and were not on concurrent CYP3A4 inhibitors or inducers.
III. The NTRK gene fusion mutation was confirmed using a validated laboratory testing method. Testing methods for NTRK gene fusion include NGS, RT-PCR, FISH, or Immunohistochemistry (ICH). The use of ICH may lead to a false positive result. ICH uses the presence of a surrogate marker (TRK proteins) to establish the likelihood of a NTRK gene fusion. The FISH method

requires the visual assessment of an experienced pathologist of several tests and is considered more subjective than NGS or RT-PCR.

IV. The trials were single-arm, open-label studies that included 55 patients with solid tumors. The tumor types that had represented AND reported a measurable Overall Response Rate (ORR) were the following:
    - Salivary gland cancer
    - Soft tissue sarcoma (STS)
    - Infantile fibrosarcoma (IFS)
    - Gastrointestinal Stromal Tumor (GIST)
    - Non-small cell lung cancer (NSCLC)
    - Colorectal cancer (CRC)
    - Melanoma
    - Thyroid carcinoma
    - Colon cancer

V. Tumors that were evaluated in one or more subjects but did not show an ORR includ cholangiocarcinoma, appendix, breast and pancreatic cancer.

VI. Adverse reactions were common with larotrectinib (Vitrakvi), and included fatigue, pyrexia, peripheral edema, CNS, gastrointestinal, respiratory, musculoskeletal, and laboratory disturbances (e.g., ASK, ALT). Adverse events leading to dose discontinuation, interruption or reduction occurred in 37% of subjects. The safety profile of larotrectinib (Vitrakvi) is likely not fully developed given the small number of subjects in the clinical trials and short trial duration. Additionally, due to rarity of the NTRK gene fusion mutation, post-marketing information is likely to remain limited.

VII. There are currently two available therapies for NTRK gene fusion positive mutations. Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek), currently there is no direct comparison data showing safety and/or efficacy differences between these therapies OR safety or efficacy of using them sequentially after progression. Additionally, caution should be exercised when making cross trial comparisons. At this time, entrectinib (Rozlytrek) provides a better value for general populations with NTRK gene fusion positive tumors given the sum of safety, efficacy, and cost information currently available.

VIII. It should also be noted that due to single-arm, open-label trial designs, as well as outcomes evaluated, no NTRK gene fusion therapies available have been shown to improve health outcomes to date.

IX. Entrectinib (Rozlytrek) is FDA-approved down to 12 years of age, but has been, and will continue to be, evaluated in younger populations. Larotrectinib (Vitrakvi) FDA-approval is nonspecific to pediatrics and adults.

Investigational or Not Medically Necessary Uses

I. Larotrectinib (Vitrakvi) does not have sufficient activity in those with resistance mutations. As of December 2019, known resistance mutations include: G595R, G623R, G696A, F617L.

II. Larotrectinib (Vitrakvi) has not been sufficiently evaluated for safety and efficacy in the following settings:
    A. Oncolytic indications as an adjunct therapy

B. Non-small cell lung cancer without NTRK fusion gene rearrangements
C. Solid tumors that do not harbor NTRK gene fusions
D. Leukemias or lymphomas

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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4. Hyman DM, Laetsch TW, Kummar S, et al. ASCO 2017. Abstract LBA2501: The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.18_suppl.LBA2501. Accessed December 5, 2018.
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6. Heymach J, Krilov L, Alberg A, et al. Clinical Cancer Advances 2018: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. *J Clin Oncol,* Vol 36, No 10 (April 1), 2018: pp 1020-1044. DOI: https://doi.org/10.1200/JCO.2017.77.0446

Policy Implementation/Update:

Date Created	January 2019
Date Effective	February 2019
Last Updated	December 2019
Last Reviewed	December 2019

Action and Summary of Changes	**Date**
Policy updated to newest formatting. Initial approval duration changed to three months from six months given safety concerns and split-fill designation, quantity limit for solution now based on BSA, removal of designated test requirement, removed requirements for lab value monitoring, requirement for lack of CV comorbidities and CNS symptoms. Addition of monotherapy requirement, documentation of intolerance of contraindication to entrectinib (Rozlytrek) and requirement the member has not previously progressed on other NTRK therapies.	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP111

Description
Thalidomide (Thalomid) is an oral immunomodulatory medication that inhibits FGF-dependent angiogenesis in vivo and exhibits antineoplastic activity. Lenalidomide (Revlimid) and pomalidomide (Pomalyst) are orally administered thalidomide analogues. These agents are thought to attack multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis, and cytokine circuits, among others.

Length of Authorization
- **Initial:**
  - i. Lenalidomide (Revlimid)
    1. Follicular lymphoma/Marginal zone lymphoma: 12 months
    2. All other indications: Six months
  - ii. Pomalidomide (Pomalyst) and thalidomide (Thalomid)
    1. All indications: Three months
- **Renewal:**
  - i. Lenalidomide (Revlimid)
    1. Follicular lymphoma/Marginal zone lymphoma: Cannot be renewed
    2. All other indications: 12 months
  - ii. Pomalidomide (Pomalyst)
    1. All indications: 12 months
  - iii. Thalidomide (Thalomid)
    1. Cutaneous manifestations of moderate to severe Erythema Nodosum Leprosum (ENL): 12 months
    2. Multiple myeloma: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
generic lenalidomide	2.5 mg capsules	Follicular lymphoma; Marginal zone lymphoma; Multiple myeloma; Myelodysplastic syndromes	28 capsules/28 days
	5 mg capsules	Follicular lymphoma; Mantle cell lymphoma; Marginal zone lymphoma; Multiple myeloma; Multiple myeloma maintenance therapy following auto-HSCT; Myelodysplastic syndromes;	28 capsules/28 days
	10 mg capsules		28 capsules/28 days
	15 mg capsules		28 capsules/28 days
	20 mg capsules		21 capsules/28 days
	25 mg capsules	Mantle cell lymphoma; Multiple myeloma	21 capsules/28 days

lenalidomide (Revlimid)	2.5 mg capsules	Follicular lymphoma; Marginal zone lymphoma; Multiple myeloma; Myelodysplastic syndromes	28 capsules/28 days
	5 mg capsules	Follicular lymphoma; Mantle cell lymphoma; Marginal zone lymphoma; Multiple myeloma; Multiple myeloma maintenance therapy following auto-HSCT; Myelodysplastic syndromes;	28 capsules/28 days
	10 mg capsules		28 capsules/28 days
	15 mg capsules		28 capsules/28 days
	20 mg capsules		21 capsules/28 days
	25 mg capsules	Mantle cell lymphoma; Multiple myeloma	21 capsules/28 days
pomalidomide (Pomalyst)	1 mg capsules	Multiple Myeloma	21 capsules/28 days
	2 mg capsules		
	3 mg capsules		
	4 mg capsules		
thalidomide (Thalomid)	50 mg capsules	Multiple Myeloma	28 capsules/28 days
	100 mg capsules		
	150 mg capsules		
	200 mg capsules		
	50 mg capsules	Erythema Nodosum Leprosum	60 capsules/30 days
	100 mg capsules		
	150 mg capsules		
	200 mg capsules		

Initial Evaluation

I. **Lenalidomide (Revlimid) and generic lenalidomide** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. Request is for generic lenalidomide; **OR**
      1. Request is for BRAND Revlimid and treatment with generic lenalidomide is contraindicated or not tolerated; **AND**
   C. A diagnosis of **multiple myeloma (MM)** when the following is met:
      1. Medication will be used with dexamethasone as part of a doublet or triplet regimen; **OR**
      2. Medication will be used as monotherapy; **OR**
   D. A diagnosis of **myelodysplastic syndrome (MDS)** when the following are met:
      1. Member has lower risk disease (e.g. IPSS Low or Intermediate-1; IPSS-R Very Low, Low, Intermediate; WPSS Very Low, Low, Intermediate); **AND**
      2. Member has transfusion-dependent anemia (i.e. 2 or more units of red blood cells in the previous 8 weeks); **AND**
         i. MDS with del(5q) abnormality; **OR**

ii. MDS without del(5q) abnormality; **AND**
a. Serum erythropoietin levels are less than 500 mU/mL; **AND**
i. Medication will be used in combination with an erythropoiesis-stimulating agent (ESA) (e.g. Procrit, Retacrit, or Aranesp) with or without granulocyte-colony stimulating factor (GCSF) (e.g., filgrastim, pegfilgrastim); **AND**
1. History of inadequate response to ESA with or without GCSF; **OR**
b. Serum erythropoietin levels are greater than 500 mU/mL; **AND**
i. History of failure, contraindication, or intolerance to immunosuppressive therapy (IST) (e.g. anti-thymocyte globulin ± cyclosporine A); **OR**

E. A diagnosis of **mantle cell lymphoma (MCL)** when the following is met:
1. Member has relapsed or progressed after two prior regimens, one of which included bortezomib; **OR**

F. A diagnosis of **follicular lymphoma (FL)** when the following are met:
1. Member was previously treated with at least one prior regimen for FL (e.g. bendamustine + rituximab/obinutuzumab, cyclophosphamide/doxorubicin/vincristine/prednisone); **AND**
2. The medication will be used in combination with rituximab; **OR**

G. A diagnosis of **marginal zone lymphoma (MZL)** when the following are met:
1. Member was previously treated with at least one prior regimen for MZL (e.g. bendamustine + rituximab, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, rituximab/cyclophosphamide/vincristine/prednisone); **AND**
2. The medication will be used in combination with rituximab

II. **Pomalidomide (Pomalyst)** may be considered medically necessary when the following criteria are met:
A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
B. A diagnosis of **multiple myeloma (MM)** when the following are met:
1. Member has relapsed and/or refractory MM; **AND**
2. Member has received at least two prior therapies for MM, including lenalidomide (Revlimid) and a proteasome inhibitor (e.g. bortezomib); **AND**
3. Medication will be initiated within 60 days of completion of the last therapy; **AND**
4. Medication will be used with dexamethasone as part of a doublet or triplet regimen

III. **Thalidomide (Thalomid)** may be considered medically necessary when the following criteria are met:
A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
1. A diagnosis of **multiple myeloma (MM)** when the following are met:

i. Medication will be used with dexamethasone as part of a doublet or triplet regimen; **OR**

B. Medication is prescribed by, or in consultation with, an infectious disease specialist

1. A diagnosis of **erythema nodosum leprosum (ENL)** when the following are met:

i. Medication will be used for the acute treatment of the cutaneous manifestations of moderate to severe ENL; **AND**

a. If moderate to severe neuritis is present, the medication will be used in combination with corticosteroids; **OR**

ii. Medication will be used as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence

IV. Lenalidomide (Revlimid) is considered not medically necessary when used for all other conditions, including but not limited to:

A. Chronic lymphocytic leukemia (CLL), relapsed or refractory

V. Lenalidomide (Revlimid), pomalidomide (Pomalyst), and thalidomide (Thalomid) is/are considered investigational when used for all other conditions, including but not limited to:

A. Kaposi sarcoma)
B. Behçet syndrome
C. Diffuse large B-cell lymphoma (DLBCL)
D. Multiple myeloma (MM) when given as part of a quadruplet ("quad") regimen
E. Myelofibrosis
F. Non-Hodgkin's lymphoma (NHL)
G. POEMS syndrome
H. Systemic light chain amyloidosis (AL)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Documentation of response to treatment defined by improvement or stabilization of disease or symptoms; **AND**

IV. Request is for pomalidomide (Pomalyst), thalidomide (Thalomid), or generic lenalidomide; **OR**

A. Request is for BRAND Revlimid and treatment with generic lenalidomide has been ineffective, contraindicated, or not tolerated

Supporting Evidence

I. **Multiple myeloma (MM)**:

Lenalidomide (Revlimid)

- Efficacy of lenalidomide (Revlimid) was established in an open-label trial comparing lenalidomide (Revlimid) with low dose dexamethasone (Rd) to melphalan, prednisone, and thalidomide (Thalomid) (MPT) in newly diagnosed MM patients who were not candidates for stem cell transplant. The primary outcome of progression free survival (PFS) was significantly longer with Rd continuous than MPT: HR 0.72 (95% CI: 0.61-0.85 p <0.0001). The improvement in median PFS time in the Rd continuous arm compared with the MPT arm was 4.3 months.
- In MM patients following auto-HSCT, efficacy was established in two multicenter, randomized, double-blind, parallel group, placebo-controlled studies. In both studies, the primary analysis of PFS was significantly longer with lenalidomide (Revlimid) compared to placebo.
- Numerous regimens have been used for the treatment of MM, both in patients who are transplant eligible and those who are not transplant eligible.
- Three-drug regimens are the mainstay of initial therapy for most patients with newly diagnosed MM. For all patients with MM, regardless of transplant status, triplet regimens have shown to induce higher response rates and depth of response in clinical trials.
    i. Lenalidomide (Revlimid)/bortezomib/dexamethasone
        1. Phase 2 and Phase 3 trials have demonstrated that initial treatment with the combination is active and well tolerated in newly diagnosed patients with MM, regardless of transplant eligibility.
        2. This combination is included as a preferred NCCN category 1 recommendation for primary therapy for both MM patients, regardless of transplant status.
    ii. Lenalidomide (Revlimid)/low-dose dexamethasone
        1. Two-drug regimens are typically reserved for elderly and/or frail patients.
        2. Lenalidomide (Revlimid) in combination with low-dose dexamethasone is a well-tolerated and effective regimen for transplant-ineligible and elderly patients.
        3. This combination is included as a preferred NCCN category 1 recommendation for primary therapy for non-transplant candidates.
    iii. Lenalidomide (Revlimid)/daratumumab (Darzalex)/dexamethasone
        1. An open-label, randomized, active control Phase 3 study compared treatment with the addition of daratumumab (Darzalex) to lenalidomide (Revlimid)/dexamethasone compared to lenalidomide (Revlimid)/dexamethasone alone in 737 patients with newly diagnosed MM ineligible for transplant.
        2. Median PFS has not been reached in the triplet combination arm compared to 31.9 months in the control arm.
        3. This combination is included as a preferred NCCN category 1 recommendation for primary therapy for non-transplant candidates.

- Lenalidomide (Revlimid) is also used in previously treated MM, typically as part of similar triplet regimens.
    i. Lenalidomide (Revlimid)/bortezomib/dexamethasone
        1. The results of Phase 1 and Phase 2 studies show that the triplet combination is well tolerated and active, with durable responses in heavily pretreated patients with relapsed and/or refractory MM, including patients who have had prior lenalidomide (Revlimid), bortezomib, thalidomide, and transplant.
        2. After a median follow-up of 44 months, the median PFS was 9.5 months and median overall survival (OS) was 30 months.
        3. This combination is included as a preferred NCCN category 2A recommendation for previously treated MM
    ii. Lenalidomide (Revlimid)/elotuzumab (Empliciti)/dexamethasone
        1. This combination is FDA approved for the treatment of patients with MM who have received one to three prior therapies.
        2. Efficacy and safety were demonstrated in a Phase 3 trial which randomized 646 patients to receive either elotuzumab (Empliciti) in combination with lenalidomide (Revlimid) and dexamethasone or lenalidomide (Revlimid)/dexamethasone alone.
        3. Median PFS in the elotuzumab (Empliciti)-containing regimen was 19.4 months vs 14.9 months in those receiving lenalidomide (Revlimid)/dexamethasone alone.
        4. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.
    iii. Lenalidomide (Revlimid)/carfilzomib (Kyprolis)/dexamethasone
        1. The combination was evaluated in a randomized, open-label trial compared to lenalidomide (Revlimid)/dexamethasone alone in patients with relapsed and/or refractory MM.
        2. Median PFS was 26.3 months for the triple combination therapy vs 17.6 months for lenalidomide (Revlimid)/dexamethasone.
        3. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.
    iv. Lenalidomide (Revlimid)/daratumumab (Darzalex)/dexamethasone
        1. A Phase 3 trial in 569 patients evaluated the addition of daratumumab (Darzalex) to lenalidomide (Revlimid)/dexamethasone vs lenalidomide (Revlimid)/dexamethasone alone.
        2. The overall response rate (ORR) was higher in the daratumumab group, and the estimated rate of PFS at 12 months was 83.2% compared with 60% in the control group.
        3. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.
    v. Lenalidomide (Revlimid)/ixazomib (Ninlaro)/dexamethasone

1. The combination is FDA approved for the treatment of patients with MM who have received at least one prior therapy.
2. The safety and efficacy were evaluated in a randomized, controlled trial in patients who had received at least one prior MM therapy (e.g. bortezomib-containing regimen). Patients were randomized to lenalidomide (Revlimid)/ixazomib (Ninlaro)/dexamethasone vs lenalidomide (Revlimid)/dexamethasone alone.
3. The triple combination resulted in a PFS of 20.6 months compared to 14.7 months for the control arm.
4. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.

Pomalidomide (Pomalyst)

- Pomalidomide (Pomalyst) is indicated for patients with multiple myeloma, in combination with dexamethasone, who have received at least two prior therapies including lenalidomide (Revlimid) and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of last therapy.
- A Phase 3 randomized, open-label study compared the efficacy and safety of pomalidomide (Pomalyst) and low-dose dexamethasone vs high-dose dexamethasone in patients with relapsed MM who were refractory to both lenalidomide (Revlimid) and bortezomib. The primary endpoint, PFS, was significantly longer in patients who received pomalidomide (Pomalyst) and low-dose dexamethasone compared to those who received high-dose dexamethasone (4.0 vs 1.9 months; $P < 0.0001$). Overall survival was significantly longer in the pomalidomide (Pomalyst) group also (12. 7 vs 8.1 months; $P = 0.0285$).
- A Phase 2, randomized open-label trial evaluated the safety and efficacy of pomalidomide (Pomalyst) alone or pomalidomide (Pomalyst) with low-dose dexamethasone in patients with relapsed or refractory MM. The ORR was 29.2% in patients who received combination therapy versus 7.4% in the monotherapy arm.
- Additional data regarding single agent pomalidomide (Pomalyst) therapy is available but is considered low quality. Pomalidomide (Pomalyst) monotherapy was evaluated in a Phase 1 trial of 24 patients and demonstrated an ORR of 50%. In a subsequent Phase 1 study, the ORR was much lower at 15%.
- Immunomodulatory agents are usually given in combination with dexamethasone and/or other agents, but the NCCN Multiple Myeloma Panel suggests considering pomalidomide (Pomalyst) monotherapy in patients who are steroid-intolerant.

Thalidomide (Thalomid)

- Although thalidomide (Thalomid) was the first immunomodulatory agent to show efficacy in MM, other agents such as lenalidomide (Revlimid) and pomalidomide (Pomalyst) have since been developed and offer a more favorable safety profile.
- The efficacy and safety of thalidomide (Thalomid) plus dexamethasone vs dexamethasone alone in multiple myeloma was evaluated in two open-label studies in symptomatic patients with newly diagnosed multiple myeloma. In one study, response rates (based on serum or urine paraprotein measurements) were

significantly higher in the combination arm (52% vs 36%). In another study, the time to progression (TTP) was statistically significantly longer in the combination arm.

- The NCCN Guideline for Multiple Myeloma does not include thalidomide (Thalomid)-based regimens as preferred or recommended for any setting. Regimens containing thalidomide (Thalomid) may be useful in certain circumstances when used in combination with other active multiple myeloma agents (e.g. bortezomib). The combination of bortezomib, thalidomide (Thalomid), and dexamethasone is a Category 1 recommendation as primary therapy for transplant candidates in certain circumstances.
- There is no evidence to support the use of thalidomide (Thalomid) as monotherapy for the treatment of multiple myeloma.

II. **Myelodysplastic syndromes (MDS):**

- Lower-risk MDS with del(5q) generally has a relatively good prognosis and is highly responsive to lenalidomide (Revlimid) therapy.
    i. A Phase 3 trial in 205 patients demonstrated superiority of lenalidomide (Revlimid) compared to placebo for achieving RBC transfusion-independence.
        1. Patients with transfusion-dependent, lower risk MDS with del(5q) were treated with low dose lenalidomide (Revlimid) (10 mg), lower dose lenalidomide (Revlimid) (5 mg), and placebo.
        2. The rates of transfusion-independence for greater than 26 weeks were 57%, 37%, and 2% respectively for low dose lenalidomide (Revlimid), lower dose lenalidomide (Revlimid), and placebo.
        3. The risk of transformation to acute myeloid leukemia (AML) was not significantly different between lenalidomide (Revlimid) and placebo.
    ii. Additionally, a Phase 2 trial in anemic transfusion-dependent patients with del(5q) also reported similar hematologic responses in two-thirds of the 148 patients with del(5q).
- The safety and efficacy of lenalidomide (Revlimid) for lower-risk MDS without del(5q) was evaluated in a Phase 3 trial in 239 patients with transfusion-dependent MDS.
    i. Patients receiving lenalidomide (Revlimid) compared to placebo had a higher rate of transfusion-independence (26.9% vs 2.5%; $p< 0.001$). Transfusion reduction of four or more units of packed RBCs was seen in 22% of lenalidomide (Revlimid)-treated patients while no reduction was seen in the placebo group.
    ii. Incidence of treatment-related mortality was 2.5% in both groups, but the incidence of myelosuppression was higher in the lenalidomide-treated group. Furthermore, when comparing lenalidomide (Revlimid) to placebo, the incidence of grade 3 or 4 neutropenia was 61.9% vs 12.7%, respectively, and the rate of thrombocytopenia was 35.6% vs 3.8%, respectively.

III. **Mantle cell lymphoma (MCL):**

- Lenalidomide (Revlimid) is approved for the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.
- The safety and efficacy of single-agent lenalidomide (Revlimid) for relapsed or refractory MCL was evaluated in a Phase 2, open-label trial in 134 patients with prior bortezomib therapy. The ORR was 28% and a median duration of response (DoR) was 16.6 months.
- An additional Phase 2 trial included 254 patients with relapsed MCL who were not candidates for intensive therapy were randomized to receive single-agent lenalidomide (Revlimid) or single-agent of the investigator's choice (e.g. rituximab, gemcitabine, fludarabine, chlorambucil, cytarabine) and were allowed to receive lenalidomide (Revlimid) at the time of progression. After a median follow-up of 15.9 months, PFS was 8.7 months for lenalidomide (Revlimid) verses 5.2 months for the control arm.
- The NCCN B-Cell Lymphomas guideline suggests the use of lenalidomide (Revlimid) outside of the relapsed/refractory setting, including as initial treatment or in the second-line setting. However, there is limited evidence to support use outside of the relapsed/refractory setting. A small Phase 2 study evaluated the use of lenalidomide (Revlimid) plus rituximab as initial therapy for patients with MCL. The ORR in the intention-to-treat population (n = 38) was 87% and 92% in the population that could be evaluated (n = 36).

IV. **Previously treated follicular lymphoma (FL)/marginal zone lymphoma (MZL):**

- The efficacy of lenalidomide (Revlimid) with rituximab in patients with relapsed or refractory follicular and marginal zone lymphoma was evaluated in the AUGMENT (NCT01938001) and MAGNIFY (NCT01996865) trials.
- AUGMENT was a randomized, double-blind, multicenter trial (n=358) in patients with relapsed or refractory follicular or marginal zone lymphoma who received lenalidomide (Revlimid) and rituximab or rituximab and placebo for a maximum of 12 cycles or until unacceptable toxicity.
    i. Efficacy results in the follicular and marginal zone lymphoma population reported a PFS of 39.4 months in the lenalidomide (Revlimid) and rituximab arm versus 14.1 months in the rituximab plus placebo arm.
- MAGNIFY is an open-label, multicenter trial (n=232) in which patients with relapsed or refractory follicular, marginal zone, or mantle cell lymphoma received 12 induction cycles of lenalidomide (Revlimid) and rituximab.
    i. Overall response by investigator assessment was 59% (104/177) [95% CI: 51, 66] for patients with follicular lymphoma. Median DoR was not reached within a median follow-up time of 7.9 months [95% CI: 4.6, 9.2]. With an overall response of 51% (23/45) [95% CI: 36, 66] for patients with marginal zone lymphoma and median DoR not reached within a median follow-up time of 11.5 months [95% CI: 8.0, 18.9].

V. **Erythema nodosum leprosum (ENL)**

- Erythema nodosum leprosum (ENL) is a serious immunological complication of leprosy, causing inflammation of skin, nerves, other organs, and general malaise.

There is limited high-quality, prospective data supporting the use of thalidomide (Thalomid) for ENL. Data are mainly derived from small randomized trials or retrospective studies conducted by the U.S. Public Health Service. These data consistently report generally successful treatment of the cutaneous manifestations of moderate to severe ENL.

- Thalidomide (Thalomid) is not indicated as monotherapy for ENL treatment in the presence of moderate to severe neuritis. Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering should be maintained on the minimum dose necessary to control the reaction. Tapering off the medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.
- Dosing with thalidomide (Thalomid) in ENL should usually continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks.
- In patients with moderate to severe neuritis associated with a severe erythema nodosum leprosum reaction, corticosteroids may be started concomitantly with thalidomide (Thalomid). Steroid usage can be tapered and discontinued when the neuritis has improved.

Investigational or Not Medically Necessary Uses

I. Kaposi sarcoma
   A. A preliminary study of thalidomide (Thalomid) has shown some activity in patients with AIDS-related KS; however, further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.
   B. Pomalidomide (Pomalyst) was studied in one ongoing, open-label, single center, single arm, Phase 1/2 trial with 28 patients with KS. There were 18 HIV-positive patients and 10 HIV-negative patients included in the trial. The HIV-positive patients continued on HAART. The primary efficacy outcome was ORR. The ORR was 71% (95% CI 51, 87) for all patients with 12 HIV-positive patients and 8 HIV-negative patients having a response. The duration of response was 12.5 months (95% CI 6.5, 24.9) for HIV-positive patients and 10.5 months (95% CI 3.9, 24.2) for HIV-negative patients. NCCN guidelines recommend pomalidomide (Pomalyst) as the preferred subsequent systemic therapy for relapsed/refractory therapy after first-line systemic options liposomal doxorubicin or paclitaxel; however, this is based on preliminary evidence from an early-phase, single center, open-label trial. Further evaluation in larger, well-controlled studies are needed to support the use of pomalidomide (Pomalyst) in the setting of KS.

II. Behçet syndrome
   A. The efficacy of thalidomide monotherapy for mucocutaneous manifestations of Behçet syndrome was evaluated in 96 patients compared to placebo. Only a minority of thalidomide (Thalomid)-treated patients responded to treatment, and some symptoms worsened. Furthermore, 7% of thalidomide-treated patients developed peripheral neuropathy.

B. The use of thalidomide (Thalomid) for Behçet syndrome has fallen out of favor due to lack of proven efficacy and significant risk of neuropathy and teratogenicity.

III. Chronic lymphocytic leukemia (CLL)
   A. Lenalidomide (Revlimid) was studied in patients with previously treated CLL in a randomized, double-blind, placebo-controlled, Phase 3 trial (CONTINUUM). Patients included in the trial had been treated with two lines of therapy with at least a partial response after second-line therapy, had received a purine analogue, bendamustine, anti-CD20 antibody, chlorambucil, or alemtuzumab as first-line or second-line treatment; and had an Eastern Cooperative Oncology Group performance score of 0–2. Co-primary endpoints were PFS and OS; the primary endpoint was later changed to OS after the data cutoff for analysis. With a median follow-up of 31.5 months, there was no significant difference in OS between the lenalidomide (Revlimid) and the placebo groups (median 70·4 months, 95% CI 57·5–not estimable [NE] vs NE, 95% CI 62·8–NE; hazard ratio [HR] 0·96, 95% CI 0·63–1·48; p=0·86).

IV. Diffuse large B-cell lymphoma (DLBCL)
   A. NCCN guidelines list lenalidomide (Revlimid) maintenance for patients 60-80 years of age as a Category 2B recommendation. This is based off the results of an open-label, single-arm, Phase 2 trial in 48 adults with de novo DLBCL. Further evaluation in higher quality trials is needed to support its use.
   B. In the relapsed setting, lenalidomide (Revlimid) was studied in small, Phase 2, open-label trials consisting of low-quality evidence. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.

V. Multiple myeloma, as part of quadruple (“quad”) regimen
   A. Although triplet regimens remain the standard of care for MM, there is growing interest in quad regimens which may include the addition of monoclonal antibodies [e.g. daratumumab (Darzalex), elotuzumab (Empliciti)] to standard triplet backbone regimens. The current evidence available to support this use is limited to case series or small trials. Larger studies evaluating the safety and efficacy of these regimens are underway.

VI. Non-Hodgkin's lymphoma (NHL)
   A. Lenalidomide (Revlimid) was evaluated in patients with relapsed or refractory aggressive NHL, in an open-label, Phase 2 trial (n=49). Treatment with lenalidomide (Revlimid) led to an ORR of 35% and a median PFS of 4 months. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.

VII. Myelofibrosis
   A. Lenalidomide (Revlimid) was evaluated in a small, open-label, Phase 2 trial in combination with prednisone that reported a treatment response in 10 of 42 subjects, with 37 patients reporting a grade 3 or 4 toxicity. In an analysis of three consecutive Phase 2 trials of patients with myelofibrosis (n=125), single agent lenalidomide (Revlimid) and lenalidomide (Revlimid) plus prednisone produced higher response rates than thalidomide (Thalomid), though not statistically significant (p=0.06). Further studies are warranted. An additional trial by Daver et al. that evaluated lenalidomide (Revlimid) in combination with ruxolitinib (Jakafi) was terminated early due to failure to meet the predetermined efficacy rules for treatment success.

B. Pomalidomide (Pomalyst) has been evaluated as a treatment option for MF-associated anemia. Results from two small randomized studies produced conflicting results.
C. Enrollment in a clinical trial should be considered for all patients with myelofibrosis-associated anemia.

VIII. POEMS syndrome
A. Regimens used as systemic therapy for POEMS syndrome with widespread osteosclerotic lesions or bone marrow involvement are modelled after those used in other conditions, such as MM. There are limited data to guide choice in therapy.
B. Case reports have demonstrated clinical improvement after treatment with lenalidomide (Revlimid) with or without dexamethasone. Two small, uncontrolled studies reported responses in over 70% with 60 to 75% progression free at three years.
C. Thalidomide (Thalomid) has also shown activity but is associated with a less favorable side effect profile.
D. Larger, well-controlled trials are needed to confirm the safety and efficacy of these agents for POEMS syndrome.

IX. Systemic light chain amyloidosis (AL)
A. There is insufficient evidence to support the use of lenalidomide (Revlimid) or pomalidomide (Pomalyst) for the management of AL. Both medications are listed in NCCN guidelines among several other treatment options; however, the optimal treatment of the underlying plasma cell disorder has not been identified. Treatment of AL should be in the context of a clinical trial when possible.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added generic lenalidomide to policy with requirement to step through generic lenalidomide prior to use of branded Revlimid	05/2023
Addition of new indication for Kaposi Sarcoma for Pomalyst as experimental and investigational	06/2020
• For multiple myeloma indications, updated language to clarify use as either monotherapy, or with dexamethasone as part of a double-drug or triple-drug regimen • Added CLL to the not medically necessary section • Added the following experimental/investigational indications: - As part of a quadruple regimen for MM - Systemic light chain amyloidosis - POEMS - Behçet syndrome	04/2020
Added pomalidomide (Pomalyst) and thalidomide (Thalomid) agents to policy; removed black box warnings and precautions readily available in compendia; removed laboratory criteria.	12/2019
Converted lenalidomide (Revlimid) to policy format. Added new indication of follicular lymphoma and marginal zone lymphoma. Allowed coverage as monotherapy in multiple myeloma maintenance following autologous hematopoietic stem cell transplant. Allowed a route to coverage in myelodysplastic syndromes without a deletion 5q abnormality following phase III trial data.	08/2019
Excluded package insert/monitoring question and removed renewal question regarding regular hematological laboratory tests, extended initial approval from 3 months to 6 months.	01/2018
Previous reviews	09/2012, 10/2012, 10/2014, 09/2015, 01/2016
Policy created	08/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP282

Description

Leniolisib (Joenja) is an orally administered phosphoinositide 3-kinase delta (PI3Kδ) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
leniolisib (Joenja)	Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)	70 mg tablets	60 tablets/30 days

Initial Evaluation

I. **Leniolisib (Joenja)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Member weighs ≥ 45 kg; **AND**
   C. Medication is prescribed by, or in consultation with, an immunologist, geneticist, or a provider specializing in the management of immunodeficiencies; **AND**
   D. Medication will not be used in combination with immunosuppressive therapy (e.g., B lymphocyte depletion therapy, rituximab); **AND**
   E. A diagnosis of **Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)** when the following are met:
      1. Documentation of APDS-associated mutation with pathogenic variants in PIK3CD or PIK3R1 genes; **AND**
      2. Documentation of at least one measurable enlarged lymph node lesion observed by computed tomography (CT scan) or magnetic resonance imaging (MRI scan); **AND**
      3. Documentation of baseline naïve B cell percentage as assessed by flow cytometry; **AND**
      4. Member has one of the following clinical findings and manifestations of APDS as documented in the medical records:
         i. History of repeated infections (e.g., sinus, ear, or lung infections, herpes viral infection) requiring long-term antibiotic or antiviral prophylaxis; **OR**
         ii. Organ dysfunction (e.g., bronchiectasis, liver impairment); **OR**
         iii. History of nodal or extra-nodal lymphoproliferation; **AND**
      5. Treatment with one agent in each of the following classes has been ineffective, contraindicated, or not tolerated:
         i. Systemic corticosteroids (e.g., prednisone, methylprednisolone, budesonide)

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

ii. Immunoglobulin G (IgG) replacement therapy (IRT)
iii. Other immunosuppressants (e.g., rituximab, sirolimus)

II. Leniolisib (Joenja) is considered investigational when used for all other conditions except APDS

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication will not be used in combination with immunosuppressive therapy (e.g., B lymphocyte depletion therapy, rituximab); **AND**
IV. Documentation showing that the member has exhibited improvement or stability of disease symptoms as noted by one of the following:
    - Reduction in nodal or extra-nodal lymphoproliferation (lymph node size) from pre-treatment baseline
    - Increase in naïve B cell percentage from pre-treatment baseline

Supporting Evidence

I. Leniolisib (Joenja) is a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor FDA-approved for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adult and pediatric patients (≥ 12 years of age). It is available as a 70 mg oral tablet administered twice daily. Use in patients under the age of 12 has not yet shown safety and efficacy.
II. The recommended dosage of leniolisib (Joenja) in adult and pediatric patients 12 years of age and older, weighing 45 kg or greater, is 70 mg administered orally twice daily approximately 12 hours apart, with or without food. There is no recommended dosage for patients weighing less than 45 kg.
III. APDS is a rare primary immunodeficiency caused by mutations in PIK3CD or PIK3R1 genes, characterized by severe, recurrent sinopulmonary infections, lymphoproliferation, bronchiectasis, cytopenias, and may progress to permanent lung damage or lymphoma. APDS affects approximately 1 to 2 persons per million in the US. Given the rarity and complexity of diagnosis and management of APDS, the treatment of APDS must be initiated by, or in consultation with, an immunologist, geneticist, or a provider specializing in the management of immunodeficiencies.
IV. Leniolisib (Joenja) was evaluated for the treatment of APDS via a clinical trial, which enrolled patients with nodal and/or extranodal lymphoproliferation, as measured by index nodal lesion selected by the Cheson methodology on CT or MRI and clinical findings and manifestations compatible with APDS (e.g., history of repeated oto-sino-pulmonary infections, organ dysfunction). Immunosuppressive medications or PI3Kδ inhibitors (selective or non-selective) were prohibited within 6 weeks of baseline (Day -1 and the visit prior to first study drug administration) and throughout the study. In addition, patients who had previous or concurrent B cell depleters (e.g., rituximab) within 6 months of baseline were excluded from the study,

unless absolute B lymphocytes in the blood were normal. B cell depleters were prohibited throughout the study. At this time, safety, and efficacy of leniolisib (Joenja) in combination with B cell depleting immunosuppressive therapy (e.g., rituximab) is not known. Additionally, the proposed therapeutic goal for the use of leniolisib (Joenja) is to improve the naïve B lymphocyte counts. Use of B cell depleting therapies may antagonize the effect of leniolisib (Joenja).

V. In the absence of curative treatments, management of APDS is symptom-based and consists of non-specific therapies including ongoing antimicrobial prophylaxis, immunosuppressants (e.g., corticosteroids, rituximab, sirolimus), immunoglobulin replacement therapy (IRT), surgeries (e.g., tonsillectomy, splenectomy), and hematopoietic stem cell transplant (HSCT).

VI. There are no treatment guidelines for the management of APDS and the pharmacotherapy approaches remain patient-specific and heterogeneous. Leniolisib (Joenja) is the first targeted PI3Kδ inhibitor, and the first drug FDA-approved for the treatment of APDS. Leniolisib (Joenja) is expected to be the first-line therapy for all patients with a confirmed diagnosis of APDS with other therapeutic interventions (e.g., antibiotics, IRT, corticosteroids) being utilized as adjunct therapies.

VII. The safety and efficacy of leniolisib (Joenja) were evaluated in a Phase 3, blinded, randomized, placebo controlled clinical trial (Study 2201-02). Patients (N=31): 12 to 75 years old with mutation in PIK3CD or PIK3R1, a history of clinical symptoms of APDS, and at least one measurable lymph node enlargement, were randomized 2:1 to receive leniolisib (Joenja) or placebo. While concurrent use of immunosuppressants was prohibited during the trial, patients were allowed to take glucocorticoids (e.g., prednisone) ≤ 25 mg per day (58%) and previously established IRT (68%). The negative change in the index lymph node diameters and the positive change in the naïve B cells percentage (baseline to day 85) were measured as co-primary endpoints. Leniolisib (Joenja) treatment for 85 days reported a baseline mean log10-sum of product diameter (SPD) reductions in the index lesions (lymph nodes) of -0.27 for leniolisib (Joenja) versus -0.02 for placebo (treatment difference of -0.25 (95%CI, -0.38, -0.12; p 0.0006). Additionally, the change in naïve B cell percentage from baseline to day 85 (only assessed in patients who had <48% baseline naïve B cells, and who were not censored during trial; n=13) showed a 37.39% increase in naïve B cell percentage in the treatment group versus a 0.09% increase in placebo (*p* 0.0002).

VIII. The analysis of naïve B cell percent improvement was confounded due to the censoring of 13 patients from the treatment group and five from the placebo group (protocol deviations, ≥48% naïve B cells at baseline, and lack of baseline or day 85 data). However, in a supportive analysis inclusive of all patients (excluding those without baseline or day 85 measurements), the naïve B cells percentage improvement was consistent and showed a mean difference between leniolisib (Joenja, n = 13) and placebo (n = 8) at 27.94% (95% CI: 15.02, 40.85; p 0.0003).

IX. Key and exploratory secondary outcomes such as improvements in spleen size, autoimmune cytopenia, and patient-reported quality of life (SF-36) at 12 weeks were not statistically significant; however, showed a favorable trend toward leniolisib (Joenja).

X. A single-arm, open-label extension (OLE) trial (N=35) for leniolisib (Joenja) did not report additional safety signals. Further reduction of SPD of index lesions and spleen volume were reported as well as up to 32% increase in naïve B cells with up to 252 days of treatment. These outcomes remain observational. During OLE, the patient reported QoL measures (mean change from baseline of the SF-36 and the WPAI-CIQ) remained unchanged. Additionally, study participants continued to receive antibiotics at a similar rate as those in Study 2201-02.

XI. The quality of evidence is considered low. Although objective measures, the changes in SPD index lesions and naïve B cells have not been validated or correlated with clinically meaningful outcomes in APDS such as patients' quality of life, reduction in infections, bronchiectasis, and incidence of lymphoma or death. Study 2201-02 had a small sample size, a short outcome assessment time frame, and a confounded data set due to the censoring of patients as well as the allowance of concurrent use of systemic corticosteroids and IRT. Although indicative of short-term benefits; significant hesitancy remains when considering the long-term application and the true effect of leniolisib (Joenja). Further clinical trials may help elucidate the efficacy and confirmation of the benefit of leniolisib (Joenja).

XII. Leniolisib (Joenja) is currently being evaluated in a Phase 3 trial in children aged four to 11 years.

XIII. Based on treatment exposure in all participants (N=31), adverse events (AEs) were reported by 85.7% of patients in leniolisib (Joenja) and in 90.0% in the placebo group; most commonly grade 1 (74.2%). Serious AEs were reported in five (16%) patients, none of whom were ascribed to the study drug. The most common AE in the treatment arm versus placebo included headache (24% vs 20%), sinusitis (19% vs 0%), and atopic dermatitis (14% vs 0%).

XIV. There were no treatment discontinuations or deaths during the clinical trial. Although no contraindications are listed, the leniolisib (Joenja) label includes warnings related to embryo-fetal toxicity. The real-world safety profile of leniolisib (Joenja) remains undetermined.

XV. Due to the lack of long-term efficacy data, and the low confidence in the clinically meaningful outcomes in APDS, true efficacy benefits and place in therapy for leniolisib (Joenja) remain relatively uncertain. Although expected to be a first-line agent, majority of the APDS patients may remain candidates for standard-of-care front-line therapies such as antibiotic and antiviral prophylaxis, use of systemic corticosteroids, Immunoglobulin G (IgG) replacement therapy (IRT), and other immunosuppressants (e.g., rituximab, sirolimus). Given the long-term safety, efficacy, real-world practice experience and therapy cost, these agents may remain practical alternatives to leniolisib (Joenja).

Investigational or Not Medically Necessary Uses

I. Leniolisib (Joenja) has not been FDA-approved, or sufficiently studied for safety and efficacy for any other condition(s) than APDS

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Related Policies

Currently, there are no related policies.

Policy Implementation/Update:

Policy Implementation/Update:	Date
Policy created	08/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP130

Description

Letermovir (Prevymis) is an orally administered antiviral agent that inhibits cytomegalovirus (CMV) deoxyribonucleic acid (DNA) terminase complex which helps prevent CMV infection in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) and adult CMV-seronegative recipients of a kidney transplant from a seropositive donor [D+/R-].

Length of Authorization

- Initial: up to 200 days post-transplant
- Renewal: no renewal

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
letermovir (Prevymis)	240 mg tablet	Prophylaxis for CMV Infection Post-HSCT and Kidney Transplant	30 tablets/30 days
	480 mg tablet		

Initial Evaluation

I. **Letermovir (Prevymis)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist, hematologist, infectious disease, or transplant specialist; **AND**
   C. Member will be using letermovir (Prevymis) for the prevention of CMV infection or disease; **AND**
   D. Provider attestation that member is at high risk of CMV infection; **AND**
   E. The request is for letermovir (Prevymis 480 mg tablet); **OR**
      1. If the request is for letermovir (Prevymis) 240 mg, it will be used in combination with cyclosporine; **AND**
   F. A diagnosis of one of the following:
      1. **Allogeneic hematopoietic stem cell transplant (HSCT); AND**
         i. Member is cytomegalovirus (CMV)-seropositive HSCT recipient; **AND**
         ii. Documentation of transplant date has been recorded in chart notes; **AND**
         iii. Provider attestation that letermovir (Prevymis) will not be used past 100-days post-transplant; **OR**
            a. If patient is at high-risk for late CMV infection, provider attests that letermovir (Prevymis) will not be used past 200-days post-transplant; **AND**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

i. Member has received, or will receive, letermovir (Prevymis) as primary prophylaxis during the first 100-days post-transplant; **OR**

2. **Kidney transplant; AND**
   i. Member is a CMV-seronegative kidney transplant recipient; **AND**
   ii. Kidney donor is CMV-seropositive; **AND**
   iii. Documentation of transplant date has been recorded in chart notes; **AND**
   iv. Provider attestation that letermovir (Prevymis) will be initiated between days 0 and 7 post-transplant; **AND**
   v. Provider attestation that letermovir (Prevymis) will not be used past 200 days post-transplant; **AND**
   vi. Member has an intolerance or contraindication to valganciclovir

II. Letermovir (Prevymis) is considered investigational when used for all other conditions, including but not limited to:
   A. Prevention of CMV infection or disease settings other than HSCT or kidney transplant
   B. Treatment for CMV infection or disease
   C. Prevention of CMV infection beyond 200 days post-transplant
   D. Pre-emptive therapy of CMV infection

Supporting Evidence

I. According to the prescribing information, letermovir (Prevymis) has only been FDA-approved in the setting of CMV prophylaxis in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) and adult CMV-seronegative recipients of a kidney transplant from a CMV-seropositive donor [D+/R-]. Safety and efficacy in the pediatric population has not been established.

II. Considering the complexity of care for patients receiving HSCT or kidney transplant, the agent requested must be prescribed by, or in consultation with, an oncologist, hematologist, infectious disease, or transplant specialist.

III. The recommended dose of letermovir (Prevymis) according to the prescribing information is 480mg daily. If letermovir (Prevymis) is intended to be used in combination with cyclosporine as part of anti-rejection regimen, the dose of letermovir (Prevymis) should be reduced to 240mg daily due to a drug-drug interaction that causes an increase in serum blood concentrations of both drugs.

IV. Allogeneic hematopoietic stem cell transplant (HSCT)

- The safety and efficacy of letermovir (Prevymis) was studied in a multicenter, double-blind, placebo-controlled, Phase 3 trial in adult CMV-seropositive recipients [R+] of those who have received an allogeneic hematopoietic stem cell transplant (HSCT). Of the 325 participants who received letermovir (Prevymis), 38% failed prophylaxis compared to 61% in the placebo arm [95% CI (32.5, 14.6)].
- A review by Chen et al. 2018 demonstrated that among the six antiviral therapies studied, ganciclovir and letermovir (Prevymis) were the most effective in reducing

incidence of CMV reactivation when used as universal prophylaxis agents. Results further suggest that patients undergoing allogeneic HSCT would significantly benefit from universal prophylaxis with an agent that is tolerable after HSCT. The data suggest that although effective at reducing CMV reactivation and disease, ganciclovir use cannot be recommended as a universal prophylaxis agent because of an increased risk of myelosuppression and subsequent drug discontinuation. In contrast, the data suggests that letermovir (Prevymis) has an excellent safety profile with no myelosuppression, and its use should be considered for this indication in patients at risk. Letermovir (Prevymis) was associated with a decrease in CMV-related outcomes and all-cause mortality through 24 weeks after HSCT. Data around acyclovir found that although a delay in the onset of CMV reactivation was demonstrated, acyclovir showed nonsignificant efficacy in preventing CMV disease. Valacyclovir, which has a greater bioavailability than acyclovir was compared with acyclovir and found to be associated with a lower rate of viremia with similar rate of survival to acyclovir in CMV R+ or D+ allogeneic HCT recipients. High-dose acyclovir and valacyclovir are less myelosuppressive than ganciclovir and appear to have some efficacy for CMV prophylaxis, but these agents have inferior in vitro activity against CMV than ganciclovir. Though ganciclovir has promising efficacy, treatment is limited in this HSCT patient due to its increased risk of myelosuppression.

- Extended use of letermovir (Prevymis) post-HSCT up to 200 days was studied in a randomized, double-blind, placebo-controlled, phase 3 clinical trial of 218 patients who had been treated with 100-days of primary prophylaxis with letermovir (Prevymis). The primary efficacy endpoint of percentage of patients with clinically significant CMV infection from week 14 (~100 days) post-transplant through week 28 (~200 days) post-transplant was experienced in 2.8% of patients in the letermovir (Prevymis) group compared to 18.9% of patients in the placebo group (-16.1, 95% CI [-25.8 to -6.5]; p-value = 0.0005). Reported adverse events were in alignment with those reported in the pivotal clinical trials and no new safety concerns were observed.
- Patients enrolled in the extended use trial had high risk of CMV disease, and the prescribing information for letermovir (Prevymis) indicates that extended use up to 200 days post-transplant can be used in patients at risk for late CMV infection and disease. IDSA guidelines suggest that risk factors for late onset CMV disease include [D+/R-] serostatus, shorter courses of prophylaxis, higher levels of immunosuppression, and allograft rejection (i.e., graft versus host disease [GVHD]).

V. Kidney Transplant

- Letermovir (Prevymis) was evaluated in a randomized, active-controlled, double-masked, double-dummy, non-inferiority trial in 601 patients who were CMV-seronegative recipients of a kidney transplant from a CMV-seropositive donor [D+/R-]. Patients were randomized to receive letermovir (Prevymis) or valganciclovir (VGCV) for 28 weeks and were observed for 52 weeks. The primary efficacy outcome was incidence of CMV disease through week 52, which was exhibited in 10.4% of patients in the letermovir (Prevymis) group and 11.8% of patients in the VGCV group (stratum-adjusted difference, −1.4% [95% CI, −6.5% to 3.8%]). Notably,

no patients in the letermovir (Prevymis) group developed CMV disease through week 28 compared to 5 patients (1.7%) in the VGCV group (stratum-adjusted difference, −1.7%[95%CI, −3.4%to0.1%]).

- The most commonly reported adverse events in the letermovir group were diarrhea (31.5%), tremor (18.2%), and urinary tract infection (14%), while the most common adverse event leading to discontinuation were neutropenia (1%) and leukopenia (1%). However, drug-related leukopenia and neutropenia occurred less often in the letermovir (Prevymis) group (11.3% and 2.7%, respectively) than in the VGCV group (37.0% and 16.5%, respectively). The safety profile of letermovir (Prevymis) appears to be favorable compared to VGCV.
- The Infectious Disease Society of America (IDSA) and Transplant Society guidelines on the management of CMV in solid organ transplant indicate that standard of care for CMV prevention in kidney transplant patients is extended use (200 days) of either ganciclovir (GCV) or VGCV. However, extended use of VGCV has been associated with higher rates of myelosuppression, manifesting primarily as leukopenia and neutropenia. Letermovir (Prevymis) may be considered appropriate in patients who are at a higher risk of myelosuppression given its favorable safety profile and observed lower risk of myelotoxicity.
- According to the prescribing information for letermovir (Prevymis), therapy should be initiated during the first week post-transplant and continued through day 200 post-transplant for all kidney transplant recipients.

Investigational or Not Medically Necessary Uses

I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the following indications below:
   A. Prevention of CMV infection or disease in all other settings EXCEPT HSCT or kidney transplant
   B. Treatment for CMV infection or disease
   C. Prevention of CMV infection beyond 200 days post-transplant
   D. Pre-emptive therapy of CMV infection

References

1. Prevymis [Prescribing Information]. Whitehouse Station, NJ: MERCK & CO, Inc. August 2023.
2. Chen K, Cheng MP, Hammond SP, et al. Antiviral Prophylaxis for Cytomegalovirus Infection in Allogeneic Hematopoietic Cell Transplantation. Blood Adv. 2018 Aug 28; 2(16): 2159–2175. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6113617/
3. UpToDate, Inc. Prevention of viral infections in hematopoietic cell transplant recipients. UpToDate [database online]. Waltham, MA. Last updated August 28, 2023. Available at: http://www.uptodate.com/home/index.html.
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5. Haidar G, Boeckh M, Singh N. Cytomegalovirus Infection in Solid Organ and Hematopoietic Cell Transplantation: State of Evidence. The Journal of Infections Diseases. 2020:221(S1):S23-31.
6. Limaye AP, Budde K, Humar A, et al. Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients: A Randomized Clinical Trial. JAMA. 2023;330(1):33-42. doi:10.1001/jama.2023.9106

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria for extended use post-HSCT and kidney transplant indications; Updated supporting evidence	09/2023
Removed requirement of valacyclovir or ganciclovir trial given reduced efficacy and/or safety in comparison to letermovir	10/2020
Policy created	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP044

Description

Levodopa (Inbrija) is an orally inhaled metabolic precursor to dopamine used to relieve symptoms of Parkinson's disease.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
levodopa (Inbrija)	42 mg capsules	Parkinson's Disease	120 capsules/30 days*

*Maximally allowed does upon clinical review for medical necessity: 300 capsules/30 days

Initial Evaluation

I. Levodopa (Inbrija) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in consultation with, a neurologist; **AND**
   B. Not used in combination with apomorphine (Apokyn, Kynmobi); **AND**
   C. Documentation that member does **not** have a diagnosis of chronic respiratory disease (e.g. COPD, asthma, etc.); **AND**
   D. A diagnosis of **Parkinson's Disease (PD)** when the following are met:
      1. Documentation that the member has moderate to severe Parkinson's disease symptoms; **AND**
      2. Is currently on an oral levodopa regimen at least 3 times a day for a minimum of 2 weeks prior to starting levodopa (Inbrija); **AND**
      3. Documentation that the member has a decrease in wearing off symptoms in response to the member's usual morning dose of levodopa; **AND**
      4. Prescriber attest that member will be using levodopa (Inbrija) in combination with carbidopa/levodopa; **AND**
      5. The quantity requested is 120 capsules per 30 days; **OR**
         i. Documentation of medical necessity for dose escalation; **AND**
         ii. Attestation that the member has been taught how to prepare and use the inhaler system appropriately; **AND**
         iii. Attestation that the member is able to administer the full dose of levodopa (Inbrija); **AND**
      6. Treatment with the following has been ineffective, contraindicated or not tolerated:
         i. Carbidopa/levodopa IR up to five times a day OR carbidopa/levodopa XR; **AND**

ii. ONE of the following:
    a. Dopamine agonist (e.g. pramipexole, ropinirole, rotigotine)
    b. monoamine oxide –B (MAO-B) inhibitor (e.g. selegiline, rasagiline, safinamide)
    c. Catechol-O-methyl transferase (COMT) inhibitors (e.g. entacapone, tolcapone).

II. Levodopa (Inbrija) is considered investigational when used for all other conditions, including but not limited to:
    A. Mild Parkinson's disease symptoms
    B. Parkinson's disease WITHOUT documentation of motor fluctuations, "wearing off" phenomenon

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescriber attests that member will be using levodopa (Inbrija) in combination with carbidopa/levodopa ; **AND**
IV. Documentation that member has a reduction in wearing off period from baseline

Supporting Evidence

I. Moderate to severe Parkinson's disease symptoms were defined in the pivotal SPAM[SM]-PD trial as a modified Hoehn and Yahr (H&Y) rating 22 of stages 1-3 in the ON state and recognizable, predictable OFF episodes totaling ≥2 hours per day (excluding early-morning OFF time).
II. A UPDRS Part III score of ≥ 25% after the patient's usual morning dose of levodopa reflects that the patient's wearing off motor symptoms are responsive to levodopa treatment.
III. Patients who were taking apomorphine (Apokyn) were excluded from the SPAM[SM]-PD trial
IV. Due to the safety concerns, patients with chronic respiratory disease are excluded from the SPAM[SM]-PD trial.
V. Levodopa (Inbrija) has only been shown to be effective in combination with carbidopa/levodopa.
VI. According to the American Family Physician diagnosis and treatment guideline for Parkinson's disease, the treatment algorithm for motor complication is:
    - Fractionate carbidopa/levodopa therapy five times a day and consider adding a dopamine agonist, MAO-B inhibitor, OR COMT inhibitor.
VII. Levodopa (Inbrija) has not been studied in patients with mild Parkinson's disease or Parkinson 's disease without motor fluctuations; therefore, it would be considered investigational when Inbrija is requested in those settings.

References

1. Inbrija [Prescribing Information]. Acorda Therapeutics: Ardsley, NY. December 2018.
2. LeWitt P, Hauser RA, Pahwa R, et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Neurol. 2019 Feb;18(2):145-154. doi: 10.1016/S1474-4422(18)30405-8.
3. UpToDate, Inc. Motor fluctuations and dyskinesia in Parkinson disease. UpToDate [Online Database]. Waltham, MA. Last updated July 12, 2018. Available from: http://uptodate.com/home/index.html. Accessed February 11, 2019.
4. Rao S., M.D., Hofmann L., M.D., and Shakil A., M.D. Parkinson's Disease: Diagnosis and Treatment. University of Texas Southwestern Medical School at Dallas Family Medicine Residency Program, Dallas, Texas. Am Fam Physician. 2006 Dec 15;74(12):2046-2054.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated formatting of QL table, improved clarity of policy requirement around previous agents trialed, added renewal requirement of continuing carbidopa/levodopa, and removed renewal requirement of 'absence of unacceptable toxicities.' Addition of new standard renewal language noting previous approvals and member is not continuing via samples.	04/2021
Policy Created	05/2019

Policy Type: PA Pharmacy Coverage Policy: UMP195

Description

Lofexidine (Lucemyra) is an orally administered alpha-2 adrenergic agonist.

Length of Authorization

- Initial: 14 days
- Renewal: cannot be renewed

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lofexidine (Lucemyra)	0.18 mg tablets	Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults	224 tablets/14 days

Initial Evaluation

I. Lofexidine (Lucemyra) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Member will NOT be transitioned to buprenorphine or methadone; **AND**
   C. Member will initiate therapy with naltrexone (Vivitrol) **prior** to lofexidine (Lucemyra) course completion; **AND**
   D. Total duration of therapy will not exceed 14 days; **AND**
   E. A diagnosis of **treatment for opioid use disorder needing withdrawal from opioid use** when the following are met:
      1. History of use with clonidine; **AND**
      2. History of use with tizanidine; **OR**
      3. Documentation of clinical rationale for why tizanidine AND clonidine is not medically appropriate

II. Lofexidine (Lucemyra) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Treatment transition to buprenorphine or methadone
   B. Treatment duration longer than 14 days

III. Lofexidine (Lucemyra) is considered investigational when used for all other conditions, including but not limited to:
   A. Use for marijuana dependence
   B. Use for heroin dependence

C. Acute opioid withdrawal symptoms

Supporting Evidence

I. A retrospective clinical review by Gregory and colleagues reviewed the use of a three-drug regimen including tizanidine, gabapentin, and hydroxyzine for the mitigation of withdrawal symptoms in 84 patients. Primary outcomes were completion of a medically supervised withdrawal and initiation of injectable extended release (ER) naltrexone treatment. Results showed that 94% of patients completed the medically supervised withdrawal phase, and 89% successfully transitioned to ER naltrexone.

II. Use of lofexidine (Lucemyra), in combination with an opioid agonist or partial agonist, for the treatment of opioid withdrawal symptoms increases the risk of QT interval and/or reduces the efficacy of either therapy. Combination use is considered not medically necessary.

Investigational or Not Medically Necessary Uses

I. Lofexidine (Lucemyra) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Use for marijuana dependence
   B. Use for heroin dependence
   C. Acute opioid withdrawal symptoms

References

1. Lucemyra [Prescribing Information]. Louisville, KY: US WorldMeds, LLC. November 2019.
2. Gregory Rudolf, Jim Walsh, Abigail Plawman, Paul Gianutsos, William Alto, Lloyd Mancl & Vania Rudolf (2018) A novel non-opioid protocol for medically supervised opioid withdrawal and transition to antagonist treatment, The American Journal of Drug and Alcohol Abuse, 44:3, 302-309.

Policy Implementation/Update:

Action and Summary of Changes	Date
Transitioned to policy format	10/2020
Previous Reviews	07/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP131

Description

Lomitapide (Juxtapid) is a microsomal triglyceride transfer protein inhibitor used to reduce low density lipoprotein-cholesterol (LDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lomitapide (Juxtapid)	5 mg capsules	Homozygous familial hypercholesterolemia (HoFH)	30 capsules /30 days
	10 mg capsules		
	20 mg capsules		
	30 mg capsules		
	40 mg capsules		
	60 mg capsules		

Initial Evaluation

I. Lomitapide (Juxtapid) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist, endocrinologist or lipid specialist; **AND**
   C. Member has a diagnosis of **homozygous familial hypercholesterolemia (HoFH)** as confirmed by one of the following:
      1. Genetic confirmation of two mutant alleles at the LDLR, Apo-B, PCSK9, or ARH adaptor protein 1/LDLRAP1 gene locus; **OR**
      2. Untreated LDL-C >500 mg/dL; **OR**
      3. **T**reated LDL-C ≥ 300 mg/dL with <u>one</u> of the following:
         i. Cutaneous or tendon xanthoma before ten years of age; **OR**
         ii. History of heterozygous familial hypercholesterolemia (HeFH) in both parents; **AND**
   D. Member will be on concurrent treatment with a high dose statin **<u>plus</u>** another lipid lowering therapy (e.g. ezetimibe, fibrate, nicotinic acid, LDL-apheresis) unless all are contraindicated, or not tolerated; **AND**
   E. Treatment with a PCSK-9 inhibitor [e.g. alirocumab (Praluent), evolocumab (Repatha)] has been ineffective, contraindicated, or not tolerated

II. Lomitapide (Juxtapid) is considered investigational when used in combination with a PCSK9 inhibitor, and for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Absence of unacceptable toxicity from the medication. Examples of unacceptable toxicity may include, but are not limited to: elevations in transaminases (i.e. ALT, AST), hepatic steatosis with or without concomitant increases in transaminases; **AND**
IV. Member continues to receive other lipid-lowering therapy (e.g. statin, ezetimibe); **AND**
V. Clinical documentation (e.g. chart notes, laboratory values) confirming reduction of LDL-C while on therapy; **AND**
VI. Medication will not be used in combination with a PCSK9 inhibitor

Supporting Evidence

I. Lomitapide (Juxtapid) is indicated for the treatment of HoFH, a genetic disease marked by very high LDL-C levels.
II. The diagnosis of HoFH is made with genetic testing or clinical criteria.
    - A causative mutation in the LDLR, APOB, or PCSK9 gene(s) confirms a HoFH diagnosis.
    - Criteria for a clinical diagnosis according, to the Simon Broome Register Group, include untreated LDL-C >500 mg/dL, treated LDL-C ≥300 mg/dL, cutaneous or tendon xanthoma before age 10 years, or elevated LDL-C levels consistent with heterozygous FH in both parents.
III. All patients in the pivotal clinical trial for lomitapide (Juxtapid) met diagnostic criteria for HoFH based either on clinical criteria or on documented mutation(s) in both alleles of the LDL receptor or of genes known to affect LDL receptor function.
IV. The safety and efficacy of lomitapide (Juxtapid) for HoFH was evaluated in an open-label, Phase 3, non-randomized, dose-escalating study. The study included 29 adult patients with HoFH where the majority of patients received concurrent high-dose statin and more than half underwent regular apheresis. After 26 weeks of treatment the LDL-C was reduced by about 50% from baseline (336 to 166 mg/dL).
V. The safety and efficacy of lomitapide (Juxtapid) has not been established in pediatric patients.
VI. The effect of lomitapide (Juxtapid) on cardiovascular morbidity and mortality has not been determined.
VII. Due to the risk of hepatotoxicity, lomitapide (Juxtapid) has a REMS program to ensure safe and appropriate use, thereby limiting distribution to only certified healthcare providers and pharmacies. The requirements of the program include: limiting use to patients with a clinical or laboratory diagnosis of HoFH, excluding pregnancy and those with significant hepatic impairment (Child-Pugh B or C). Additional, elements of the program emphasize close

monitoring of hepatic function and patient education regarding a low-fat diet. Further information is available at www.JUXTAPIDREMSProgram.com.

VIII. Besides lomitapide (Juxtapid), other treatment options for HoFH include evolocumab (Repatha), LDL-apheresis, and standard lipid-lowering agents (e.g. statins, ezetimibe); however, treatment with these agents should be an adjunct to diet and exercise.

Investigational or Not Medically Necessary Uses

I. The benefit of lomitapide (Juxtapid) for indications outside of HoFH have not been established and may not outweigh the rare, but serious adverse events. The FDA approved labeling for lomitapide (Juxtapid) specifically states that it should not be used in patients with hypercholesterolemia who do not have HoFH due to the lack of safety and efficacy outside of this setting.

II. The safety and efficacy of these agents have not been established in combination with PCSK9 inhibitors.

References

1. Juxtapid [Prescribing Information]. Cambridge, MA: Aegerion Pharmaceuticals; August 2017
2. Cuchel, M, Meagher, EA, du Toit Theron, H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet*. 2013 Jan 5;381(9860):40-6. PMID: 23122768
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4. Rosenson, RS. Familial hypercholesterolemia in adults: Overview. In; UpToDate. Saperia, GM (Ed), UpToDate, Waltham, MA, 2019
5. Rosenson, RS. Treatment of drug-resistant hypercholesterolemia. In: UpToDate, Saperia, GM (Ed), UpToDate, Waltham, MA, 2019

Policy Implementation/Update:

Date Created	May 2013
Date Effective	May 2013
Last Updated	December 2019
Last Reviewed	11/2015, 12/2019

Action and Summary of Changes	Date
• Transitioned to policy format • Removed mipomersen (Kynamro) from policy due to discontinuation status as of 5/31/2018 • Added requirement for specialty prescriber • Added minimum age requirement • Added details regarding confirmation of a diagnosis of HoFH • Clarified that use must be concurrent with standard lipid-lowering agents • Indicated that combination of lomitapide (Juxtapid) with PCSK9 inhibitors or use for hypercholesterolemia without HoFH is considered investigational	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP227

Description

Lonafarnib (Zokinvy) is a farnesyltransferase inhibitor.

Length of Authorization

- Initial: Four months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lonafarnib (Zokinvy)	50 mg capsules	Hutchinson-Gilford Progeria Syndrome (HGPS); processing-deficient Progeroid Laminopathies (PL)	**Initial:** Maximum 230mg/m^2/day **Renewal:** Maximum 300mg/m^2/day
	75 mg capsules		

Initial Evaluation

I. Lonafarnib (Zokinvy) may be considered medically necessary when the following criteria are met:
   A. Member is one year of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pediatrician or specialist in progeroid syndromes, genetics, or metabolic disorders; **AND**
   C. Documentation of members body surface area (BSA); **AND**
   D. Member has a BSA of 0.39m^2 or greater; **AND**
   E. Provider attestation the member's cardiovascular status will be monitored [e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography]; **AND**
   F. A diagnosis of one of the following:
      1. **Hutchinson-Gilford Progeria Syndrome (HGPS); AND**
         i. Member has genetic test confirmation of a lamin A gene mutation; **OR**
      2. **Processing-deficient Progeroid Laminopathies (PL); AND**
         i. Member has genetic test confirmation of:
            a. Heterozygous LMNA mutation with progerin-like protein accumulation; **OR**
            b. Homozygous or compound heterozygous ZMPSTE24 mutations.

II. Lonafarnib (Zokinvy) is considered <u>experimental and investigational</u> when criteria above are not met and/or when used for:

A. Processing-proficient Progeroid Laminopathies
B. Other than above mentioned Progeroid Syndromes
   i. Wiedemann-Rautenstrauch syndrome
   ii. Werner syndrome
   iii. Bloom syndrome
   iv. Rothmund-Thomson syndrome
   v. Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy
   vi. Fanconi anaemia
   vii. Seckel syndrome
   viii. Ataxia telangiectasia
   ix. Dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, a pediatrician or specialist in progeroid syndromes, genetics or metabolic disorders; **AND**
IV. Documentation of members body surface area (BSA) measured in the past three months; **AND**
V. Provider attests the member has exhibited improvement or stability of disease symptoms [e.g., cardiovascular status (e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography), bone mineral density].

Supporting Evidence

I. The safety and efficacy of lonafarnib (Zokinvy) has not been studied in pediatric patients less than 12 months of age. The activity of cytochrome P450 (CYP)3A4 and CYP3A5 is low in newborns, approximately 5% to 15% of that of an adult and only achieves full activity at six months of age. Considering these enzymes play a key role in the metabolism of lonafarnib (Zokinvy), it is expected that the clearance would be reduced and there is an increased risk of commonly observed treatment emergent adverse events (TEAEs).
II. The safety and efficacy of lonafarnib (Zokinvy) has only been studied in patients with the body surface area (BSA) ranging from 0.38 m^2 to 0.75 m^2. Due to the lack of clinical trial data on safety and efficacy, and unknown dosage strength, it is not indicated in patients with the BSA less than 0.39m^2.
III. Hutchinson-Gilford Progeria Syndrome (HPS) and processing-deficient PLs are rare and fatal genetic diseases. Considering the complexity of the disease state it is necessary for lonafarnib (Zokinvy) to be prescribed by or in consultation with a specialist in progeroid syndromes, genetics, or metabolic disorders.
IV. Patients with HGPS and processing-deficient PLs experience hypertension, strokes, angina, enlarged heart, and heart failure. Progressive atherosclerosis is common, generally leading to

death from myocardial infarction or stroke at the age of approximately 15 years. It is crucial to monitor the cardiovascular status [e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography]. In a study that sought to better understand cardiovascular disease associated with HGPS, elevated PWVcf, increased intima-media and adventitia echodensity, abnormal ABI, and increased ICA mean flow velocity were identified as pervasive disease features in HGPS. Researchers noted that non-invasive measures including PWVcf, carotid wall echodensity and ICA flow velocity offer quantitative insights into accelerated vasculopathy with HGPS and may therefore, provide indicators of disease progression or remission with therapies.

V. The safety and efficacy of lonafarnib (Zokinvy) have been studied in a observational cohort survival study, which retrospectively compared survival data from two, open-label, single-arm, Phase 2 trials (Study 1 and Study 2) in 62 patients to those from a natural history cohort in 62 patients with HGPS.
    - The primary efficacy outcome was all-cause mortality. Among the 62 patients in the treatment group four died (6.3%) and among the 62 patients in the matched untreated group 17 died (27%). None of these deaths were considered by investigators to be treatment related.
    - Through the first three years of follow up, the mean lifespan of HGPS patients treated with lonafarnib increased by three months, and increased by two and a half years through the last follow-up time (11 years) compared to untreated patients.
    - Study 1 included 28 patients (26 with classic HGPS, one with non-classic HGPS, and one with processing-deficient PL with an LMNA heterozygous mutation). Treatment was initiated with 115mg/m^2 twice daily and after four months of treatment patients who were tolerating treatment had a dose increase to 150 mg/m^2 twice daily.
        - The primary efficacy endpoint of the achievement of at least a 50% increase in the annual rate of weight gain over the rate documented at study entry by the study team, was met by eleven of 28 patients (39.3%).
        - The secondary outcome was change in carotid artery ultrasonography and corrected PWVcf. Echodensity of the carotid artery intima media (10th and 50th percentile), adventitia deep near wall (10th and 50th percentile), and adventitia luminal near wall (50th percentile) all decreased statistically significantly from baseline to end of therapy (all $p<0.05$). PWVcf improved with a median percent decrease from baseline of 15.3% (range: -43.6%, 34.1%; p=0.0028).
    - Study 2 consisted of two phases. In the first phase patients received lonafarnib (Zokinvy) in conjunction with zoledronic acid and pravastatin for five years. In the second phase patients received lonafarnib (Zokinvy) at a dose of 150mg/m^2 twice daily for three years.
        - The study enrolled 26 patients from Study 1 and 13 treatment naïve patients.
        - The primary efficacy endpoint of weight gain (at least 10% increase in the annual rate) or echodensity was met by 22 (71%) of patients.
    - The most common adverse reactions (≥25%) in the clinical trials were vomiting, diarrhea, infection, nausea, decreased appetite, fatigue, upper respiratory tract infection, abdominal pain, musculoskeletal pain, electrolyte abnormalities, decreased weight, headache, myelosuppression, increased aspartate aminotransferase, decreased blood bicarbonate, cough, hypertension, and increased alanine aminotransferase

VI. Progeroid laminopathies (PLs) are due to various mutations either in the LMNA gene and/or the ZMPSTE24 gene. The processing-deficient PLs are specifically due to heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations. These conditions are more rare than HGPS, and were underrepresented in the clinical trials.

Investigational or Not Medically Necessary Uses

I. Lonafarnib (Zokinvy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Progeroid syndromes (Wiedemann-Rautenstrauch syndrome, Werner syndrome, Bloom syndrome, Rothmund-Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy, Fanconi anaemia, Seckel syndrome, Ataxia telangiectasia, Dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome) are a group of very rare genetic disorders that are characterized by clinical features that mimic physiological ageing, such as hair loss, short stature, skin tightness, cardiovascular diseases and osteoporosis. But considering the mechanism of action, lonafarnib (Zokinvy) would not be effective in these populations.
   B. Processing-proficient Progeroid Laminopathies – considering the pathophysiology of the disease state and the mechanism of action, lonafarnib (Zokinvy) would not be effective in these populations.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP052

Description

Granulocyte-colony stimulating factors (G-CSF) act on the hematopoietic cells by binding to specific cell surface receptors thereby stimulating the production, maturation, and activation of neutrophils.

Length of Authorization

- Initial: Four months
- Renewal: Four months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pegfilgrastim (Neulasta)	Prophylactic use in patients with non-myeloid malignancy; Neutropenic complications from prior chemotherapy cycle; Exposure to myelosuppressive doses of radiation; Bone marrow transplantation failure or engraftment delay; Peripheral progenitor cell (PBPC) mobilization and transplant	6 mg/0.6 mL prefilled syringe	Two prefilled syringes per 28-day supply
pegfilgrastim (Neulasta Onpro)		6 mg/0.6 mL prefilled syringe with on-body injector kit	Two kits per 28-day supply
pegfilgrastim-cbqv (Udenyca)		6 mg/0.6 mL prefilled syringe	Two prefilled syringes per 28-day supply
		6 mg/0.6 mL autoinjector	Two autoinjectors per 28-day supply
pegfilgrastim-jmdb (Fulphila)		6 mg/0.6 mL prefilled syringe	Two prefilled syringes per 28-day supply
pegfilgrastim-bmez (Ziextenzo)			
pegfilgrastim-apgf (Nyvepria)			
pegfilgrastim-pbbk (Fylnetra)			
pegfilgrastim-fpgk (Stimufend)			

Initial Evaluation

I. **Pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila)** may be considered medically necessary when the following criteria below are met:

A. A diagnosis of the following:

1. **Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant; OR**
2. **A neutropenic complication from a prior cycle of the same chemotherapy; OR**
3. **Bone Marrow Transplantation (BMT) failure or Engraftment Delay; OR**
4. **Member acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome); OR**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

5. **Prophylactic use in patients with non-myeloid malignancy; AND**
    i. Member is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 20% or greater; **OR**
    ii. Member is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 10% or greater **AND** has one or more of the following:
        a. Age 65 years or older AND receiving full dose intensity chemotherapy; **OR**
        b. History of recurrent febrile neutropenia from chemotherapy; **OR**
        c. Extensive prior exposure to chemotherapy; **OR**
        d. Previous exposure of pelvis, or other areas of large amounts of bone marrow, to radiation; **OR**
        e. Pre-existing neutropenia (ANC ≤ 1000/mm3) or bone marrow involvement with tumor; **OR**
        f. Member has a condition that can potentially increase the risk of serious infection (e.g. HIV/AIDS) ; **OR**
        g. Infection/open wounds; **OR**
        h. Recent surgery; **OR**
        i. Poor performance status; **OR**
        j. Poor renal function (creatinine clearance <50mL/min) ; **OR**
        k. Liver dysfunction (elevated bilirubin >2.0mg/dL) ; **OR**
        l. Chronic immunosuppression in the post-transplant setting including organ transplant.

II. **Pegfilgrastim (Neulasta, Neulasta Onpro), pegfilgrastim-cbqv (Udenyca), pegfilgrastim-pbbk (Fylnetra), pegfilgrastim-bmez (Ziextenzo), and pegfilgrastim-fpgk (Stimufend)** may be considered medically necessary when the following criteria below are met:
    A. Criteria I(A) above is met; **AND**
    B. Treatment with pegfilgrastim-jmdb (Fulphila) AND pegfilgrastim-apgf (Nyvepria) have been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Same as initial prior authorization policy criteria.

Supporting Evidence

I. Indications listed under section I are supported by FDA-labeled indication(s) or are recommended per Compendia.
II. Quantity limits are based on usual FDA dosing of pegfilgrastim as once per chemotherapy cycle, but no sooner than 14 days before and 24 hours after chemotherapy administration. Generally, chemotherapy is administered every 2-3 weeks, whereby frequency of pegfilgrastim is not expected to be more often than every two weeks. There are insufficient data to support use of weekly pegfilgrastim. For other indications, such as transplant, therapy is continued until adequate neutrophil recovery is achieved. Accordingly, quantity exceptions may be considered when frequent administration of pegfilgrastim is deemed medically necessary.

III. Duration of approval is based on usual duration of chemotherapy or radiation therapy cycles. There is no guideline consensus on optimal duration of G-CSF or GM-CSF treatment or prophylaxis, therefore continued use is driven by clinical scenario and lab monitoring.

IV. Risk of developing febrile neutropenia is related to intensity and toxicity of chemotherapy regimen, as well as patient-specific factors. Expected incidence of febrile neutropenia percentages for myelosuppressive chemotherapy regimens can be found in the NCCN Hematopoietic Growth Factors Clinical Practice Guideline at NCCN.org. NCCN and ASCO guidelines recommend use of a G-CSF for prophylaxis when risk is 20% or greater. When risk is between 10-20%, prophylactic G-CSF is recommended when patients have one or more of the risk factors listed above. Routine prophylaxis with G-CSF for febrile neutropenia when risk is less than 10% is not recommended.

V. All FDA-approved biosimilars undergo a rigorous testing process to compare safety, purity, and potency between the proposed biosimilar and the parent or originator product, otherwise known as the reference product, to ensure there are no clinically meaningful differences. Only minor differences between products are allowed, such as in clinically inactive components. Biosimilars may be approved for all, or a subset, of the indications for the reference product. It is not uncommon for biosimilars to have fewer labeled indications if the reference product has remaining patent or exclusivity rights. It can be expected that biosimilar products will have the same clinical efficacy and safety profile as the reference product due to thorough FDA testing. With a goal to increase access to high-quality, cost-effective care, biosimilars may fill an unmet need as a more affordable alternative to brand biologic therapies. Notably, NCCN Guidelines similarly recommend that FDA-approved biosimilars be used as substitutes for originator filgrastim and pegfilgrastim. In addition, ASCO recommends that pegfilgrastim, filgrastim and biosimilars be considered therapeutically equivalent, with product selection being based on convenience, cost and clinical situation (i.e., chemotherapy frequency). As such, trial of preferred biosimilars pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila) is required prior to approval of non-preferred pegfilgrastim products.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Short-acting Granulocyte-colony stimulating factor (CSF) and Granulocyte macrophage-CSF (GM-CSF)	Bone marrow transplant
	Peripheral progenitor cell (PBPC) mobilization and transplant
	Prophylactic use in patients with non-myeloid malignancy
	Treatment of chemotherapy-induced febrile neutropenia
	Neutropenic complications from prior cycle
	Acute myeloid leukemia (AML) patient following induction or consolidation chemotherapy
	Bone marrow transplantation failure or engraftment delay
	Severe chronic neutropenia
	Myelodysplastic syndrome
	Exposure to myelosuppressive doses of radiation

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to reflect new preferred product strategy (pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila) [**Effective 01/01/2024**]	12/2023
Added Udenyca autoinjector to QL table	03/2023
Added new product pegfilgrastim-fpgk (Stimufend) after trial of pegfilgrastim-jmdb (Fulphila) AND pegfilgrastim-bmez (Ziextenzo)	09/2022
Updated policy supporting evidence and references. Added related policies table. Added new product Fylnetra (pegfilgrastim-pbbk) after trial of pegfilgrastim-jmdb (Fulphila) AND pegfilgrastim-bmez (Ziextenzo)	08/2022
Updated policy name from "pegfilgrastim (Neulasta®; Neulasta Onpro®; Fulphila®; Udenyca®; Ziextenzo®, Nyvepria™)" to "Long-acting Granulocyte colony stimulating factor"	04/2022
Updated pegfilgrastim-jmdb (Fulphila) as preferred product; removed pegfilgrastim-cbqv (Udenyca) from preferred products. (**Effective 7/1/2021**)	05/2021
Updated preferred products to add Ziextenzo (effective 1/1/2021) and move Neulasta/Neulasta Onpro to non-preferred (effective 1/1/2021). Added Nyvepria, biosimilar to Neulasta.	11/2020
Updated policy to allow for 28 days supply	02/2020
Added Ziextenzo, biosimilar to Neulasta; update quantity limits to allow for 30 days supply	12/2019
Added Udenyca, biosimilar to Neulasta	01/2019
Neulasta, Neulasta Onpro preferred GCSF	12/2018
Added Fulphila, biosimilar to Neulasta	07/2018
Policy created	02/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP219

Split Fill Management*

Description

Mannitol (Bronchitol) is an orally administered sugar alcohol inhalation powder.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
mannitol (Bronchitol)	40 mg capsules	Cystic Fibrosis	560 capsules/28 days

Initial Evaluation

I. **Mannitol (Bronchitol)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   C. A diagnosis of **Cystic Fibrosis** when the following are met:
      1. Provider attestation member has passed mannitol (Bronchitol) tolerance test; **AND**
      2. Treatment with hypertonic saline has been ineffective, contraindicated, or not tolerated

II. Mannitol (Bronchitol) is considered investigational when used for all other conditions, including but not limited to:
   A. Bronchiectasis
   B. Parkinson's Disease
   C. Chronic Obstructive Pulmonary Disease (COPD)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms [e.g., improvement in FEV1, decrease in pulmonary exacerbations, decrease in hospitalization rate, improved quality of life].

Supporting Evidence

I. FDA approval for mannitol (Bronchitol) is based on three international, Phase 3, randomized, double blind, 26-week trials [CF301 (n=324), CF302 (n=318), CF303 (n=423)] which evaluated mannitol (Bronchitol) compared to subtherapeutic mannitol (control) in CF.
    - CF301 and CF302 included patients six years of age and older.
    - CF303 included adult patients only.

II. Trials CF301 and CF303 met their primary outcome of a change in FEV1 over 26 weeks. However, none of the trials met statistically significant differences in pulmonary exacerbation rates nor in quality of life improvements.
    - CF301 Treatment difference: 92.9 mL (95% CI: Not Reported; P <0.001)
    - CF303 Treatment difference: 54 mL (95% CI: 8-100; P= 0.02)

III. Patients in the three clinical trials were able to continue use of dornase alfa (Pulmozyme); however, use of hypertonic saline was not permitted. To date, no studies have been conducted using mannitol (Bronchitol) concomitantly with hypertonic saline and there are no head-to-head trials comparing the two therapies. Safety and efficacy of concomitant use of mannitol (Bronchitol) and hypertonic saline has not been established.

IV. Although mannitol (Bronchitol) was evaluated in two trials that included pediatric patients (CF301 and CF302), safety and efficacy in this population remains uncertain. The manufacturer submitted data from pediatric trials CF301 and CF302 to the FDA in 2012 seeking approval in patients six years of age and older. The FDA issued a complete response letter due to inadequate efficacy as trial CF302 did not meet its primary endpoint, coupled with an increased risk of hemoptysis, especially in the pediatric population. The FDA then recommended a third study be completed to show efficacy evidence in adult patients and confirm an acceptable safety profile. Additionally, per the package insert, mannitol (Bronchitol) is not indicated for use in children and adolescents. The safety and effectiveness of mannitol (Bronchitol) has not been established in pediatric patients for cystic fibrosis. Patients aged six to 17 years were included in two 26-week, double-blind clinical trials (Trials CF301 and CF302). In these trials, 154 patients under 18 years of age received mannitol (Bronchitol) and 105 patients received control (50 mg inhaled mannitol). Hemoptysis was reported in 12 of 154 (7.8%) patients who received mannitol (Bronchitol) and in 2 of 105 (1.9%) patients who received control.

V. Guidelines recommend chronic use of hypertonic saline in CF patients regardless of lung disease severity (*Grade B, moderate recommendation*). Dornase alfa (Pulmozyme) is also recommended as maintenance therapy for all levels of lung disease severity (*Grade B, moderate recommendation*), with a strong recommendation (*Grade A)* in those with moderate to severe disease. Guidelines have not been updated to include mannitol (Bronchitol) in the treatment CF.

VI. Given current guideline recommendations for use of hypertonic saline to improve lung function and quality of life and reduce exacerbations, coupled with lack of head-to-head trials comparing mannitol (Bronchitol) to hypertonic saline and lack of statistically significant differences in pulmonary exacerbation rates nor in quality of life improvements with mannitol (Bronchitol) use

in CF301, CF302, or CF303 studies, use of hypertonic saline prior to mannitol (Bronchitol) is required.

Investigational or Not Medically Necessary Uses

I. Mannitol (Bronchitol) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Bronchiectasis
      i. A Phase 3 trial (NCT00669331) evaluating mannitol (Bronchitol) to control (50 mg mannitol) found use of mannitol (Bronchitol) in patients with clinically significant bronchiectasis did not significantly reduce exacerbation rates. Further evaluation is needed to confirm use of mannitol (Bronchitol) in this population.
   B. Parkinson's Disease
      i. As of December 2020, trials are currently recruiting in this setting.
   C. COPD
      i. Clinical trials evaluating mannitol (Bronchitol) in COPD were withdrawn due to recruitment failures.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP250

Description

Maralixibat (Livmarli) is an orally administered reversible ileal bile acid transporter (IBAT) inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: Six months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
maralixibat (Livmarli)	9.5 mg/mL solution	Cholestatic pruritis in patients with Alagille Syndrome one year of age and older	Monthly quantity to allow for a maximum of 380 mcg/kg/day (maximum of 3 mL)

Initial Evaluation

I. **Maralixibat (Livmarli)** may be considered medically necessary when the following criteria are met:
   A. Member is one year of age or older; **AND**
   B. Documentation of member's weight, measured within past three months; **AND**
   C. Medication is prescribed by, or in consultation with, a hepatologist or gastroenterologist; **AND**
   D. A diagnosis of **Alagille Syndrome** when the following are met:
      1. Provider attestation member has cholestasis including at least one of the following:
         i. Total serum bile acids greater than three times the upper limit of normal for age; **OR**
         ii. Conjugated bilirubin greater than 1 mg/dL; **OR**
         iii. Unexplained fat-soluble vitamin deficiency; **OR**
         iv. Gamma glutamyl transferase (GGT) greater than three times the upper limit of normal for age; **OR**
         v. Intractable pruritis explainable only by liver disease; **AND**
      2. Diagnosis is confirmed by a molecular genetic test; **OR**
         i. Diagnosis is confirmed by evidence of bile duct paucity on liver biopsy; **AND**
            a. Provider attestation ALGS is present in a first degree relative; **OR**
            b. Provider attestation member has presence of 3 or more clinical features of the disease (e.g., cholestasis, consistent cardiac, renal, ocular disease, butterfly vertebrae, or characteristic Alagille facies); **AND**

E. Member does not have decompensated cirrhosis or prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy); **AND**
F. Provider attestation member has moderate to severe pruritis; **AND**
G. Treatment with all the following have been ineffective, contraindicated, or not tolerated:
    1. Ursodiol; **AND**
    2. Bile acid sequestrant (e.g., cholestyramine, colesevelam); **AND**
    3. Rifampin; **AND**
    4. Opioid antagonist (e.g., naltrexone); **AND**
    5. Serotonin inhibitor (e.g., sertraline, ondansetron)

I. Maralixibat (Livmarli) is considered investigational when used for all other conditions, including but not limited to:
    A. ALGS in patients less than 12 months of age
    B. Progressive familial intrahepatic cholestasis (PFIC)
    C. Benign recurrent intrahepatic cholestasis 1 and 2 (BRIC1 and BRIC2)
    D. Biliary atresia (BA)
    E. Primary sclerosing cholangitis (PSC)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in pruritis, quality of sleep); **AND**
IV. Member has not had a liver transplant since the last prior authorization period; **AND**
V. Member has not progressed to decompensated cirrhosis or experienced hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy)

Supporting Evidence

I. Alagille Syndrome (ALGS) is a rare, genetic, autosomal dominant disorder, caused by mutations in the genes encoding jagged1 (JAG1) or neurogenic locus notch homolog protein 2 (NOTCH2), both involved in the Notch signaling pathway. It is a multisystem disorder affecting the liver, cardiovascular system, skeleton, face and eyes. Phenotypic presentation of the disease is variable; however, complications can include cholestasis, pruritis, progressive liver disease, failure to thrive, and xanthomas, all of which lead to liver transplantation. Pruritis is the hallmark symptom of this disease and is thought to be caused by a buildup of pruritogens that accompany bile acids. Bile acid buildup occurs due to impaired development of bile ducts leading to bile duct paucity (reduction of interlobular bile ducts).
II. Maralixibat (Livmarli) is FDA-approved for the treatment of cholestatic pruritis associated with ALGS in patients one year of age and older. The age of presentation ranges from 16 weeks to 10

years and most patients are diagnosed in the first year of life. The maralixibat (Livmarli) clinical trial program did not evaluate patients < 12 months of age; therefore, drug safety and efficacy in this population has not been established.

III. Diagnosis of ALGS is based on a combination of clinical features of the disease, lab findings, imaging, genetic testing, and liver biopsy. Clinical features include hepatic manifestations such as chronic cholestasis and bile duct paucity, characteristic facial features (deep-set eyes and a flat nasal bridge), ophthalmic abnormalities, skeletal involvement, cardiovascular, and renal abnormalities. Cholestasis occurs in 87-100% of patients but may present as mild or not clinically identifiable in certain cases of ALGS. The most sensitive test to confirm cholestasis is via elevations in fasting serum bile acids (normal levels depend on age but are usually <20 umol/L); however, this may not be readily available. Other biomarkers that can be used to confirm cholestasis are elevated gamma glutamyl transferase (GGT) levels (normal levels depend on age but are usually < 200 IU/L) and conjugated/direct serum bilirubin levels (normal levels are usually less than 0.3 mg/dL). Additionally, cholestasis may be suspected in patients experiencing unexplained fat-soluble vitamin deficiency or intractable pruritis explainable only by liver disease. Patients affected with ALGS often present with multiple elevated biomarkers of cholestasis and peak values include bile acid levels> 100 times normal, total bilirubin > 20 mg/dL, and GGT > 2,000 U/L.

IV. Molecular generic test is considered confirmatory for ALGS syndrome. Majority of patients have mutations in JAG1 (94%) with only a small subset (<1%) having mutations in NOTCH2. Additionally, mutations that are variants of unknown significance can also cause ALGS. Genetic evaluation for JAG1 and NOTCH2 mutations is currently available on a commercial basis, though screening for NOTCH2 is limited to a small number of locations at this time.

V. If patients are not screened for ALGS using a genetic test or if JAG1 or NOTCH2 mutations are not identified, patients may be diagnosed using a combination of clinical criteria, liver biopsy which screens for bile duct paucity, and presence of ALGS in first degree relatives. Bile duct paucity is one of the most common characteristics of ALGS and occurs in 90% of patients; however, it may not be present in many patients younger than six months of age and may not be present in mild disease presentation. Bile duct paucity is determined using a ratio of bile ducts to portal tracts of less than 0.5 in a liver biopsy with an adequate number (10) of portal tracts present. The normal number of bile ducts in a portal tract increases throughout the first years of life, reaching a normal ratio of nearly 2 by adolescence.

VI. Diagnostic Criteria for Alagille Syndrome:

ALGS in a first degree relative	Paucity	JAG1 or NOTCH2 mutation*	Number of criteria needed**
Present or absent	Present	Identified	Any or no features
None (proband)	Present	Not identified	3 or more features
None (proband)	Absent or unknown	Not identified	4 or more features
None (proband)	Absent or unknown	Identified	1 or more features
Present	Present	Not identified	1 or more features
Present	Absent or unknown	Not identified	2 or more features
Present	Absent or unknown	Identified	Any or no features

*Not identified = not identified on mutation screening, or not screened for

** Major clinical criteria include cholestasis, consistent cardiac, renal, ocular disease, butterfly vertebrae, or characteristic Alagille facies of childhood or adulthood

VII. Maralixibat (Livmarli) was not studied in patients with decompensated cirrhosis or in patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy). Due to unknown safety and efficacy in this population, maralixibat (Livmarli) should be permanently discontinued if patients progress to portal hypertension or experience a hepatic decompensation event. Additionally, maralixibat (Livmarli) is associated with causing liver test abnormalities and may or may not exacerbate liver injury in patients with severe liver disease (e.g., decompensated cirrhosis, portal hypertension). More studies are needed in this setting to confirm drug safety in significant liver disease.

VIII. Majority of patients with ALGS receive liver transplantation before they reach adulthood. Intractable pruritis is a reason for evaluation for liver transplantation and placement on transplant list, regardless of the extent of direct liver involvement from ALGS. Majority of liver transplants in ALGS are considered successful with most patients alive without a need for re-transplantation. It is considered a curative treatment for the symptoms of pruritis. Therefore, maralixibat (Livmarli) is not expected to be medically necessary in patients with liver transplants as these patients would likely be cured of pruritis.

IX. Severe cholestatic pruritis occurs in up to 45% of patients with ALGS and has negative impacts on quality of life. Itching is often described as the most burdensome symptom of ALGS. According to one study evaluating the burden of ALGS and pruritis among 26 patients and 24 caregivers, 15% of patients experienced severe itching, 31% experienced moderate itching, 24% experienced mild itching, and 27% experienced very mild itching. Pivotal trial evaluating maralixibat (Livmarli) studied patients with moderate to severe pruritis at baseline as measured by the ItchRO(Obs) score. The value of maralixibat (Livmarli) in patients with mild pruritis has not been established and the drug may be medically necessary only in patients with history of significant scratching or medium scratching at baseline, consistent with moderate to severe pruritis presentation.

X. Treatment of ALGS is aimed at maintaining optimal nutrition, preventing fat-soluble vitamin deficiencies, addressing pruritis, improving bile flow, and treating any extrahepatic features. There are no FDA approved agents for pruritis associated with ALGS except for maralixibat (Livmarli) at this time; however, there are agents that are commonly used off-label. For relief of pruritis unresponsive to antihistamines, ursodeoxycholic acid, rifampin, bile-acid sequestrants, naltrexone, and sertraline may be used. Antihistamines should not be exclusive therapy but can be dosed at night when pruritis interferes with sleep. Treatment response to pharmacological agents is often unpredictable; however, depending on the degree of pruritis, some experience relief of pruritis symptoms. Patients refractory to pharmacological therapy may undergo partial external biliary diversion or ileal exclusion surgery to remove excess bile prior to liver transplantation.

XI. There is lack of robust studies of standard of care agents (ursodiol, bile acid sequestrants, rifampin, naltrexone, sertraline) in the treatment of ALGS; however, evidence related to pruritis is available from studies in other cholestatic disease states, retrospective and open-label ALGS studies, and historical treatment experience with the drugs. Trial of all standard of care agents prior to maralixibat (Livmarli) is both a cost effective and clinically appropriate strategy as each drug exerts effects on pruritis via distinct therapeutic pathways and inefficacy with one or more agent(s) does not confer inefficacy with subsequent drugs.

- **Ursodiol** - commonly used as the first-line treatment option due to its anti-cholestatic properties which are exerted by improved hepatobiliary secretory function and reduced bile toxicity. It is the only medication that may affect liver disease progression and is recommended by the European Association for the Study of the Liver (EASL) guidelines as the initial pharmacological treatment for cholestatic pruritis. Additionally, several rare disease organizations such as The Childhood Liver Disease Research Network and National Organization for Rare Disorders (NORD) and expert reviews recommend ursodiol as first line in patients with ALGS. The effect of ursodiol on pruritis is an area that requires more research; however, an open-label study, retrospective cohort study, and case reports note positive treatment response in pediatric patients with ALGS and other intrahepatic liver diseases (Kronsten, 2013; Narkewicz, 1998;).
- Subsequent treatment options are aimed at reducing symptoms of pruritis. Pruritis can be a feature of any cholestatic disease, thus there are many treatment options available with variable evidence.
- **Bile acid sequestrant** - cholestyramine is FDA-approved for the treatment of pruritis associated with cholestasis in adults and is often used as one of the first-line treatment options for pediatric patients with pruritis associated with cholestasis. Despite a limited evidence base, cholestyramine is listed as a treatment option for ALGS by The Childhood Liver Disease Research Network and NORD and is recommended first-line by EASL guidelines for the treatment of pruritis associated with cholestasis. There is additionally one retrospective study indicating efficacy in some patients. The lack of evidence is largely because the agent entered widespread use before the era of evidence-based medicine. Additionally, colestipol and colesevelam have also been evaluated in the treatment of pruritis and are generally better tolerated than cholestyramine (Cies, 2007; Kronsten, 2013).
- **Rifampin** - commonly used after treatment failure with ursodiol/cholestyramine and is recommended for the treatment of cholestatic pruritis by EASL guidelines, rare disease organizations, and expert reviews. Additionally, there are various reports in literature showing positive results on pruritis due to chronic cholestasis, including retrospective, case controlled, and prospective trials in other cholestatic diseases in children and adults. For example, one meta-analysis of five randomized prospective controlled trials in adults and children concluded that rifampin is safe and effective for treatment of pruritis in patients with cholestasis associated with chronic liver diseases (majority of patients had primary biliary cirrhosis). Additionally, one prospective study, one retrospective study, and cases reports are also available in patients with ALGS (Khurana, 2006; Yerushalmi, 1999; Kronsten, 2013).
- **Opioid antagonist** - naltrexone is recommended for the treatment of pruritis associated with cholestatic liver disease by the EASL guidelines as a subsequent option for patients failing cholestyramine and rifampin and is mentioned by expert reviews and rare disease organizations (NORD). Efficacy is supported by a meta-analysis which concluded that opioid antagonists significantly reduced cholestasis-related pruritis (Tandon, 2007). Safety and efficacy of naltrexone in children is scarce; however, naltrexone can be safely used by pediatric patients with cholestatic

liver disease and its use has been described in a retrospective study, case reports and case series in patients with ALGS (Kronsten, 2013; Zellos, 2010; Mozer-Glassberg, 2011).

- **Serotonin Inhibitors** - EASL guidelines recommended sertraline as a fourth-line treatment option for patients with cholestatic pruritis. Efficacy and safety are supported by one randomized double-blind, placebo-controlled study in patients with pruritis due to liver disease (Mayo, 2007) and one prospective multicenter study in children with refractory cholestatic pruritis related to PFIC and Alagille syndrome (Thebaut, 2017). Ondansetron has been studied in several cholestatic liver diseases with mixed results. One placebo-controlled trial studied intravenous ondansetron in adult patients with cholestatic pruritis and showed improvement in itch intensity by 50%. Another randomized, double-blind cross over study determined there was significant but moderate reduction in visual analogue scale (VAS) score when ondansetron was compared to placebo in patients with chronic liver disease. Another study showed that ondansetron therapy effectively reduced pruritis in 5 out of 13 patients; however, the reduction in itch intensity did not correlate to substantial decrease in objective scratching activity. A fourth clinical trial compared ondansetron to placebo and found no significant differences in pruritis scores or scratching activity (Ebhohon, 2023).

XII. Maralixibat (Livmarli) was studied in a pivotal Phase 2b, double-blind, placebo-controlled, randomized drug withdrawal (RWD) trial ICONIC, two randomized, double-blind, placebo-controlled Phase 2 trials ITCH and IMAGO, as well as ongoing open-label trial MERGE. The pivotal study included 31 pediatric patients (median age: 5.4 years) with ALGS (JAG1 mutation: 100%), native liver, elevated serum bile acids (mean: 283umol/L), and moderate to severe pruritis (mean weekly average ItchRO(Obs) score: 2.9). At baseline, patients were treated with standard of care agents (ursodeoxycholic acid: 81%; rifampin 74%; naltrexone: 3%; sertraline: 3%) that were continued during the trial. Patients were excluded if they had prior surgical interruption of the enterohepatic circulation, liver transplantation, and decompensated cirrhosis. The primary endpoints were the least square (LS) mean change in serum bile acid (sBA) levels and LS mean difference in pruritis severity as measured by the ItchRO(Obs) score between maralixibat (Livmarli) and placebo during the RWD period. Both endpoints met statistical significance and it was determined that there were substantial number of patients experiencing clinically meaningful change in pruritis scores while on treatment with maralixibat (Livmarli).

XIII. Pooled safety data is available in 86 patients with ALGS with median duration of exposure of 32.3 months. Most common (≥5%) any grade adverse events (AE) included diarrhea (55.8%), abdominal pain (53.5%), vomiting (40.7%), fat-soluble vitamin deficiency (25.6%), transaminases increased (18.6%), gastrointestinal bleeding (10.4%), bone fractures (9.3%), and nausea (8.1%). Three patients experienced vomiting as a serious AE requiring hospitalization or intravenous fluid administration. Treatment interruptions or dose reduction occurred in 5 (6%) patients due to diarrhea, abdominal pain, or vomiting. Seven (8.1%) patients discontinued due to ALT increase. There are no black box warnings or contraindications at this time. Warnings and precautions include liver test abnormalities, gastrointestinal adverse reactions, and fat-soluble vitamin deficiency.

Investigational or Not Medically Necessary Uses

I. Maralixibat (Livmarli) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. ALGS in patients < 12 months of age
      i. Maralixibat (Livmarli) is being studied in one open-label, single-arm, Phase 2 trial in patients < 12 months of age with ALGS or progressive familial intrahepatic cholestasis (PFIC). The primary outcome of the study is the frequency of treatment-emergent adverse events, and a secondary outcome in change in fasting serum bile acids (sBA) levels. Study results are not available at this time. Study completion date is expected in January 2023 (NCT04729751).
   B. Progressive familial intrahepatic cholestasis (PFIC)
      i. Maralixibat (Livmarli) is being studied in one randomized, double-blind, placebo-controlled Phase 3 study in patients with PFIC. The primary outcome studied is the mean change in pruritis as assessed by ItchRO(Obs) score. Secondary outcomes include treatment response and mean change in serum bile acids. Study results are not available at this time. Study completion date is expected in July 2022 (NCT03905330).
      ii. Maralixibat (Livmarli) is being studied in one open-label, single-arm, Phase 2 trial in patients < 12 months of age with ALGS or PFIC. The primary outcome of the study is the frequency of treatment-emergent adverse events, and a secondary outcome in change in fasting serum bile acids (sBA) levels. Study results are not available at this time. Study completion date is expected in January 2023 (NCT04729751).
   C. Benign recurrent intrahepatic cholestasis 1 and 2 (BRIC1 and BRIC2)
      i. BRIC1 and BRIC2 are milder versions of PFIC1 and PFIC2. BRIC1 and 2 occur on the same genes as PFIC1 and 2, respectively. However, cholestatic events are described as recurrent and unpredictable. Cholestatic episodes often last for a couple of weeks, vary in severity and duration and do not progress to liver failure. Therefore, there is uncertainty whether the duration of disease would offset treatment benefit. Further research and collection of evidence in patients with BRIC1 and BRIC2 is warranted at this time. There are no ongoing clinical trials of maralixibat (Livmarli) in patients with BRIC1 or BRIC2
   D. Biliary atresia (BA)
      i. BA is a rare condition presenting in infants in which the bile ducts outside and inside the liver are scarred and blocked, impeding bile flow. The cause is largely unknown and can include viral, toxic, immunologic and generic etiologies. Maralixibat (Livmarli) is being studied in infants with BA after Hepatoportoenterostomy (also known as the Kasai procedure) in a Phase 2, double-blind, randomized, placebo-controlled study. The primary endpoint evaluated is the mean change in total serum bilirubin levels; secondary endpoints include changes in serum bile acid (sBA) levels, and time to liver transplantation or death. Study results are not available at this time. Study completion date is expected in August 2024 (NCT04524390).
   E. Primary sclerosing cholangitis (PBC)

i. PBC is a rare, chronic, progressive, autoimmune, cholestatic liver disease characterized by damage to intrahepatic bile ducts. Maralixibat (Livmarli) was studied in a phase 2, randomized, placebo-controlled trial in 66 patients aged 18-80 years with PBC and significant pruritis. The primary outcome was change in Adult Itch Reported Outcome (ItchRO) average weekly sum score (0, no itching; 70, maximum itching) from baseline to week 13/early termination (ET). Mean ItchRO weekly sum scores decreased from baseline to week 13/ET with maralixibat (Livmarli) (–26.5; 95% confidence interval [CI], –31.8, –21.2) and placebo (–23.4; 95% CI, –30.3, –16.4). The difference between groups was not significant (P = 0.48). Due to non-statistically significant results, maralixibat (Livmarli) was not associated with improvements in pruritis when compared to placebo and more studies are needed to evaluate this therapy in PBC.

Appendix

I. Maralixibat (Livmarli) Individual Dose Volume by Patient Weight

Member weight (kg)	Days 1-7 (190 mcg/kg/day)	Beginning Day 8 (380 mcg/kg/day)	PA#1: quantity per 28-day supply for month one (mL)	PA#2: quantity per 28-day supply for month two through six (mL)	Renewal: quantity per 28-day supply
	Volume QD (mL)	Volume QD (mL)			
5 to 6	0.1	0.2	4.9	5.6	5.6
7 to 9	0.15	0.3	7.4	8.4	8.4
10 to 12	0.2	0.45	10.9	12.6	12.6
13 to 15	0.3	0.6	14.7	16.8	16.8
16 to 19	0.35	0.7	17.2	19.6	19.6
20 to 24	0.45	0.9	22.1	25.2	25.2
25 to 29	0.5	1	24.5	28	28
30 to 34	0.6	1.25	30.5	35	35
35 to 39	0.7	1.5	36.4	42	42
40 to 49	0.9	1.75	43.1	49	49
50 to 59	1	2.25	54.3	63	63
60 to 69	1.25	2.5	61.3	70	70
70 or higher	1.5	3	73.5	84	84

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease State
odevixibat (Bylvay™)	Progressive familial intrahepatic cholestasis (PFIC); Alagille Syndrome (ALGS)

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Policy Implementation/Update:

Action and Summary of Changes	Date
Renewal evaluation changed from 12 to six months; added ondansetron as an example of accepted medications in serotonin inhibitor class, updated supportive evidence section, added related policies section.	07/2023
Policy created	02/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP249

Description

Maribavir (Livtencity) is an orally administered benzimidazole riboside.

Length of Authorization

- Initial: Eight weeks
- Renewal: Eight weeks

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
maribavir (Livtencity)	200 mg tablets	Post-transplant CMV infection/disease that is refractory to other treatments	112 tablets/28 days

Initial Evaluation

I. **Maribavir (Livtencity)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist, hematologist, infectious disease, or transplant specialist; **AND**
   C. Medication is prescribed for the treatment of cytomegalovirus (CMV) infection or disease; **AND**
      1. Member is seropositive for CMV; **AND**
      2. Member has received a solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT); **AND**
      3. Medication will not be used in combination with other medications for CMV (e.g., valganciclovir, ganciclovir, foscarnet, cidofovir, letermovir [Prevymis]); **AND**
      4. The member is resistant or refractory to at least one of the following medications, unless all are contraindicated;
         i. Valganciclovir
         ii. Ganciclovir
         iii. Foscarnet
         iv. Cidofovir

II. Maribavir (Livtencity) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. CMV infection that is not resistant or refractory to other conventional therapies (e.g., valganciclovir, ganciclovir, foscarnet, cidofovir)

III. Maribavir (Livtencity) is considered investigational when used for all other conditions, including but not limited to:
   A. Maribavir (Livtencity) used in combination with other CMV therapies
   B. CMV prophylaxis
   C. HIV AIDS-related CMV

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, an oncologist, hematologist, infectious disease or transplant specialist; **AND**
IV. Medication is prescribed for cytomegalovirus (CMV) infection or disease; **AND**
   A. Provider attests to all of the following:
      a. Member experienced a positive response to an initial treatment course, as indicated by CMV viremia clearance or resolution of CMV disease symptoms; **AND**
      b. There has been a gap in therapy following the initial eight-week treatment course; **AND**
      c. A blood and/or plasma test has been completed, showing an increase in CMV viremia level following the end of the last treatment course of maribavir (Livtencity); **AND**
      d. Testing has been done, following the most recent treatment course, confirming the member is not resistant to maribavir (Livtencity)

Supporting Evidence

I. Cytomegalovirus (CMV) is an infection associated with immunosuppression. In the setting of solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT), CMV is a serious complication. Patients may experience CMV syndrome (e.g., fever, malaise, myalgias, arthralgias, leukopenia, thrombocytopenia), end-organ disease (retinitis, pneumonitis, hepatitis), and mortality. CMV infection is a significant risk factor for mortality, development of graft vs. host disease, graft loss, and organ dysfunction if not treated appropriately. Therapy for CMV is complex and may be administered prophylactically, preemptively, or may be reserved for the treatment of CMV syndrome or disease. Treatment approach varies depending on transplant type, serostatus, risk profile, and organ function; thus, management and oversight from a specialist to guide and monitor therapy is warranted.
II. Ganciclovir (IV), valganciclovir, foscarnet (IV), and cidofovir (IV) are used off-label for post-transplant CMV, and have known safety and efficacy; however, all target viral protein UL54, and are susceptible to cross resistance. Maribavir (Livtencity) is a benzimidazole riboside with inhibition against UL97 that has activity and efficacy in patients that are resistant to conventional therapies. It is FDA-approved for post-transplant CMV infection/disease in those resistant or refractory to at least one conventional therapy.

III. Maribavir (Livtencity) was evaluated in a pivotal Phase 3 clinical trial that was a randomized, open-label study against investigator assigned therapy (IAT) for eight weeks. Patients were adults with confirmed CMV viremia, were resistant or refractory to one or more conventional therapies (i.e., ganciclovir, valganciclovir, foscarnet, cidofovir), and had received HSCT or SOT. The clinical trial allowed enrollment of patients 12 years of age and older; however, no patients under the age of 18 enrolled in the trial. Maribavir (Livtencity) is FDA-approved for patients 12 years of age and older (weighing at least 35 kg). The exposure of drug therapy is expected to be similar to that of adult patients, and support for use in patients 12-18 years of age is based on the fact that course of disease is expected to be similar in pediatric and adult populations and pharmacokinetic data indicates drug exposure is expected to be similar. Use of therapy in the 12-18 age population likely has benefits that outweigh the risks given patients will be resistant/refractory to other treatment options.

IV. Maribavir (Livtencity) showed statistical and clinical superiority to the IAT treatment arm in CMV DNA levels at the end of eight weeks of treatment, as well as maintenance of treatment effect at week 16 (with an eight-week treatment free period following the eight weeks of therapy). There was no difference in all-cause mortality. Limitations of the clinical trial were the high discontinuation rate in the IAT treatment arm and variety of regimens included in the IAT treatment arm. This limits the ability to conclude true superiority of maribavir (Livtencity) over any or all conventional therapies, notably in the refractory population. It is predicted that maribavir (Livtencity) would be superior in those that are resistant to conventional therapies; however, the population included in the trial was a mix of patients that were resistant and refractory. Of note, therapy has not been correlated with a survival benefit, and for the majority of patients this medication does not maintain clearance long-term (i.e., beyond 16 weeks after treatment initiation with an eight-week therapy course). There is a high rate of CMV recurrence, partially due to resistance. Virologic relapse generally occurs four-to-eight weeks after treatment discontinuation. Furthermore, use of therapy in the first-line setting may confer resistance to valganciclovir and ganciclovir, and may then limit available effective treatment options in the second-line setting.

V. It is unknown if maribavir (Livtencity) will be efficacious in the prophylactic setting or outside of post-transplant related CMV infection. There are other medications FDA-approved and recommended in these settings. Use of conventional therapies, and guidance from treatment guidelines should be followed as untreated or inappropriately treated CMV may lead to serious complications including graft-loss and/or mortality. Confirmed CMV viremia via seropositive status is indicative of CMV infection, and should be confirmed prior to use of this therapy. Maribavir (Livtencity) continues to be evaluated in the first-line setting (not relapsed or refractory); however, given the known safety, efficacy, ability to overcome UL54 resistance, and cost effectiveness of conventional agents, maribavir (Livtencity) should be reserved for the relapsed/refractory population. Although the safety profile of maribavir (Livtencity) differs from that of conventional therapies, conventional therapies (e.g., valganciclovir, ganciclovir, foscarnet, cidofovir) should be considered for all patients that lack contraindication to them given extensive clinical experience, more established safety profile, and cost effectiveness. The known adverse effects from valganciclovir, ganciclovir, foscarnet, and cidofovir are predictable and have known management strategies to mitigate toxicities and maximize treatment. In the setting of contraindication to all conventional therapies (i.e., valganciclovir, ganciclovir, foscarnet, and cidofovir), treatment with maribavir (Livtencity) is a reasonable option. In a Phase 2 clinical trial, therapy showed efficacy, as well as a similar safety profile compared to the Phase 3 pivotal trial for the relapsed/refractory population. A Phase 3 trial is underway to confirm.

VI. Maribavir (Livtencity) has not been evaluated in combination with other CMV therapies. When used in combination with therapies such as valganciclovir and ganciclovir, maribavir (Livtencity) may antagonize the effects of other medications. Given the reduced efficacy and potential additive safety concerns, concomitant use is not allowed.

VII. Maribavir (Livtencity) was evaluated for an eight-week treatment course in clinical trials. Safety and efficacy with a longer course of therapy has not been evaluated. It is unknown at this time if extended therapy would impact duration of viremia clearance and/or reduce the rate/risk of recurrence; thus, duration of therapy is limited to that which has shown clinical value in controlled clinical trials. A favorable response to therapy includes clearance of CMV DNA (<137 IU/mL), or a significant reduction in CMV DNA coupled with resolution and/or improvement in CMV disease symptoms. If adherence is achieved, failure to meet these treatment goals is indicative of resistance or refractory to maribavir (Livtencity). After eight weeks of therapy, maribavir (Livtencity) should be discontinued and patients should have a gap in therapy to determine success of treatment. If CMV DNA levels rapidly increase following an eight-week treatment course, further therapy may be warranted. Subsequent treatment courses of maribavir (Livtencity) have not been evaluated for safety and efficacy; however, retreatment could be reasonable if an initial treatment course was successful, there are rapidly increasing CMV DNA levels following a prior successful treatment course, and if resistance testing has been done which indicates the patient has not conferred resistance to maribavir (Livtencity). Similar to conventional treatment options, maribavir (Livtencity) has a high rate of resistance, and resistance mutations result in failure to meet CMV viremia clearance.

Investigational or Not Medically Necessary Uses

I. Maribavir (Livtencity) is considered not medically necessary for treatment of CMV in the first-line setting given availability of several conventional treatment options with known efficacy, known safety profile, and superior cost-effectiveness. Therapy should ideally be reserved for patients with UL54 resistance, as maribavir (Livtencity) has the ability to overcome this; however, if maribavir (Livtencity) is utilized as a first-line treatment, UL97 resistance-associated substitutions may confer cross-resistance to ganciclovir and valganciclovir rendering fewer effective treatment options in the second-line setting.

II. Maribavir (Livtencity) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Maribavir (Livtencity) used in combination with other CMV therapies
    B. CMV prophylaxis
    C. HIV AIDS-related CMV

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP253

Description

Mavacamten (Camzyos) is an orally administered selective allosteric inhibitor of cardiac myosin ATPase.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
mavacamten (Camzyos)	2.5 mg capsule	Symptomatic NYHA Class II-III obstructive hypertrophic cardiomyopathy (oHCM)	30 capsules/30 days
	5 mg capsule		
	10 mg capsule		
	15 mg capsule		

Initial Evaluation

I. **Mavacamten (Camzyos)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist who practices at or consults with a Center of Excellence for hypertrophic cardiomyopathy; **AND**
   C. A diagnosis of **symptomatic NYHA Class II-III obstructive hypertrophic cardiomyopathy (oHCM)** when the following are met:
      1. Provider attestation the member has undergone a comprehensive cardiac workup to diagnose hypertrophic cardiomyopathy (e.g., physical exam, ECG, ECHO, CMR, etc.); **AND**
      2. Provider attestation that baseline obstruction by left ventricular outflow tract (LVOT) gradient is 50 mm Hg or greater; **AND**
      3. Provider attestation that member has NYHA Class II-III symptoms of heart failure, including but not limited to, fatigue, dyspnea, chest pain, palpitations, and syncope; **AND**
   D. Treatment with one of the following regimens has been ineffective, contraindicated, or not tolerated:
      1. Beta-blocker (e.g., metoprolol, carvedilol, bisoprolol, etc.) in combination with non-dihydropyridine calcium channel blocker (e.g., verapamil, diltiazem); **OR**
      2. Disopyramide in combination with beta-blocker and/or non-dihydropyridine calcium channel blocker.

II. Mavacamten (Camzyos) is considered investigational when used for all other conditions, including but not limited to:
   A. Asymptomatic oHCM
   B. Non-obstructive hypertrophic cardiomyopathy
   C. Dilated, arrhythmogenic or restrictive cardiomyopathy
   D. Cardiac amyloidosis or amyloid cardiomyopathy
   E. Fabry disease

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease [e.g., improved fatigue, dyspnea, chest pain, palpitations, and/or syncope, improved exercise capacity, reduction in LVOT gradient, etc.].

Supporting Evidence

I. Length of authorization for initial approval is six months as clinical benefits of mavacamten were realized in clinical trials as early as 18 weeks and were evaluated at 30 weeks of therapy. Treatment response is expected to be realized at six months duration.
II. Hypertrophic cardiomyopathy (HCM) is a genetic disease of the sarcomeres in cardiac muscle that causes structural and hemodynamic abnormalities of the heart. The disease typically manifests as left ventricular hypertrophy which can lead to LVOT obstruction, diastolic or systolic dysfunction, myocardial ischemia, and mitral regurgitation. Diagnosis of HCM is made by a cardiologist through a comprehensive cardiac workup, including, but not limited to, an electrocardiogram (ECG) and echocardiograph (ECHO) or cardiac magnetic resonance imaging (CMR). The LVOT gradient, an indicator of obstruction, is measured by ECHO, CMR, or invasive assessment through cardiac catheterization; a value of 30 mm Hg or greater indicates obstruction, while resting or provoked gradients at or greater than 50 mm Hg represent a threshold for septal reduction therapy in patients who have drug-refractory symptoms. Symptoms of HCM include fatigue, dyspnea, chest pain, palpitations, and syncope. Several disease-related complications may also occur, including atrial fibrillation, ventricular arrhythmia, progressive heart failure, and embolic stroke. Given the specialized monitoring this condition entails, a specialist prescriber who practices at or consults with a Center of Excellence designed to care for HCM patients is required.
III. Current guidelines (2014 European Society of Cardiology, 2020 American Heart Association/American College of Cardiology) provide treatment recommendations for HCM based on presence of heart failure symptoms, obstruction, and disease-related comorbidities. Treatment is not recommended for asymptomatic patients. In patients with symptoms of heart

failure and obstruction (oHCM), BB (metoprolol, carvedilol, bisoprolol) or non-dihydropyridine calcium CCB (verapamil, diltiazem), monotherapy is recommended. Second-line therapies include combination BB plus CCB, or addition of antiarrhythmic disopyramide to BB and/or CCB. If symptoms persist despite maximal pharmacologic therapy, septal reduction therapy (SRT) is indicated in the form of surgical myectomy or alcohol ablation; SRT may also be considered as an alternative to escalation of pharmacologic therapy if symptoms are severe. In patients with symptomatic HCM without obstruction, treatment includes BB, CCB, ACE-inhibitors and angiotensin-receptor blockers (ARB), and diuretics. Treatment of comorbid atrial fibrillation, ventricular arrhythmia, and thromboembolic risk includes rate and rhythm control strategies and anticoagulants; cardioversion, ICD placement, catheter ablation, and heart transplant may also be used if symptoms are severe or drug-refractory.

- Treatment Summary: In patients refractory to single-agent BB or CCB, escalation to combination BB plus CCB or addition of disopyramide to one or both of these therapies are viable treatment options. Given the known efficacy, established safety profile, and cost effectiveness of these medications, at least one dual therapy regimen is required prior to mavacamten.

IV. The FDA-approval of mavacamten (Camzyos) for oHCM was based on the results of one 30-week international, randomized, double-blind, placebo-controlled Phase 3 study: EXPLORER-HCM. A total of 251 adults with symptomatic oHCM were enrolled, as defined by unexplained left ventricular hypertrophy and at least one peak LVOT gradient 50 mm Hg or greater at rest, after Valsalva, or post-exercise, NYHA class II or III symptoms, left ventricular ejection fraction (LVEF) 55% or greater, and LVOT at screening of 30 mm Hg or greater. Population characteristics were as follows: 73% NYHA class II, 75% on BB, 16.5% on CCB, 14% with atrial fibrillation, 7.5% previous septal reduction procedure, average LVEF 74%. Mavacamten doses were titrated as guided by ECHO to achieve a target left ventricular outflow tract (LVOT) gradient of less than 30 mm Hg and drug plasma concentration of 350-700 ng/mL. The primary endpoint was the number of patients who achieved a clinical response composite at week 30, as defined by a ≥ 1.5 mL/kg/min increase in peak oxygen consumption (pVO^2) and ≥ 1 NYHA class improvement or ≥ 3 mL/kg/min increase in pVO2 and no worsening of NYHA class; this was met in 37% of the mavacamten group compared to 17% of the placebo group, with a clinically meaningful and statistically significant difference relative to placebo. Key secondary endpoints included change from baseline to week 30 in post-exercise left ventricular outflow tract (LVOT) gradient, pVO2, patient reported outcome measure of symptom reduction and physical function (Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score, KCCQ-CSS) and number of patients with at least one NYHA class improvement; all secondary endpoints were met with a clinically meaningful difference relative to placebo. The most common adverse events were nasopharyngitis, dizziness, headache, and dyspnea.

V. Consistent with the mechanism of action, mavacamten (Camzyos) reduces LVEF and can cause systolic dysfunction, which can also be exacerbated when taken with certain cytochrome P450 inhibitors/inducers. As a result, mavacamten carries a warning for heart failure and is only available through a restricted REMS program called Camzyos REMS. ECHO assessments are required before and during treatment with mavacamten (Camzyos).

Investigational or Not Medically Necessary Uses

I. Mavacamten (Camzyos) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Asymptomatic oHCM
   B. Non-obstructive hypertrophic cardiomyopathy
   C. Dilated, arrhythmogenic or restrictive cardiomyopathy
   D. Cardiac amyloidosis or amyloid cardiomyopathy
   E. Fabry disease

References

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6. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(39):2733-2779.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created.	02/2022

Policy Type: PA Pharmacy Coverage Policy: UMP232

Description

Mecamylamine (Vecamyl) is an orally administered sympathetic ganglionic blocker, which blocks cholinergic stimuli at nicotinic receptors leading to blood vessels dilation and reduction in blood pressure.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Mecamylamine (Vecamyl)	2.5 mg tablet	Moderately severe to severe hypertension	300 tablets/30 days
		Uncomplicated malignant hypertension	

Initial Evaluation

I. Mecamylamine (Vecamyl) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist; **AND**
   C. A diagnosis of **Moderately severe to severe hypertension OR Uncomplicated malignant hypertension** when the following are met:
      1. Treatment with at least one agent from FIVE of the following classes of antihypertensive agents has been ineffective or not tolerated (Note, if a class of agents is contraindicated, a trial and failure of at least five agents or combinations thereof from the remaining groups is required):
         i. Thiazide diuretics (e.g. hydrochlorothiazide)
         ii. Angiotensin-converting enzyme inhibitors (e.g. lisinopril, captopril, benazepril)
         iii. Angiotensin II receptor antagonists (e.g. losartan, valsartan)
         iv. Beta blockers (e.g. metoprolol)
         v. Calcium channel blockers (e.g. amlodipine, diltiazem)
         vi. Direct renin inhibitors (e.g. aliskiren)
         vii. Other (e.g. clonidine, hydralazine, doxazosin) **AND**

2. Treatment with at least one parenteral antihypertensive agent (e.g. IV nitroprusside, nicardipine, clevidipine, labetalol) has been ineffective, contraindicated, or not tolerated.

II. Mecamylamine (Vecamyl) is considered investigational when used for all other conditions, including but not limited to:
   A. Major depressive disorder (MDD)
   B. Giles de la Tourette's syndrome
   C. Hyperreflexia
   D. Nicotine dependence

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms [e.g. reduction in blood pressure].

Supporting Evidence

I. Mecamylamine (Vecamyl) is a nicotinic parasympathetic ganglionic blocker, which prevents stimulation of postsynaptic receptors by acetylcholine released from presynaptic nerve endings. The hypotensive effect of mecamylamine (Vecamyl) is attributed to reduction in sympathetic tone, vasodilation, and reduced cardiac output. It is considered a nonselective antagonist that easily passes through the blood-brain barrier, and thus, having the potential to affect nicotinic acetylcholine receptors in the central nervous system.
II. Mecamylamine (Vecamyl) is FDA approved for use in patients 18 years of age and older. Efficacy and safety of this drug are not established in the pediatric population.
III. Mecamylamine (Vecamyl) should be given with great discretion, if at all, when renal insufficiency is manifested by a rising or elevated BUN. The drug is contraindicated in uremia. Patients receiving antibiotics and sulfonamides should generally not be treated with ganglion blockers. Other contraindications are glaucoma, organic pyloric stenosis, or hypersensitivity to the product.
IV. The package insert for mecamylamine (Vecamyl) does not include any clinical trials as it was approved using an abbreviated new drug application (ANDA) of the innovator product, mecamylamine (Inversine). Approved on March 1, 1956, Inversine was available prior to the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, which led to inclusion of Inversine as an approved DESI drug; however, the distribution of Inversine was discontinued in 2009.

V. An observational clinical study (N=17) in 1957 examined the effects of mecamylamine monotherapy for blood pressure reduction from baseline (>150/100 mm Hg). Each patient was initiated on mecamylamine 2.5mg twice daily before undergoing a set dose titration. Treatment response was defined as a decrease in mean blood pressure by at least 20 mm Hg or a reduction of blood pressure to the normotensive level (defined by the investigators as less than 150/100 mm Hg). Response rate to mecamylamine was reported to be 52% at average 34 mg/day dose, while the other half of subject population (non-responders) had no blood pressure reductions despite doubling the average dose.

VI. Mecamylamine (Vecamyl) is not an acceptable alternative agent to consider for supplemental use after first-line antihypertensive agents have failed to provide adequate response. More predictably effective agents with proven effects on morbidity and mortality and with safer side effect profiles have replaced mecamylamine for use in both essential and accelerated hypertension.

VII. It should be noted that parenteral antihypertensives (e.g. IV nitroprusside, nicardipine, clevipine, labetalol etc.) are most often used in the initial treatment of malignant hypertension due to their faster onset of action. Trial of a parenteral antihypertensive agent is warranted before consideration of mecamylamine (Vecamyl) as the next therapeutic agent.

VIII. The Clinical Practice Guidelines from the American College of Cardiology/American Heart Association Task Force (2017) do not include ganglionic blockers (e.g. mecamylamine (Vecamyl)) as a recommended primary or secondary treatment option. The Evidence-Based Guideline for the Management of High Blood Pressure in Adults from the panel members of the eighth joint national committee (2014) advise selection among four specific medication classes (thiazide type diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers) as initial treatment and inclusion of other classes (e.g. beta blockers, direct renin inhibitors, alpha1 blockers, centrally acting drugs and direct vasodialator) as secondary choices in treatment.

Investigational or Not Medically Necessary Uses

I. Major depressive disorder (MDD)
   A. The principal focus of research on mecamylamine largely involves its potent blockade of nicotinic receptors in central nervous system at doses that do not have a significant effect on parasympathetic function (2.5-10 mg/day). Recently mecamylamine was studied via two short-term, phase III clinical trials, as an add-on treatment to existing antidepressant agents. These trials did not show significant difference in treatment groups compared to a placebo.

II. Giles de la Tourette's syndrome and Hyperreflexia
   A. Use of mecamylamine for the treatment of Giles de la Tourette's syndrome and hyperreflexia has been studied in retrospective case studies and the quality of evidence in these settings is considered low.

III. Nicotine dependence
   A. A randomized, double-blind, placebo controlled clinical trial (N=48) assessed efficacy of mecamylamine in combination with transdermal nicotine patches as compared to placebo in combination with nicotine patch. Although this study reported greater abstinence rates

in treatment group at week 7 (50% versus 16%), the trial was not adequately powered to analyze effect size and the primary outcome assessment was based on patient self-reporting. Additionally, all subjects received transdermal nicotine, which confounded the outcomes assessment. Mecamylamine has not been FDA-approved in this setting.

References

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2. Shytle RD, Penny, E, et. al. Mecamylamine (Inversine): an old antihypertensive with new research directions. Journal of Human Hypertension. 2002; (16): 453-457.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Transition of old criteria document to the policy format; added requirement of drug being prescribed by a specialist; removed criteria for validation of contraindications before treatment start; added E/I uses; added supporting evidence	05/2021
Criteria created	09/2013

Policy Type: PA/SP Pharmacy Coverage Policy: UMP133

Description

Mecasermin (Increlex) is an injection that is indicated for the treatment of growth failure in children with severe primary insulin-like growth factor (IGF-1) deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
mecasermin (Increlex)	40 mg/4 mL multiple dose vial	Severe primary insulin-like growth factor (IGF-1) deficiency; Growth hormone (GH) gene deletion with neutralizing antibodies to GH	7.2 mg/kg/30 days

Initial Evaluation

I. Mecasermin (Increlex) may be considered medically necessary when the following criteria below are met:
   A. Member is a between 2-18 years of age; **AND**
   B. Medication is prescribed by, or in consultation with, a pediatric endocrinologist or a pediatric nephrologist; **AND**
   C. Member has evidence of non-closure of the epiphyseal plate confirmed by radiograph; **AND**
   D. A diagnosis of one of the following:
      1. **Severe primary insulin-like growth factor (IGF-1) deficiency**
         i. Member meets ALL of the following:
            a. Height standard deviation score ≤ -3.0; **AND**
            b. Basal IGF-1 standard deviation score ≤ -3.0; **AND**
            c. Normal or elevated growth hormone (GH) level, [serum growth hormone level of ≥ 10 ngm/mL to at least two stimuli (insulin, levodopa, arginine, clonidine, or glucagon)]; **OR**
      2. **Growth hormone (GH) gene deletion**
         i. Member has developed neutralizing antibodies to GH; **AND**
         ii. Member has normal thyroid function (TSH in the range of 0.5-6 uIU/mL); **AND**

iii. Member is not malnourished (BMI < 18 kg/m^2); **AND**
iv. Member does not have active or suspected neoplasia (e.g. cancer)

II. Mecasermin (Increlex) is considered investigational when used for all other conditions, including but not limited to:
A. Secondary forms of IGF-1 deficiency such as:
1. GH deficiency
2. Malnutrition
3. Hypothyroidism
4. Chronic treatment with pharmacologic doses of anti-inflammatory steroids

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
II. Member has shown a response in the first 6 months of the IGF-1 therapy (e.g. increase in height, increase in height velocity); **AND**
III. Member has evidence of non-closure of the epiphyseal plate, confirmed by radiograph

Supporting Evidence

I. Mecasermin (Increlex) is for the long-term treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency (primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Severe primary IGFD is defined by:
- Height standard deviation score ≤ -3.0
- Basal IGF-1 standard deviation score ≤ -3.0
- Normal or elevated GH

II. Insulin-like growth factor (IGF-1) is the principal hormonal mediator of statural growth. Under normal circumstances, growth hormone (GH) binds to its receptor in the liver and other tissues, and stimulates the synthesis/secretion of IGF-1.
- In target tissues, the type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signaling, which stimulates multiple processes leading to statural growth.
- The metabolic actions of IGF-1 are, in part, directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues.

III. Severe primary IGF-1 deficiency includes members with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient; therefore, they cannot be expected to respond adequately to exogenous GH treatment.
IV. Mecasermin (Increlex) is not a substitute to growth hormone (GH) for approved GH indication.
V. Mecasermin (Increlex) is not indicated for use after epiphyseal closure.

Investigational Use

I. Mecasermin (Increlex) is not intended for use in members with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

References

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2. UpToDate, Inc. Growth hormone insensitivity syndromes. UpToDate [database online]. Waltham, MA. Updated March 8, 2019. Available at: http://www.uptodate.com/home/index.html. Accessed November 9, 2019.

Policy Implementation/Update:

Date Created	September 2008
Date Effective	October 2008
Last Updated	November 2019
Last Reviewed	12/2008, 11/2019

Action and Summary of Changes	Date
Criteria updated to new policy format. Specific changes include: removal of bone age requirement (If male, bone age is less than 16 years of age; or if female, bone age is less than 14 years of age) and update on child 2 years of age or older.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP134

Description

Mechlorethamine (Valchlor) is a topical nitrogen analog of sulfur mustard and is a biologic alkylating agent.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
mechlorethamine (Valchlor)	0.016% topical gel/jelly	Mycosis fungoides-type cutaneous T-cell lymphoma, in those that have received prior skin-directed therapy	60 grams (1 tube)/30 days

Initial Evaluation

I. Mechlorethamine (Valchlor) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an oncologist or dermatologist; **AND**
   C. Will not be used in combination with bexarotene (Targretin); **AND**
   D. A diagnosis of **cutaneous T-cell lymphoma** when the following are met:
      1. The disease is stage IA or IB (i.e., limited, localized); **AND**
      2. The member is relapsed, refractory, or intolerant to at least one other skin-directed therapy (e.g., corticosteroids, phototherapy, imiquimod, topical retinoids, carmustine, local radiation).

II. Mechlorethamine (Valchlor) is considered investigational when used for all other conditions, including but not limited to:
   A. Contact dermatitis
   B. Non-Hodgkin lymphoma
   C. Lichen planopilaris

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
IV. Member has exhibited response to therapy such as improvement in CAILS score, decrease in affected surface area, or decrease in plaque/scale elevation or severity.

Supporting Evidence

I. Mechlorethamine (Valchlor) gel was assessed in a randomized, observer-blinded, active-controlled (versus compounded mechlorethamine ointment), non-inferiority clinical trial of subjects with stage IA, IB, and II A mycosis fungoides-type cutaneous T-cell lymphoma. Subjects had received at least one prior skin-directed therapy, including the following: topical corticosteroids, phototherapy, bexarotene (Targretin) gel, topical nitrogen mustard. The median number of prior therapies was two. Mechlorethamine (Valchlor) was applied topically on a daily basis for 12 months. Subjects were evaluated for a response on a monthly basis for the first six months and then every two months for the last six months using the Composite Assessment of Index Lesion Severity (CAILS) score. This score is obtained by adding the severity score of each of the following categories for up to five index lesions: erythema, scaling, plaque elevation, and surface area. Response was defined by a 50% or greater reduction in baseline score. A complete response was defined as achieving a score of 0. Subjects were also evaluated using the Severity Weighted Assessment Tool (SWAT). The SWAT score is derived by measuring each involved area as a percentage of total body surface area (% BSA) and multiplying it by a severity weighting factor. Response was defined as a 50% or greater reduction in baseline SWAT score. Sixty percent of subjects achieved a response in CAILS score versus 48% with the comparator arm. For the SWAT score, 50% in the mechlorethamine (Valchlor) arm met criteria for response versus 46% of the comparator arm. Mechlorethamine (Valchlor) statistical non-inferiority was met.
II. The mean average daily use in the trial was 1-2 tubes per month. The cost of one tube of mechlorethamine (Valchlor) is $4,000-$5,000 per month; thus for a quantity exception to be considered, clinical review of body surface area affected, application amount, frequency, adherence, etc. is warranted.

Investigational or Not Medically Necessary Uses

I. Mechlorethamine (Valchlor) has not been sufficiently evaluated for safety and/or efficacy in the following settings:
    A. Contact dermatitis
    B. Non-Hodgkin lymphoma
    C. Lichen planopilaris

References

1. Valchlor [Prescribing Information]. Malvern, PA: Ceptaris Therapeutics, Inc. August 2013.
2. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol. 2013;149(1):25-32.

Policy Implementation/Update:

Date Created	January 2014
Date Effective	March 2014
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format. Criteria updated to allow for oncologist prescribing. Renewal criteria changed to require specialist prescriber and specified parameters for improvement.	11/2019

Policy Type: QE Pharmacy Coverage Policy: UMP233

Description
All medications covered by this policy work to induce catharsis by the osmotic effects of the unabsorbed sulfate salts and polyethylene glycol (PEG) in the GI tract. Specifically, sulfate salts provide sulfate anions, which are poorly absorbed, and PEG, which is primarily unabsorbed, causes water to be retained in the GI tract resulting in watery diarrhea.

Length of Authorization
- Initial: One time with each request*
  **Can be approved multiple times, as requested by provider, if policy is met*
- Renewal: See "Initial" Authorization

Medications Included in this Policy

Product Name	Dosage Form	Indication
All therapies with the FDA approval for use in colonoscopy preparation	Multiple	Colonoscopy preparation

Initial Evaluation

I. **Colonoscopy preparation medications** may be considered medically necessary when the following criteria are met:
   A. Medication requested is being used as bowel preparation for colonoscopy

II. Colonoscopy preparation medications are excluded when the following criteria is met:
   A. Use is for treatment of constipation

Renewal Evaluation

I. See initial evaluation.

Supporting Evidence

I. In compliance with the United States Preventative Services Task Force (USPSTF), FDA-approved bowel preparations (non-OTC) are covered at a zero-cost share for up to 2 fills per year for members between the ages of 50-75 years with a valid prescription. The purpose of this policy is to review requests exceeding 2 fills per year to ensure use in preparation for a colonoscopy before allowing payment at a zero-cost share.

References

1. United States Department of Labor. FAQ About Affordable Care Act Implementation (Part 31). April 20, 2016. Accessed via https://www.dol.gov/ebsa/faqs/faq-aca31.html on July 30, 2016.
2. Facts & Comparisons. Bowel Evacuants. Accessed via http://online.factsandcomparisons.com/MonoDisp.aspx?monoid=fandc-hcp10331&book=DFC on July 30, 2016.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated requirement for medication used to cover all use for colonoscopy prep instead of just in the setting of colorectal cancer screening	08/2021
Criteria transitioned to policy format	05/2021
Criteria created	07/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP046

Description

Mepolizumab (Nucala) is a subcutaneously administered monoclonal antibody (IgG1 Kappa) that antagonizes interleukin-5 (IL-5).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
mepolizumab (Nucala)	100 mg/mL syringe, 100 mg/mL autoinjector	Asthma (severe)	1 syringe/autoinjector/28 days
		Eosinophilic granulomatosis with polyangiitis	3 syringes/autoinjectors/28 days
		Hypereosinophilic Syndrome	3 syringes/autoinjectors/28 days
		Chronic Rhinosinusitis with Nasal Polyps	1 syringe/autoinjector/28 days
	40mg/0.4mL prefilled syringe	Asthma (severe)	1 syringe/28 days
Provider Administered Agents*,++			
mepolizumab (Nucala)	100 mg/vial	Asthma (severe)	1 vial/28 days
		Eosinophilic granulomatosis with polyangiitis	3 vials/28 days
		Hypereosinophilic Syndrome	3 vials/28 days
		Chronic Rhinosinusitis with Nasal Polyps	1 vial/28 days

**Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit.*

++Certain groups have opted into the pharmacy benefit optimization (PBO) program in which case selected infused specialty medications will only be covered under the pharmacy benefit, and claims submitted under the medical benefit will be denied as provider liability. For more details, please reference: https://www.modahealth.com/medical/injectables/

Initial Evaluation

I. **Mepolizumab (Nucala**) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); **AND**
   B. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, dupilumab, omalizumab, reslizumab, etc.); **AND**
   C. A diagnosis of one of the following:
      1. **Asthma (severe)**; **AND**

i. Member is six years of age or older; **AND**
ii. Member has **SEVERE** asthma as defined by <u>one</u> of the following:
    a. Symptoms throughout the day
    b. Nighttime awakenings, often 7x/week
    c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs several times per day
    d. Extremely limited normal activities
    e. Lung function (percent predicted FEV1) <60%
    f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**
iii. Member must have asthma with an eosinophilic phenotype defined as blood eosinophils ≥300 cells/µL within previous 12 months OR ≥150 cells/µL within 6 weeks of dosing; **AND**
iv. Member must have two or more exacerbations in the previous year requiring daily oral corticosteroids for at least 3 days (in addition to the regular maintenance therapy defined below); **AND**
v. Member is currently being treated with:
    a. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
        i. One additional asthma controller medication (e.g., long-acting beta-2 agonist [LABA] {e.g., Serevent Diskus}, long-acting muscarinic antagonist [LAMA] {e.g., Spiriva Respimat}, leukotriene receptor antagonist [e.g., Singular], or theophylline); **OR**
    b. A maximally tolerated ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **AND**
vi. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of mepolizumab (Nucala), unless contraindicated; **OR**

2. **Eosinophilic Granulomatosis with Polyangiitis (EGPA)**; **AND**
    i. Member is 18 years of age or older; **AND**
    ii. Member has a confirmed diagnosis of EGPA (aka Churg-Strauss Syndrome) as defined by <u>ALL</u> of the following:
        a. History or presence of asthma; **AND**
        b. Blood eosinophil level 10% or an absolute eosinophil count >1000 cells/mm3; **AND**
        c. TWO or more of the following:
            i. Histopathologic evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration or eosinophil rich granulomatous inflammation
            ii. Neuropathy
            iii. Pulmonary infiltrates
            iv. Sinonasal abnormalities

v. Cardiomyopathy
vi. Glomerulonephritis
vii. Alveolar hemorrhage
viii. Palpable purpura
ix. Antineutrophil Cytoplasmic Antibody (ANCA) positivity; **AND**

iii. Member must have blood eosinophils ≥150 cells/µL within 6 weeks of dosing; **AND**
iv. Member has been on stable doses of concomitant oral corticosteroid therapy for at least 4 weeks (i.e., prednisone or prednisolone at a dose of 7.5 mg/day); **AND**
v. Physician has assessed baseline disease severity utilizing an objective measure/tool (e.g., Birmingham Vasculitis Activity Score [BVAS], history of asthma symptoms and/or exacerbations duration of remission or rate of relapses, etc.); **OR**

3. **Hypereosinophilic Syndrome (HES); AND**
   i. Member is 12 years of age or older; **AND**
   ii. Provider attests to ALL of the following:
      a. Member has been diagnosed with HES for at least 6 months prior to starting treatment; **AND**
      b. Member is confirmed to have F1P1L1-PDGFRα kinase-negative disease; **AND**
      c. Member does NOT have non-hematologic secondary HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy); **AND**
      d. Background HES therapy (e.g., oral corticosteroid, immunosuppressive, and/or cytotoxic therapy) will be continued with the use of mepolizumab (Nucala), unless contraindicated; **AND**
   iii. Member must have ALL of the following:
      a. Two or more HES flares (see Supporting Evidence below) in the previous year; **AND**
      b. Blood eosinophils ≥1000 cells/µL within 4 weeks of dosing; **AND**
      c. Has been on stable doses of at least one other HES therapy (e.g., oral corticosteroids, immunosuppressive agents [hydroxyurea, cyclosporine, methotrexate, tacrolimus, azathioprine], cytotoxic therapy [imatinib], etc) for at least 4 weeks; **OR**
4. **Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)**; **AND**
   i. Member is 18 years of age or older; **AND**
   ii. Provider attests that the member has ALL of the following:
      a. Diagnosis of bilateral sinonasal polyposis as evidenced by an endoscopy or computed tomography (CT); **AND**

b. Member has impaired Health-Related Quality of Life due to ongoing nasal congestion, blockage, or obstruction with moderate to severe symptom severity; **AND**
c. Member has at least **one** of the following symptoms:
i. Nasal discharge
ii. Facial pain or pressure
iii. Reduction or loss of smell; **AND**

iii. Provider attestation or clinical documentation of current persistent symptomatic nasal polyps despite maximal treatment with ALL of the following, unless ineffective, not tolerated, or contraindicated:
a. Intranasal corticosteroid; **AND**
b. Oral systemic corticosteroid therapy within the last 12 months; **AND**

iv. Background intranasal corticosteroids (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of Nucala, unless contraindicated

II. Mepolizumab (Nucala) is considered investigational when used for all other conditions, including but not limited to:
A. Non-severe, non-eosinophilic phenotype asthma
B. GPA (Wegener's granulomatosis) with polyangiitis
C. MPA (microscopic polyangiitis)
D. HES (hypereosinophilic syndrome) with F1P1L1-PDGFRα kinase-positive disease
E. Acute rhinosinusitis or Chronic Rhinosinusitis WITHOUT nasal polyps

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, dupilumab, omalizumab, reslizumab, etc.); **AND**
IV. A diagnosis of one of the following:
A. **Asthma (severe); AND**
i. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **AND**
ii. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of mepolizumab (Nucala), unless contraindicated; **OR**
B. **Eosinophilic Granulomatosis with Polyangiitis; AND**

1. Member has exhibited improvement or stability of disease symptoms as evidenced in one or more of the following:
    1. Member is in remission [defined as a Birmingham Vasculitis Activity Score (BVAS) score=0 and a prednisone/prednisolone daily dose of ≤ 7.5 mg]
    2. Decrease in maintenance dose of systemic corticosteroids
    3. Improvement in BVAS score compared to baseline
    4. Improvement in asthma symptoms or asthma exacerbations
    5. Improvement in duration of remission or decrease in the rate of relapses; **OR**

C. **Hypereosinophilic Syndrome; AND**
1. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in HES flares, improved fatigue, reduced oral corticosteroid requirements, decreased eosinophil levels); **OR**

D. **Chronic Rhinosinusitis with Nasal Polyps (CRSwNP); AND**
1. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in nasal congestion/obstruction severity, reduction in nasal polyps, improvement in sense of smell); **AND**
2. Background intranasal corticosteroids (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of Nucala, unless contraindicated.

Supporting Evidence

I. There is a lack of evidence supporting treatment with dual use of biologic therapies and a potential for increased risk of side effects.

II. Mepolizumab (Nucala) is indicated as an add-on maintenance treatment for members 6 years and older with a diagnosis of severe eosinophilic asthma (SEA), treatment for adult members with eosinophilic granulomatosis with polyangiitis, and treatment for members 12 years and older with hypereosinophilic syndrome for at least 6 months without an identifiable non-hematologic secondary cause. The age expansion approval by the FDA from 12 years of age to 6 years of age in children with a diagnosis of SEA was based on an open-label study that was conducted in children age 6 to 11 years of age with SEA. In this study, pharmacokinetics, pharmacodynamics, and long-term safety were evaluated and determined consistent with the known safety profile associated with members aged 12 years and older.

III. The FDA approval of mepolizumab (Nucala) in the setting of severe eosinophilic asthma were evaluated in 3 randomized, placebo controlled, multicenter trials of 24 to 52 weeks in duration. The primary outcome was the rate of exacerbation, and it was reduced by 47% (95% confidence interval [CI], 28 to 60) among members receiving intravenous mepolizumab and by 53% (95% CI, 36 to 65) among those receiving subcutaneous mepolizumab, as compared with those receiving placebo (P<0.001 for both comparisons). The members enrolled in this trial were 12 to 82 years of age.
    - Trial inclusion criteria required patients to have a history of 2 or more exacerbations requiring systemic corticosteroids in the previous year despite regular use of high-

dose ICS plus additional controller(s) with, or without, oral corticosteroids (OCS). Patients were required to have at least 1 of the following 4 prespecified criteria in the previous 12 months: blood eosinophil count ≥300 cells/mcL, sputum eosinophil count ≥3%, exhaled nitric oxide concentration ≥50 ppb, or deterioration of asthma control after ≤25% reduction in regular maintenance ICS/OCS.

IV. The FDA approval of mepolizumab (Nucala) in the setting of eosinophilic granulomatosis with polyangiitis was evaluated in a multicenter, double-blind, parallel-group, phase 3 trial. The two primary end points were the accrued weeks of remission over a 52-week period, according to categorical quantification, and the proportion of participants in remission at both week 36 and week 48. In the mepolizumab treatment arm, there was significantly more accrued weeks of remission than placebo (28% vs. 3% of the participants had ≥24 weeks of accrued remission; odds ratio, 5.91; 95% confidence interval [CI], 2.68 to 13.03; P<0.001) and a higher percentage of participants in remission at both week 36 and week 48 (32% vs. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; P<0.001). The members that were enrolled in this trial were at least 18 years of age.

V. The FDA approval of mepolizumab (Nucala) in the setting of hypereosinophilic syndrome was evaluated in a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial. Patients were randomized 1:1 to receive mepolizumab (Nucala) or placebo, plus an existing HES therapy. The primary endpoint evaluated the proportion of patients who experienced a flare during the 32-week study period compared to placebo, which was 28% compared to 56% (OR 0.28, 95% CI 0.12- 0.64, p=0.002). The patients enrolled in this trial were at least 12 years of age.

- Trial inclusion criteria required patients to have F1P1L1-PDGFRA-negative HES for at least 6 months, uncontrolled HES (defined as a history of at least 2 flares within the past 12 months and blood eosinophil count >1500 cells/µL and/or tissue eosinophilia), blood eosinophil count >1000 cells/µL, on stable background HES therapy (includes, but not limited to, oral corticosteroid [OCS], immunosuppressive, and/or cytotoxic therapy) for at least 4 weeks before randomization.
- HES flare defined as:
    i. An HES-related clinical manifestation, based on a physician-documented change in clinical signs or symptoms, necessitating an increase in the maintenance OCS dose >10 mg prednisone equivalent/day for 5 days OR an increase in/addition of any cytotoxic and/or immunosuppressive HES therapy.OR
    ii. Receipt of 2+ courses of blinded OCS during the treatment period

VI. The Global Initiative for Asthma (GINA) 2020 update recommends the addition of respiratory biologics, with respect to their allergic biomarkers after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 (medium dose ICS-LABA) or Step 5 (high dose ICS-LABA) therapy. Other controller options for Step 4 include high dose ICS-LABA, add-on tiotropium, or add-on leukotriene receptor antagonist (LTRA). Other controller options for Step 5 include add-on anti-IL5 or add-on low dose OCS, although guidelines note to consider side effects.

VII. Chronic rhinosinusitis (CRS) is defined as an inflammatory condition involving the paranasal sinuses and linings of the nasal passages, which persists for 12 weeks or longer per both the

American Academy of Allergy Asthma and Immunology (AAAA-I) and the American Academy of Otolaryngology-Head and Neck (AAO-HN) guidelines. The diagnosis requires at least two of four cardinal signs/symptoms (mucopurulent drainage, nasal obstruction, facial pain/pressure/fullness, and decreased sense of smell). Goals of therapy include control of mucosal inflammation and edema, maintenance of adequate sinus ventilation and drainage, treatment of colonizing or infection micro-organisms, if present, and reduction in the number of acute exacerbations. A significant proportion of patients also have nasal polyps (CRSwNP), roughly 25-30% of those with just CRS, and the standard of care includes intranasal corticosteroids, intranasal saline, oral corticosteroids in short burst therapy, and oral antibiotics if needed.

VIII. A total of 407 patients with CRSwNP were evaluated in one randomized, placebo-controlled, multicenter, 52-week treatment trial (SYNAPSE Study). Patients received mepolizumab (Nucala) 100 mg or placebo subcutaneously once every 4 weeks. Patients had recurrent and symptomatic CRSwNP and had at least one surgery for the removal of nasal polyps within the previous 10 years. Patients were required to have nasal obstruction symptoms with a visual analog scale (VAS) score of >5 out of a maximum score of 10. Patients were also required to have an endoscopic bilateral nasal polyp score (NPS) of ≥5 out of 8 with NPS ≥2 in each nasal cavity. Of the patients enrolled, 35% were female, 93% were White, with ages ranged from 18 to 82 years, a mean VAS score of 9 on a scale of 0-10, and a mean bilateral endoscopic NPS of 5.5 on a scale of 0-8. The co-primary endpoints were change from baseline to Week 52 in total endoscopic NPS (0 to 8 scale) as graded by independent blinded assessors and change from baseline in nasal obstruction VAS score (0 to 10 scale) during Weeks 49 to 52. The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52 in this trial.

IX. Patients who received mepolizumab (Nucala) 100 mg met a statistically significant improvement (decrease) in bilateral NPS at Week 52 and nasal obstruction VAS score from Weeks 49 to 52 at the end of the 52-week treatment period. See below table.

Scores (range)	Placebo n=201		Mepolizumab (Nucala) n=206		Mean Difference vs. Placebo (95% CI)
	Baseline Mean (SD)*	Mean Change (SE)◦	Baseline Mean (SD)*	Mean Change (SE)◦	
NPS (0-8)	5.6 (1.41)	0.06 (0.14)	5.4 (1.17)	-0.87 (0.14)	-0.93 (-1.31, -0.55)
Nasal obstruction VAS (0-10)	9.02 (0.83)	-2.54 (0.25)	8.92 (0.83)	-4.40 (0.25)	-1.86 (-2.53, 1.19)

* SD- standard deviation; ◦ SE- standard error

X. The AAAA-I, AAO-HN, and the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020, recommend intranasal corticosteroids to be continued and mepolizumab (Nucala) to be add-on therapy.

Investigational or Not Medically Necessary Uses

I. Mepolizumab (Nucala) has not been adequately studied for the following conditions and does not have established safety and efficacy in these populations:
   A. Non-severe, non-eosinophilic phenotype asthma

i. Mepolizumab (Nucala) has not been studied in members with non-severe, non-eosinophilic phenotype asthma; therefore, it would be considered investigational when Nucala is requested in that setting.

B. GPA (Wegener's granulomatosis) with polyangiitis and MPA (microscopic polyangiitis)
   i. Both GPA and MPA diagnoses were excluded in the phase 3 trial (A Study to Investigate Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis).

C. HES (hypereosinophilic syndrome) with F1P1L1-PDGFRα kinase-positive disease
   i. Mepolizumab (Nucala) has not been studied in members with F1P1L1-PDGFRα kinase-positive disease; therefore, it would be considered investigational when Nucala is requested in this setting.

References

1. Nucala [Prescribing Information]. Philadelphia, PA: GlaxoSmithKline LLC. Updated Sept 2020. Accessed Jan 2021.
2. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab Treatment in Members with Severe Eosinophilic Asthma. N Engl J Med 2014; 371:1198-1207. DOI: 10.1056/NEJMoa1403290.
3. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. N Engl J Med 2017; 376:1921-1932. DOI: 10.1056/NEJMoa1702079.
4. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2020 Update. Available from: http://www.ginasthma.org. Accessed January 2021.
5. Roufosse F, Kahn JE, Rothenberg ME, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2020;146(6):1397-1405. DOI: 10.1016/j.jaci.2020.08.037.
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7. American Academy of Otolaryngology- Head and Neck Surgery Adult Sinusitis Guidelines: Adult Sinusitis - Clinical Practice Guideline (aafp.org)
8. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020 Feb 20;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600. PMID: 32077450. https://epos2020.com/Documents/supplement_29.pdf
9. American Academy of Allergy Asthma and Immunology Rhinitis 2020 Clinical Update: Rhinitis 2020: A practice parameter update (aaaai.org)

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 40mg prefilled syringe	02/2022
Policy updated to reflect the new CRSwNP indication.	09/2021
Policy updated to reflect the new HES indication. Updated renewal length of authorization from 6 month to 12 months. Also added prescribed by or in consultation with a specialist requirement. For initial criteria: asthma: revised "severe eosinophilic asthma" verbiage to "asthma (severe)" in attempts to align with other respiratory biologic policies, revised verbiage for add-on maintenance treatment requirements to medium- to high-dose, or maximally tolerated ICS and one additional asthma controller medication OR maximally tolerated ICS/LABA combination, added requirement of continued use with background controller medications. For renewal criteria: removed criteria requirement confirming lack of toxicity to therapy; added "member has received a previous prior authorization approval for this agent through this health plan; AND member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise."; asthma: reformatted renewal criteria and added member exhibition	03/2021

of “stability” in addition to improvement of disease symptoms, added environmental triggers and continued background controller medications for asthma renewal criteria; EPGA: updated verbiage to “member has exhibited improvement or stability of disease symptoms”. For supporting evidence: for asthma, added trial inclusion criteria and GINA 2020 guideline recommendations.	
Policy updated to reflect the newly approved age expansion for SEA from members 12 years and older to 6 years or older. Also added leukotriene modifiers as an example of a controller medication per GINA guidelines. To the EGPA section, examples of an objective measure/tool were added to align with renewal criteria and changed classification criteria for eosinophils to > 10% per ACR classification.	10/2019
New Policy	06/2019

Policy Type: PA Pharmacy Coverage Policy: UMP205

Description

Metoclopramide (Gimoti) is nasally administered dopamine (D2) antagonist.

Length of Authorization

- Initial: Three months
- Renewal: Three months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
metoclopramide (Gimoti)	15 mg intranasal spray	Acute and recurrent diabetic gastroparesis	10 ml/28 days

Initial Evaluation

I. Metoclopramide (Gimoti) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is diagnosed with diabetic gastroparesis; **AND**
   C. Treatment with oral metoclopramide has been ineffective, contraindicated (e.g., member has inability to swallow), or not tolerated

II. Metoclopramide (Gimoti) is considered investigational when used for all other conditions, including but not limited to:
   A. Gastroparesis in nondiabetic patients
   B. Nausea and/or vomiting
   C. Chemotherapy-induced nausea and vomiting, prophylaxis
   D. Dyspepsia
   E. Migraine

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited initial improvement of disease symptoms [e.g., reduction in nausea, abdominal pain, bloating, or improvement in early satiety early satiety] **AND**

IV. Provider attests that member continues to have symptoms and benefit of repeated therapy outweighs the risks

Supporting Evidence

I. Per the American College of Gastroenterology, initial recommended pharmacological approaches to treatment should include prokinetic therapy with oral metoclopramide (cited as the first line agent).
II. The effectiveness of metoclopramide (Gimoti) has been established based on studies of oral metoclopramide.
III. Per FDA label, the use of metoclopramide (all dosage forms and routes of administration) for longer than 12 weeks should be avoided due to risk of developing tardive dyskinesia with long-term use.
IV. Per FDA label, metoclopramide (Gimoti) is not recommended as initial therapy in patients 65 years and older. Geriatric patients receiving an alternative metoclopramide product at a stable dosage of 10 mg four times daily can be switched to metoclopramide (Gimoti).
V. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for using metoclopramide (Gimoti) for indications other than for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis.
VI. Metoclopramide (Gimoti) was studied in three multicenter, randomized clinical trials. There is variance in the dose and outcomes studied, but clinically significant results defined by improvement in symptom severity from moderate to mild were seen in all clinical trials.
VII. Individual clinical trials of metoclopramide (Gimoti) are considered low quality due to open-label trial design, small sample sizes, and applicability concerns given underrepresentation of type 1 diabetic patients; however, the overall quality of the evidence is considered moderate at this time due to collection of data available through metoclopramide trials and metoclopramide (Gimoti) trials.
VIII. The safety profile of metoclopramide (Gimoti) is similar to that of metoclopramide tablets.

Investigational or Not Medically Necessary Uses

I. Metoclopramide (Gimoti) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
    A. Nondiabetic gastroparesis
    B. Nausea and/or vomiting
    C. Chemotherapy-induced nausea and vomiting, prophylaxis
    D. Dyspepsia
    E. Migraine

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP093

Description

Metreleptin (Myalept) is a leptin analog that binds to and activates the human leptin receptor as replacement therapy to treat generalized lipodystrophy due to congenital or acquired generalized lipodystrophy.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
metreleptin (Myalept)	11.3 mg powder (5 mg/mL) vial	Congenital Lipodystrophy; Acquired Generalized Lipodystrophy	60 mL/30 days

Initial Evaluation

I. Metreleptin (Myalept) may be considered medically necessary when the following criteria below are met:
   A. Member is one year of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. A diagnosis of **Congenital Lipodystrophy OR Acquired Generalize Lipodystrophy** when the following are met:
      1. Provider attests that the fasting leptin concentration at baseline is below the normal range; **AND**
      2. Member has a diagnosis of type 2 diabetes mellitus (T2DM) or insulin resistance; **AND**
      3. Member has a persistent hemoglobin A1c (HbA1c) > 7% despite dietary intervention and medication management (e.g., metformin) for T2DM; **AND**
      4. Member has a diagnosis of hypertriglyceridemia; **AND**
      5. Member has persistent triglyceride levels > 250 mg/dL despite dietary intervention and medication management for hypertriglyceridemia (e.g., fibrates, omega-3 fatty acids); **AND**
      6. Member does not have any hematologic abnormalities (e.g., leukopenia, neutropenia, bone marrow abnormalities, lymphadenopathy).

II. Metreleptin (Myalept) is considered investigational when used for all other conditions, including but not limited to:

A. Partial lipodystrophy
B. Localized lipodystrophy
C. Liver disease (e.g., nonalcoholic steatohepatitis [NASH])
D. Human Immunodeficiency Virus (HIV) – related lipodystrophy
E. Metabolic disease (e.g., T2DM, hypertriglyceridemia)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
II. The member is not continuing therapy based off established therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for continuation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms as defined by, a reduction from baseline for **one** of the following parameters:
    A. HbA1c
    B. Fasting glucose
    C. Triglycerides; **AND**
IV. Member does not have any hematologic abnormalities (e.g., leukopenia, neutropenia, bone marrow abnormalities, lymphadenopathy).

Supporting Evidence

I. Although the guideline states that there is no age limit for initiation of metreleptin (Myalept), and there were reported case studies where children as young as six months have been treated, the actual pediatric inclusion population in the FDA approval of metreleptin (Myalept) was 1 to 17 years of age.
II. According to the guideline (The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline), there is no defined serum leptin levels that have established to rule out the diagnosis of lipodystrophy. Therefore, specific lab values may not be very informative for the diagnosis of congenital or acquired generalized lipodystrophy.
III. Members with congenital or acquired generalized lipodystrophy and T2DM, metformin is a first-line agent for diabetes and insulin resistance, along with, other considerations for antihyperglycemia agents: insulin is effective for hyperglycemia, and thiazolidinediones, which should be used with caution in generalized lipodystrophy as their efficacy has not been established in that setting.
IV. Members with congenital or acquired generalized lipodystrophy and hypertriglyceridemia, fibrates and/or long-chain omega-3 fatty acids should be used for hypertriglyceridemia.
V. As part of the metreleptin (Myalept) Risk Evaluation and Mitigation Strategy (REMS) program, provider will need to evaluate members with acquired generalized lipodystrophy for significant hematologic abnormalities due to the reported risk of T-cell lymphoma in that population.

Investigational or Not Medically Necessary Uses

I. There is limited evidence to suggest the safety and efficacy of metreleptin (Myalept) outside of the FDA-approved indications of congenital or acquired generalized lipodystrophy. Additionally, the following indications listed below were denoted to have a "limitation of use" in the metreleptin (Myalept) package insert.
   A. Partial lipodystrophy
   B. Liver disease (e.g., nonalcoholic steatohepatitis [NASH])
   C. Human Immunodeficiency Virus (HIV) – related lipodystrophy
   D. Metabolic disease (e.g., T2DM, hypertriglyceridemia)

References

1. Myalept [Prescribing Information]. Cambridge, MA: Aegerion Pharmaceuticals, Inc. August 2015.
2. Brown RJ, Araujo-Vilar D, Cheung PT, et al. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. The Journal of Clinical Endocrinology & Metabolism, Volume 101, Issue 12, 1 December 2016, Pages 4500–4511. Available at: https://doi.org/10.1210/jc.2016-2466

Policy Implementation/Update:

Date Created	September 2014
Date Effective	September 2014
Last Updated	October 2019
Last Reviewed	10/2019

Action and Summary of Changes	Date
Criteria transitioned into policy with the following updates: addition of supporting evidence, addition of investigational section along with supporting evidence, inserted lab values for type 2 diabetes and hypertriglyceridemia, added sample language to the renewal section, and assess for stability parameters upon renewal.	10/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP201

Description

Metyrosine (Demser, generic) is an orally administered tyrosine hydroxylase inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
metyrosine (Demser, generic)	250 mg capsule	pheochromocytoma	480 capsules/30 days

Initial Evaluation

I. **Metyrosine** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. The request is for **generic** metyrosine; **OR**
      1. Treatment with **generic** metyrosine has been ineffective, not tolerated, or contraindicated; **AND**
   D. A diagnosis of **pheochromocytoma** when the following are met:
      1. Member has a surgical resection planned; **AND**
         i. Treatment with an alpha blocker (e.g., phenoxybenzamine, prazosin, terazosin, doxazosin) in combination with a beta blocker (e.g., propranolol, metoprolol, atenolol) was ineffective, contraindicated, or not tolerated; **OR**
      2. Member has a contraindication to surgery, or has malignant pheochromocytoma; **AND**
         i. Treatment with the following has been ineffective, contraindicated, or not tolerated:
            a. A selective alpha blocker (e.g., doxazosin, terazosin or prazosin); **AND**
            b. Generic phenoxybenzamine

II. Metyrosine is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Velocardiofacial syndrome-associated psychosis
   B. Bipolar disorder
   C. Schizophrenia
   D. Gilles de la Tourette's syndrome
   E. Sarcoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member requires long-term pharmacologic treatment following surgery or has malignant pheochromocytoma; **AND**
IV. Treatment with the following has been ineffective, contraindicated, or not tolerated:
    A. A selective alpha blocker (e.g., doxazosin, terazosin or prazosin); **AND**
    B. Generic phenoxybenzamine; **AND**
V. Member has exhibited improvement or stability of disease symptoms [e.g., hypertension, diaphoresis, headache, palpitations, tachycardia, syncope, anxiety] while on therapy; **AND**
VI. The request is for **generic** metyrosine; **OR**
    A. Treatment with **generic** metyrosine has been ineffective, not tolerated, or contraindicated

Supporting Evidence

I. Pheochromocytoma is a rare neuroendocrine tumor that hypersecrete one or more catecholamines (epinephrine, norepinephrine, and dopamine) and ff left untreated, cardiovascular morbidity and mortality are high. Once diagnosed, patients should undergo surgical resection of the pheochromocytoma following appropriate medical preparation. Preop medications are used for volume expansion and to control hypertension and preventing a hypertensive crisis during surgery. Patients with undiagnosed pheochromocytomas who undergo surgery for other reasons (and therefore have not undergone preoperative medical therapy), have an increased surgical mortality rate due to lethal hypertensive crises, malignant arrhythmias, and multiorgan failure. No randomized, controlled trials have compared the different approaches, and there is no universally accepted method of preparation for surgery in patients with pheochromocytoma.
II. Guidelines recommend preoperative combined alpha and beta blockade to prevent perioperative cardiovascular complications. Both selective (e.g. phenoxybenzamine) and non-selective (e.g. doxazosin, terazosin, prazosin) alpha-blockers have been used, there is insufficient evidence to recommend one over the other. After adequate alpha blockade has been achieved, beta blockade is initiated, which typically occurs two to three days preoperatively. Metyrosine can then be considered in patients who cannot be treated with the typical combined alpha and beta blockade protocol because of intolerance or cardiopulmonary reasons. Preoperative medical treatment is recommended for 7 to 14 days to allow adequate time to normalize blood pressure and heart rate.
III. Metyrosine is FDA approved for preoperative preparation of patients for surgery, management of patients when surgery is contraindicated, or chronic treatment of patients with malignant pheochromocytoma.
IV. The recommended initial dose of metyrosine for adults and children 12 years of age or older is 250 mg four times daily. Treatment is dosed based on clinical symptoms and catecholamine

excretion and may be increased by 250 to 500 mg every day to a maximum of 4.0 grams per day in divided doses.

V. There are no curative treatments for metastatic pheochromocytoma, unless the sites of disease are surgically resectable. Even in the metastatic setting standard treatment consists of surgery and palliative care. If all identifiable disease is resectable, including a limited number of distant metastases, surgery can provide occasional long-term remission. If disease is unresectable, surgical debulking will not improve survival; however, it is occasionally indicated for symptom relief. Per UptoDate, selective alpha-1-adrenergic blocking agents (e.g., prazosin, terazosin, or doxazosin) are utilized in many centers or are preferred to phenoxybenzamine when long-term pharmacologic treatment is indicated (e.g., for metastatic pheochromocytoma), due to their more favorable side-effect profiles and lower financial cost.

VI. Most patients with pheochromocytoma treated with metyrosine experience decreased frequency and severity of hypertensive attacks with their associated headache, nausea, sweating, and tachycardia.

VII. The maximum biochemical effect usually occurs within two to three days, and the urinary concentration of catecholamines and their metabolites usually returns to pretreatment levels within three to four days after treatment is discontinued. In some patients the total excretion of catecholamines and catecholamine metabolites may be lowered to normal or near normal levels (less than 10 mg/24 hours). In most patients, the duration of treatment has been two to eight weeks, but several patients have received metyrosine for periods of 1 to 10 years. Per the package insert, the total human experience with the drug is quite limited and few patients have been studied long term.

Investigational or Not Medically Necessary Uses

I. Metyrosine has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Velocardiofacial syndrome-associated psychosis
      i. Clinical evidence available is limited to case reports. There was a phase 2 trial (N=2) sponsored by Bausch Health (NCT01127503). However, results were not completed as the study was terminated due to enrollment, study-design and execution challenges.
   B. Bipolar disorder
      i. Ten patients with psychotic diseases were given metyrosine, up to 4 grams/day. Of the 7 patients with mania, 5 improved while receiving metyrosine and 3 continued to improve after the metyrosine was discontinued. All 3 patients who were being treated for depression became worse and later improved after the metyrosine was discontinued. Further evidence is needed to further evaluate and support this off label use in a space with several treatment options.
   C. Schizophrenia
      i. In a double-blind, crossover, placebo study severe schizophrenic symptoms could not be managed by metyrosine (2.75 grams/day). Use in this setting is not supported by available clinical evidence.
   D. Gilles de la Tourette's syndrome

i. Metyrosine in doses of 1750 to 3000 milligrams/day was not an effective treatment for Giles de la Gilles de la Tourette's syndrome. In only 2 out of 6 patients were movements greatly diminished with high doses of metyrosine. Use in this setting is not supported by available clinical evidence.

E. Sarcoma
   i. Combination therapy with a metyrosine derivative is subject of ongoing trials, currently recruiting, in this setting.

References

1. Demser [package insert]. Bridgewater, NJ. Valeant Pharmaceuticals International, Inc. December 2017
2. Uptodate. Treatment of pheochromocytoma in adults. Updated 11/25/2019
3. Uptodate. Paraganglioma and pheochromocytoma: Management of malignant disease. Updated 09/12/2019
4. Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915-1942.
5. PDQ® Adult Treatment Editorial Board. PDQ Pheochromocytoma and Paraganglioma Treatment. Bethesda, MD: National Cancer Institute. Updated 10/16/2020. Available at: https://www.cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq. [PMID: 26389312]
6. Metyrosine. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com.
7. Carandang CG, Scholten MC. Metyrosine in psychosis associated with 22q11.2 deletion syndrome: case report. J Child Adolesc Psychopharmacol. 2007;17(1):115-120.
8. Bausch Health Americas, Inc. Metyrosine (Demser®) for the Treatment of Psychotic Disorders in Patients with Velocardiofacial Syndrome. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01127503. NLM identifier: NCT01127503.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added step through generic metyrosine prior to branded Demser	03/2024
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP094

Description

Midostaurin (Rydapt) is an orally administered tyrosine kinase inhibitor (TKI) targeting FLT3 and KIT D816V receptors to induce cell apoptosis.

Length of Authorization

- Initial: Six months
- Renewal:
    i. AML: Cannot be renewed
    ii. Systemic mast cell disease: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
midostaurin (Rydapt)	25 mg capsule	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with cytarabine/daunorubicin induction and cytarabine consolidation	56 capsules/28 days
		Systemic mast cell disease: aggressive systemic mastocytosis, systemic mastocytosis with hematological neoplasm, mast cell leukemia	224 capsules/28 days

Initial Evaluation

I. Midostaurin (Rydapt) may be considered medically necessary when the following criteria below are met:
    A. Member is 18 years of age or older; **AND**
    B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
    C. A diagnosis of one of the following:
        1. **Acute myeloid leukemia (AML)**; **AND**
            i. The member has FLT3 mutation-positive AML; **AND**
            ii. Will be used in combination with standard cytarabine and daunorubicin induction AND cytarabine consolidate therapy; **AND**
            iii. Will not be used with any other oncolytic therapy outside of cytarabine and daunorubicin; **AND**
            iv. The member has received no prior therapy for AML; **OR**

2. **Systemic mast cell disease**; **AND**
    i. Systemic mast cell disease is characterized by one of the following: aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL); **AND**
    ii. Midostaurin (Rydapt) will not be used in combination with any other oncolytic medication.

II. Midostaurin (Rydapt) is considered investigational when used for all other conditions, including but not limited to:
    A. Pediatric leukemia
    B. Rectal cancer
    C. Acute myeloid leukemia in absence of FLT3 mutation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Midostaurin (Rydapt) is prescribed by, or in consultation with an oncologist; **AND**
    A. For **acute myeloid leukemia**:
        a. No renewal, one 6-month (initial) approval per lifetime.
    B. For **systemic mast cell disease**;
        a. Midostaurin (Rydapt) will not be used in combination with any other oncolytic medication; **AND**
        b. Clinical documentation of response to treatment, such as stabilization or improvement of disease, and absence of unacceptable toxicity from the medication.

Supporting Evidence

I. Midostaurin (Rydapt) was evaluated in three trials. Trial 1: in combination with chemotherapy in a randomized, double-blind, placebo-controlled trial in adults with FLT3-mutated AML. Subjects received 50 mg twice daily on days 8-21 for up to two cycles, followed by up to 12 months of midostaurin (Rydapt) therapy. Although evaluated for up to one year of therapy, the FDA-approval for midostaurin (Rydapt) indicates combination therapy with cytarabine and daunorubicin for two cycles of induction and four cycles of consolidation - for a complete total of six 28-day cycles. The primary outcome was overall survival (OS) which was statistically in favor of midostaurin (Rydapt) [HR 0.77; 95% CI 0.63-0.95, p=0.016]; however, OS data plateaued before reaching the median. Median survival could not be reliably estimated.
II. Midostaurin (Rydapt) has not been sufficiently evaluated for safety and/or efficacy in combination with any other oncolytic medication outside of cytarabine and daunorubicin in the setting of AML.

III. In Trial 2, midostaurin (Rydapt) was evaluated in a single-arm, open-label trial in ASM, SM-AHN, and MCL, collectively referred to as advanced SM. The trial included 116 adult subjects that had relapsed or progressed on or after 0-2 prior therapies. The primary outcome was complete remission (CR) plus incomplete remission (ICR) by six cycles via the Valent criteria for ASM and SM-AHN, with twenty-one percent of subjects meeting the primary endpoint (16-38%, depending on the specific type of SM). The median duration of CR+ICR was not reached at time of evaluation, and the median time to CR+ICR was 0.5 months.

IV. Trial 3 was a single-arm, open-label trial of 26 subjects with advanced SM. By Valent criteria, 10 achieved a response by two cycles that was sustained for at least eight weeks.

V. Midostaurin (Rydapt) is available in 25 mg capsules to be given as 50 mg twice daily on days 8-21 of each 28-day cycle for a total of six cycles in AML or, given as 100 mg twice daily continuously for SM.

Investigational or Not Medically Necessary Uses

I. The safety and efficacy of midostaurin (Rydapt) has not been sufficiently established in the following settings:
   A. Pediatric leukemia
   B. Rectal cancer
   C. Acute myeloid leukemia in absence of FLT3 mutation

References

1. Rydapt [Prescribing Information]. East Hanover, NJ. Novartis Pharmaceuticals Corporation. 2017.
2. Gotlib J., Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med. 2016. June 30;374(26): 2530-2541.
3. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 2.2020. Updated September 2019. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx
4. Stone RM, Mandrekar SJ, Sandfor BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017. Aug 3;377(5): 454-464.

Policy Implementation/Update:

Date Created	July 2017
Date Effective	August 2017
Last Updated	November 2019
Last Reviewed	November 2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy. Age requirement added. Clarification of appropriate line of therapy required for approval. Renewal allowance removed for AML and extended to six months for SM.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP096

Description

Migalastat (Galafold) is a pharmacologic chaperone that binds to and stabilizes specific mutant forms of alfa-galactosidase, thereby facilitating proper trafficking of the enzyme to lysosomes and increasing enzyme activity

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
migalastat (Galafold)	123 mg capsule	Fabry disease	15 capsules/30 days

Initial Evaluation

I. Migalastat (Galafold) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an endocrinologist or a specialist in genetics; **AND**
   C. Medication will not be used in combination with Enzyme Replacement Therapy (ERT); **AND**
   D. A diagnosis of **Fabry disease** when the following are met:
      1. Documentation of a confirmed diagnosis with mutation of alpha-galactosidase A (alpha-Gal A) gene; **AND**
      2. Documentation that member has a mutation in the gene encoding galactosidase alpha gene (GLA) resulting in a mutant protein that would respond to migalastat (Galafold) (i.e. member has an **amenable** GLA variant); **AND**
      3. Documentation of the member's baseline value of GL-3 inclusions per kidney interstitial capillary; **AND**
      4. Member does not have an eGFR <30 mL/minute/1.73 m2 OR ESRD requiring dialysis; **AND**
      5. Member is ERT-naïve and is not a candidate for ERT (due to contraindication, etc.); **OR**
      6. Member is ERT-experienced and not able to continue ERT therapy

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member has received a previous prior authorization approval for this agent; **AND**
III. Member does not have an eGFR <30 mL/minute/1.73 m2 OR ESRD requiring dialysis; **AND**
IV. Evidence of disease response with treatment as defined by a 50% reduction in GL-3 inclusions per kidney interstitial capillary compared to pre-treatment baseline; **AND**
V. Documentation by chart notes of disease stability or improvement in clinical symptoms

Supporting Evidence

I. Safety and efficacy of migalastat (Galafold) has not been established in pediatric patients.
II. Eligible patients in the pivotal study (Study 011) had either never received ERT or had not received ERT for at least 6 months. Efficacy and safety of migalastat (Galafold) in combination with ERT is currently in early clinical trial stages.
III. Migalastat is only suitable for people with specific amenable mutations. Only mutations for which migalastat produced substantial increases in enzyme activity were judged amenable. Migalastat does not work in people with non-amenable mutations. Patients with non-amenable GLA variants within the clinical study had no change from baseline in the primary endpoint of number of GL-3 inclusions per kidney interstitial capillary. Per the package insert, consultation with a clinical genetics professional is strongly recommended in cases where the amenable GLA variant is of uncertain clinical significance or may be benign (not causing Fabry disease). Refer to the table in the package insert listing specific GLA gene variants that are amenable to treatment with migalastat (Galafold) or listed within the following search tool found at: http://www.fabrygenevariantsearch.com. Additionally, Fabrazyme (ERT) can be used in all variants of Fabry disease for the treatment of both adults and children. Migalastat (Galafold) is only indicated in the subset of adult patients with a confirmed amenable GLA mutation.
IV. The primary endpoint in Galafold trials was the percentage of patients who had a response (≥50% reduction in the number of globotriaosylceramide inclusions per kidney interstitial capillary) at 6 months. Baseline values are needed as this was the outcome measured used in clinical trials to assess treatment effect.
V. Use of migalastat (Galafold) is not recommended in patients with severe renal impairment (eGFR <30 mL/minute/1.73 m2) or with ESRD requiring dialysis, these patients were excluded from clinical trials.
VI. Migalastat (Galafold) has not been demonstrated in clinical trials to have a clinically meaningful benefit in patients with Fabry disease relative to placebo. While one trial concluded it has "comparable" effects on renal function relative to ERT, "comparable" was not well defined and ERT also has limited evidence for efficacy in Fabry disease. The pivotal trial for migalastat (Galafold) failed to meet its primary endpoint and its outcome measure is of unknown significance as the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established. Though ERT therapy also assessed GL-3 inclusion reduction and provides low quality evidence, Fabrazyme is not specific to amendable variants and can be used in all variants of Fabry disease for the treatment of both adults and children.

References

1. Galafold [Prescribing Information]. Cranbury, NJ: Amicus Therapeutics; August 2018.
2. UpToDate, Inc. Fabry disease: Clinical features and diagnosis. UpToDate [Online Database]. Waltham, MA. Last updated July 13, 2018. Available from: http://uptodate.com/home/index.html. Accessed September 25, 2018.
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Policy Implementation/Update:

Date Created	September 2018
Date Effective	November 2018
Last Updated	November 2019
Last Reviewed	09/2019

Action and Summary of Changes	**Date**
Specified mutation needed to have a genetically confirmed diagnosis. Added requirement for agent to be prescribed by or in consultation with an endocrinologist or a specialist in genetics.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP135

Description
Miglustat (Zavesca) and eliglustat (Cerdelga) are orally administered glucosylceramide synthase inhibitors.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
miglustat (generic Zavesca)	100 mg capsules	Mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option	90 capsules/30 days
miglustat (Zavesca)	100 mg capsules		
eliglustat (Cerdelga)	84 mg capsules	Type 1 Gaucher disease; CYP2D6 extensive metabolizers (EMs) or intermediate metabolizers (IMs)	56 capsules/28 days
		Type 1 Gaucher disease; CYP2D6 poor metabolizers (PMs)	28 capsules/28 days

Initial Evaluation

I. Miglustat (Zavesca) or eliglustat (Cerdelga) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with a provider that specializes in the treatment of Gaucher disease (e.g., endocrinologist, geneticist, hematologist, etc.); **AND**
   C. Will not be used in combination with other medications used to treat type 1 Gaucher disease [e.g., imiglucerase (Cerezyme), taliglucerase (Elelyso), velaglucerase (Vpriv), other agents listed in this policy, etc.]; **AND**
   D. A diagnosis of **type 1 Gaucher disease** when the following are met:
      1. Diagnosis is confirmed by **one** of the following:
         i. Deficiency of glucocerebrosidase (acid β-glucosidase) enzyme activity in peripheral blood leukocytes or cultured fibroblasts; **OR**
         ii. Genetic testing confirming mutation in glucocerebrosidase (*GBA*) gene; **AND**

2. The request is for generic miglustat or brand miglustat (Zavesca); **AND**
    i. Treatment with **ONE** enzyme replacement therapy (ERT) [e.g., imiglucerase (Cerezyme), taliglucerase (Elelyso), velaglucerase (Vpriv)] has been ineffective, contraindicated, or not tolerated; **AND**
    ii. If the request is for brand miglustat (Zavesca), the member has an intolerance or contraindication to generic miglustat; **OR**
3. The request is for eliglustat (Cerdelga); **AND**
    i. The member has undergone CYP2D6 genotyping by an FDA-cleared test and is classified as one of the following: [Note: eliglustat (Cerdelga) is not indicated for ultra-rapid metabolizers]
        a. Poor Metabolizer (PM); **OR**
        b. Intermediate Metabolizer (IM); **OR**
        c. Extensive Metabolizer

II. Miglustat (Zavesca) and/or eliglustat (Cerdelga) are considered investigational when used for all other conditions, including but not limited to:
    A. Type 3 Gaucher disease
    B. Gangliosidases (GM1 and GM2)
    C. Cystic Fibrosis
    D. Pompe Disease
    E. HIV Infection
    F. Niemann-Pick Disease
    G. Tay-Sachs Disease
    H. Sandhoff Disease

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Miglustat (Zavesca) or eliglustat (Cerdelga) will not be used in combination with other medications used for the treatment of type 1 Gaucher disease (i.e. will be used as monotherapy); **AND**
IV. Member has exhibited improvement or stability of disease manifestations [e.g., improvements in mean liver volume and/or spleen volumes, changes in hemoglobin levels and platelet count, etc.] and/or symptoms [e.g., fatigue, bleeding episodes, bruising, bone pain, etc.]

Supporting Evidence

I. Miglustat (Zavesca) obtained FDA approval for treatment of type 1 Gaucher disease in 2003 based on the result of two open-label, uncontrolled studies and one randomized, open-label, active-controlled study. In the uncontrolled open-label trials, patients experienced a significant mean reduction in liver and spleen volume from baseline and non-significant change in platelet counts and hemoglobin concentration. These results were maintained or further decreased during the extension period of both trials. In the randomized, active-controlled study, patients were randomized to receive miglustat (Zavesca) alone, imiglucerase (Cerezyme) alone, or miglustat (Zavesca) in combination with imiglucerase (Cerezyme). There were no significant differences between the groups for mean absolute changes in liver and spleen volume and hemoglobin concentration. However, there was a significant reduction in platelet counts between the miglustat (Zavesca) and imiglucerase (Cerezyme) monotherapy groups. During the open-label extension period, all patients were transitioned to miglustat (Zavesca) monotherapy and no significant changes liver volume, spleen volume, or hemoglobin concentration were observed.

II. Eliglustat (Cerdelga) obtained FDA approval for treatment of type 1 Gaucher disease under priority review in 2014 based on the results of one randomized, double-blind, placebo-controlled study in treatment naïve patients and one randomized, open-label, active-controlled, non-inferiority study in patients transitioning from enzyme replacement therapy.

III. A randomized, double-blind, placebo-controlled trial investigated eliglustat (Cerdelga) against placebo in type 1 Gaucher disease treatment naive patients. The results showed a statistically significant improvement in percentage change in spleen volume and liver volume, absolute change in hemoglobin level, and percentage change in platelet count from baseline to nine months compared to placebo. During the open label extension phase, improvements in spleen and liver volume, hemoglobin level, and platelet count continued through the two-year trial duration and through four years in a separate uncontrolled trial.

IV. A randomized, open-label, active-controlled, non-inferiority study evaluated eliglustat (Cerdelga) versus imiglucerase in patients who were previously treated with enzyme replacement therapy. The primary composite endpoint required stability in all four component domains (hemoglobin level, platelet count, liver volume and spleen volume) based on changes between baseline and 12 months according to pre-specified thresholds of change. Eliglustat (Cerdelga) met the criteria to be declared non-inferior to imiglucerase in maintaining patient stability. During the open-label extension phase, patients continued to show stability, as previously defined in the initial 12 months of the trial, at two years of treatment.

V. Patients enrolled in the studies for miglustat (Zavesca) and eliglustat (Cerdelga) were 18 and older. The safety and/or efficacy of use in pediatric and adolescent patients has not been evaluated.

VI. Miglustat (Zavesca) and eliglustat (Cerdelga) have largely been studied as monotherapy, with the exception of one treatment arm in a single study involving miglustat (Zavesca). Long-term safety and efficacy of either agent used in combination with enzyme replacement therapy, or other agents used to treat type 1 Gaucher disease has not been evaluated.

VII. Gaucher disease is a rare autosomal recessive lysosomal storage disorder (LCD) that is caused by mutations in the glucocerebrosidase enzyme (*GBA*) and/or deficiency of the enzyme glucocerebrosidase. Diagnosis of Gaucher disease type 1 should be confirmed by a physician

specializing in the treatment of Gaucher disease via blood tests to confirm deficiency of the glucocerebrosidase enzyme (acid β-glucosidase) in peripheral leukocytes or cultured fibroblasts or genetic testing to confirm mutation in *GBA* prior. Treatment is not necessary for all patients with Gaucher disease type 1, as some patients are asymptomatic. However, treatment is generally lifelong for symptomatic patients once treatment is initiated.

VIII. According to recent guidelines, treatment with enzyme replacement therapy (ERT) remains first-line treatment for type 1 Gaucher disease and is delivered intravenously. Miglustat (Zavesca) is a second line oral treatment indicated when ERT is no longer accepted by the patient or cannot be tolerated. Eliglustat (Cerdelga) may be used as a first-line treatment alternative to ERT.

IX. Miglustat (Zavesca) is commonly discontinued due to adverse effects including diarrhea (observed in over 85% of patients during clinical trials), weight loss (~65%), tremor and peripheral neuropathy. Eliglustat (Cerdelga) is generally better tolerated with the most common adverse events comprising of arthralgia (45%), back pain (12%), fatigue (14%) and headache (13 to 40%).

X. Miglustat (Zavesca) is contraindicated in women who are or may become pregnant. Providers should discuss the risks of teratogenicity when administered to women of reproductive potential.

XI. Eliglustat (Cerdelga) was found to be heavily affected by a patient's CYP2D6 metabolizer status and therefore requires CYP2D6 genotyping before prescribing. Recommended dosing differs between poor metabolizers and intermediate/extensive metabolizers. Eliglustat (Cerdelga) is not recommended for ultra-rapid metabolizers due to difficulty obtaining reliable blood levels of the drug. Concurrent use of strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, quinidine, etc.) is not recommended and these agents should be discontinued prior to initiating therapy with eliglustat (Cerdelga).

Investigational or Not Medically Necessary Uses

I. Miglustat (Zavesca) and/or eliglustat (Cerdelga) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Type 3 Gaucher disease
   B. Gangliosidases (GM1 and GM2)
   C. Cystic Fibrosis
   D. Pompe Disease
   E. HIV Infection
   F. Niemann-Pick Disease
   G. Tay-Sachs Disease
   H. Sandhoff Disease

References

1. Stirnemann J, Belmatoug N, Camou F, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. *Int. J. Mol. Sci.* 2017, 18, 441; doi: 10.3390/ijms18020441
2. Gary SE, Ryan E, et al. Recent advances in the diagnosis and management of Gaucher disease. *Expert Rev Endocrinol Metab*. 2018 March; 13(2):107-118. Doi:10.1080/17446651.2018.1445524.

3. Wang RY, Bodamer OA, et al. Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals. ACMG Standards and Guidelines. *Genetics in Medicine*. 2011 May; 13(5).
4. Miglustat [Prescribing Information]. Actelion Pharmaceuticals US, Inc.: South San Francisco, CA. November 2017.
5. Eliglustat [Prescribing Information]. Genzyme Ireland, Ltd.: Waterford, Ireland. August 2018.

Policy Implementation/Update:

Action and Summary of Changes	Date
Transitioned criteria to new policy format and combined previous miglustat and eliglustat criteria into one policy and added the following requirements: age 18 and older, prescribed by or in consultation with specialist, used as monotherapy and diagnosis confirmed by genetic and/or blood testing	11/2020
Miglustat (Zavesca) criteria created	05/2018
Eliglustat (Cerdelga) criteria created	11/2014

Policy Type: QE Pharmacy Coverage Policy: UMP160

Description
Migraine abortive therapies, or acute treatments, include triptans, CGRP antagonists, and lasmiditan (Reyvow) which is a selective serotonin agonist.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Quantity Limit	Quantity Exception
almotriptan	6.25 mg tablet	9 tablets/30 days	20 tablets/30 days
	12.5 mg tablet	12 tablets/30 days	20 tablets/30 days
almotriptan (Axert)	12.5 mg tablet	12 tablets/30 days	20 tablets/30 days
eletriptan	20 mg tablet	9 tablets/30 days	20 tablets/30 days
	40 mg tablet		
eletriptan (Relpax)	20 mg tablet	9 tablets/30 days	20 tablets/30 days
	40 mg tablet		
frovatriptan	2.5 mg tablet	10 tablets/30 days	30 tablets/30 days
frovatriptan (Frova)	2.5 mg tablet	10 tablets/30 days	30 tablets/30 days
naratriptan	1 mg tablet	9 tablets/30 days	20 tablets/30 days
	2.5 mg tablet		
naratriptan (Amerge)	1 mg tablet	9 tablets/30 days	20 tablets/30 days
	2.5 mg tablet		
rizatriptan	5 mg tablet	12 tablets/30 days	30 tablets/30 days
	5 mg ODT		
	10 mg tablet		
	10 mg ODT		
rizatriptan (Maxalt)	5 mg tablet	12 tablets/30 days	30 tablets/30 days
	10 mg tablet		
rizatriptan (Maxalt-MLT)	10 mg tablet	12 tablets/30 days	30 tablets/30 days
sumatriptan (oral)	25 mg tablet	9 tablets/30 days	20 tablets/30 days
	50 mg tablet		
	100 mg tablet		
sumatriptan (Imitrex) (oral)	25 mg tablet	9 tablets/30 days	20 tablets/30 days
	50 mg tablet		
	100 mg tablet		
sumatriptan/ naproxen (oral)	85-500 mg tablet	9 tablets/30 days	20 tablets/30 days
sumatriptan/	85-500 mg tablet	9 tablets/30 days	20 tablets/30 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

naproxen (Treximet) (oral)			
sumatriptan (nasal)	5 mg spray	6 doses (1 box)/30 days	18 doses (3 boxes)/30 days
	20 mg spray		
sumatriptan (Imitrex) (nasal)	5 mg spray	6 doses (1 box)/30 days	18 doses (3 boxes)/30 days
	20 mg spray		
sumatriptan (Onzetra Xsail) (nasal)	11 mg powder	16 nosepieces (1 kit/8 doses)/30 days	32 nosepieces (2 kits/16 doses)/30 days
sumatriptan (Tosymra) (nasal)	10 mg spray	6 doses (1 box)/30 days	18 doses (3 boxes)/30 days
sumatriptan (SQ)	4 mg/0.5 mL	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
	6 mg/0.5mL		
sumatriptan (Imitrex) (SQ)	4 mg/0.5 mL Kit	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
	6 mg/0.5 mL solution		
sumatriptan (Imitrex Statdose) (SQ)	4 mg/0.5 mL solution	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
	6 mg/0.5 mL refill		
	6mg/0.5 ML system		
sumatriptan (Zembrace Symtouch) (SQ)	3 mg/0.5 mL solution	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
zolmitriptan (oral)	2.5 mg tablet	9 tablets/30 days	20 tablets/30 days
	5 mg tablet		
	2.5 mg ODT		
	5 mg ODT		
zolmitriptan (Zomig/ZMT) (oral)	2.5 mg tablet	9 tablets/30 days	20 tablets/30 days
	5mg tablet		
	2.5 mg ODT		
	5 mg ODT		
zolmitriptan (Zomig) (nasal)	2.5 mg spray	6 doses/30 days	18 doses (3 boxes)/30 days
	5 mg spray		
lasmiditan (Reyvow)	50 mg tablet	4 tablets/30 days	8 tablets/30 days
	100 mg tablet	8 tablets/30 days	16 tablets/30 days
ubrogepant (Ubrelvy)	50 mg tablet	8 tablets/30 days	16 tablets/30 days
	100 mg tablet	16 tablets/30 days	32 tablets/30 days
celecoxib (Elyxyb)	120 MG/4.8ML oral solution	43.2 mL (9 doses)/30 days	56.4 mL (18 doses)/30 days
diclofenac potassium (Cambia)	50 mg packet	9 packets/30 days	18 packets/30 days
zavegepant (Zavzpret) (nasal)	10mg spray	6 doses/30 days	12 doses/30 days

Initial Evaluation

I. A quantity exception may be considered medically necessary when the following criteria below are met:

A. Member has tried and failed prophylactic therapy with at least one agent listed in EACH of the three groups (these specific agents required). Please note, if a group is contraindicated, a trial and failure of three remaining agent is required:
    1. Group 1: propranolol, metoprolol, atenolol, timolol, nadolol
    2. Group 2: amitriptyline, venlafaxine
    3. Group 3: topiramate, sodium valproate, divalproex sodium; **AND**
B. The member has tried each of the prophylactic therapies for at least three months, or did not tolerate therapy with an adequate trial; **AND**
C. Provider attestation that medication overuse headache has been ruled out as the cause or contributor to the member's migraines.

II. Triptans, lasmiditan (Reyvow), and ubrogepant (Ubrelvy) are considered investigational when used for all other conditions, including but not limited to:
    A. Migraine prophylaxis

Renewal Evaluation

I. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in migraine symptom severity, duration, etc.) with the quantity previously allowed; **AND**
II. Provider attestation that the member is being monitored for medication overuse headache and the requested therapy is not causing or adding to medication overuse headache; **AND**
III. Provider attestation that the member is still in need of the quantity being requested and the member stockpiling is not occurring.

Supporting Evidence

I. This policy aims to ensure appropriate use of prescription abortive migraine therapies, limit overuse, occurrence of rebound headache, and direct members to migraine prevention therapy when appropriate.
II. Triptans have an established safety and efficacy profile for the abortive treatment of migraine; however, overuse of these therapies may result in exacerbation of migraine (i.e., medication overuse headache). Medication overuse headache (MOH) may occur with other therapies for abortive migraine treatment including, but not limited to: acetaminophen, NSAIDS, opioids, and ergot derivatives. After lifestyle modifications, non-pharmacologic therapies, and avoidance of triggers have been employed, pharmacologic therapy may be necessary. Triptans are the mainstay of therapy and are recommended as first-line treatment by governing bodies and treatment guidelines such as American Academy of Neurology, American Family Physician, and American Headache Society. Avoidance of MOH may be employed by using triptans less than two days per week on average, and package inserts for many triptan therapies recommend using less than 10 days per month. Prior to use of this frequency of triptans, prophylactic therapy for prevention of migraine may be warranted. Triptans are not indicated for the continual prophylactic treatment of migraine.
III. As of March 2020, MOH had not been noted for CGRP-antagonists or ubrogepant (Ubrelvy); however, long term safety data in treating more than 15 or eight migraines per month,

respectively, has not been evaluated. These therapies are not indicated for prevention of migraine. For ubrogepant (Ubrelvy) the daily maximum dose is 200 mg.

IV. Lasmiditan (Reyvow) has warnings for MOH in the prescribing information. The label indicates treatment of more than four migraine days per months has not been evaluated and treating 10 or more migraines per month with this or other abortive migraine therapies may contribute to worsening of migraines. The daily maximum dose is 200 mg per day.

V. The agents listed in the policy are recommended by guidelines with Level A and B recommendations (i.e., efficacious or probably efficacious). There is no available evidence, or evidence to suggest against, use of any other agent not in the list above (e.g., gabapentin, nortriptyline, calcium channel blockers, SSRIs). These agents should not be considered for an adequate trial of prophylactic therapy given the negative or no evidence.

VI. Guidelines label a "treatment success" with prophylactic therapy as a 50% reduction in migraine after three months. Additionally, some agents take one-to-three months to show efficacy. If the prophylactic therapy has not been trialed for three months, the trial is not considered adequate for prophylactic efficacy; however, many migraine sufferers are unable to tolerate the recommended prophylactic therapies.

VII. The quantity limits are based on maximum daily dose, as recommended per the FDA, as well as treating with migraine therapies ten or less days per month, package size considerations as well as safety of therapies contained in this policy.

Investigational or Not Medically Necessary Uses

I. Triptans, lasmiditan (Reyvow), and ubrogepant (Ubrelvy) have not been FDA-approved, or sufficiently studied for safety and efficacy for migraine prophylaxis.

References

1. Oregon Health & Sciences University (OHSU). Drug Class Review on Triptans Final Report Update 3. November 2005
2. Eras M., Gursoy AE., Prophylactic treatment of migraine. Noro Psikiyatr Ars. 2013;50(1):30-35.
3. Miller S. The acute and preventative treatment of episodic migraine. Ann Indian Acad Neurol. 2012;15(1):33-39.
4. Modi S., Lowder D. Medications for migraine prophylaxis. Am Fam Physician.2006;73(1):72-78.
5. Silberstein S., Tfelt-Hansen P., Dodick DW., et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia. 2008;28:484-495.
6. Lenz R., Bonafede M., Maiese B., et al. Prophylaxis and acute medication treatment patters in migraine patient initiating migraine prophylactic therapy. Amer Acad Neurol. 2016;86(1):206.
7. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. Headache. 2015;55(1):3-20.
8. Gilmore G., Geffen D., Michael M., et al. Treatment of acute migraine headaches. Am Fam Physician. 2011;83(3):271-280.
9. Ubrelvy [Prescribing Information]. Allergan. Madison, NJ. 2019.
10. Reyvow [Prescribing Information]. Eli Lilly. Indianapolis, IN. 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated wording on sumatriptan (Onzetra Xsail) (nasal) quantity limit for clarity	01/2024
Added zavegepant (Zavzpret) nasal spray and respective quantity limits	06/2023
Added in celecoxib (Elyxyb) oral solution and Cambia oral packets and respective quantity limits	12/2021
Removed Nurtec from current policy as this was moved to Aimovig, Emgality, Ajovy/CGRP policy instead	04/2021

Corrected quantity limit for Nurtec to reflect manufacturer guidance and allowance of 8/30 or 16/30	07/2020
New FDA-approved migraine therapies added to policy: lasmiditan (Reyvow), ubrogepant (Ubrelvy), rimegepant (Nurtec ODT).	04/2020
Prior authorization criteria transitioned to policy format. Addition of requirement to rule out medication overuse headache, inclusion of new agents and removal of obsolete products.	12/2019
Update to delete step therapy questions to align with current processes, created tables for QLL, changed question on prophylactic therapy options to fit with current evidence and guidelines, added duration of therapy question to ensure appropriate trial of prophylactic therapy, updated agent chart.	05/2018
Updated with clinical note regarding pediatric strength of Treximet.	10/2016
Updated with Onzentra Xsail.	05/2016
Reviewed and Updated: validated and updated product availability and quantity limit lists. Criteria updated to include trial of three therapeutic categories, removal of questions on daily triptan use and specialty provider.	01/2016
Previous Reviews	08/2014, 01/2013, 08/2012, 04/2012
Policy created	09/2011

Policy Type: PA/SP Pharmacy Coverage Policy: UMP097

Description

Miltefosine (Impavido) is an orally administered antileishmanial medication that induces apoptosis-like cell death and stops the growth of specific *Leishmania* species.

Length of Authorization

- Initial: 28 days
- Renewal: No renewal

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
miltefosine (Impavido)	50 mg capsules	Visceral leishmaniasis Cutaneous leishmaniasis Mucosal leishmaniasis	30 to 44 kg: 56 capsules/28 days OR ≥ 45 kg: 84 capsules/28ays

Initial Evaluation

I. Miltefosine (Impavido) may be considered medically necessary when the following criteria below are met:
   A. Member is 12 years of age or older; **AND**
   B. Member weighs at least 30 kg (66 lbs); **AND**
   C. Medication is prescribed by, or in consultation with an infectious disease specialist; **AND**
   D. A diagnosis of one of the following:
      1. Visceral leishmaniasis due to *Leishmania donovani*; **OR**
      2. Cutaneous leishmaniasis due to the following: *Leishmania braziliensis, Leishmania guyanensis,* or *Leishmania panamensis*; **OR**
      3. Mucosal leishmaniasis due to *Leishmania braziliensis*; **AND**
   E. Laboratory confirmation of leishmaniasis species were identified following **ONE** of the recommended tests provided by the Centers for Disease Control and Prevention (CDC) listed here:
      1. Stained slides (using tissue from biopsy specimens, impression smears or dermal scrapings)
      2. Culture medium
      3. Polymerase chain reaction (PCR)
      4. Serologic testing (e.g., rK39 Rapid Test); **AND**
   F. For the diagnosis of visceral leishmaniasis, treatment with liposomal amphotericin B (Ambisome) has been ineffective, contraindicated, or not tolerated.

II. Miltefosine (Impavido) is considered not medically necessary when criteria above are not met and/or when used for:
    A. The treatment of leishmaniasis outside of the visceral/cutaneous/mucosal settings, and not due to the species associated with visceral/cutaneous/mucosal leishmaniasis.

Supporting Evidence

I. Miltefosine (Impavido) is FDA-approved in the adolescents and adults ≥ 12 years and older weighing ≥ 30 kg (66lbs).
II. For the treatment of visceral leishmaniasis, the safety and efficacy was studied in one randomized, open-label, active-controlled (amphotericin B) trial in Bihar, India. The final cure rates for miltefosine (Impavido) and amphotericin B were 94% and 97%, respectively. Final cure was defined as initial cure at end of therapy plus absence of signs and symptoms of visceral leishmaniasis at six months follow up.
III. For the treatment of cutaneous leishmaniasis, the safety and efficacy was studied in a placebo controlled study in Colombia, Guatemala and Brazil. The finally cure rates at 95% CI with P-value <0.0001 were reported:
    A. Colombia: 82% miltefosine (Impavido) vs 30% placebo
    B. Guatemala: 48% miltefosine (Impavido) vs 20% placebo
    C. Brazil: 76.3% miltefosine (Impavido), placebo was not reported.
IV. For the treatment of mucosal leishmaniasis, the safety and efficacy was studied in a single-arm study in Bolivia that included 79 patients. At the end of therapy, reported at 12 months, 49 patients (62%) had complete resolution of edema, erythema, infiltration, and erosion from the involved mucosal sites.
V. The CDC has specific guidelines for leishmaniasis confirmation test. They can be found here: https://www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_diagnosis_guide_leishmaniasis_2016.pdf.

Investigational or Not Medically Necessary Uses

I. The treatment of leishmaniasis outside of the visceral/cutaneous/mucosal settings, and not due to the species associated with visceral/cutaneous/mucosal leishmaniasis.
    A. There is limited evidence to suggest the safety and efficacy of miltefosine (Impavido) outside of the FDA approved leishmaniasis settings and the specific species accordingly.

References

1. Impavido [Prescribing Information]. Wilmington, DE: Paladin Therapeutics, Inc. March 2014.
2. Centers for Disease Control and Prevention. Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Disease Society (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). October 2018. Available at: https://www.cdc.gov/parasites/leishmaniasis/health_professionals/index.html#dx

Policy Implementation/Update:

Date Created	April 2016
Date Effective	August 2016
Last Updated	October 2019
Last Reviewed	4/2016, 10/2019

Action and Summary of Changes	Date
Transitioned criteria into policy with the following additions: supporting evidence, investigational section and CDC diagnostic recommendations.	10/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP255

Description

Mitapivat (Pyrukynd) is an orally administered pyruvate kinase activator.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
mitapivat (Pyrukynd)	Hemolytic anemia in patients with pyruvate kinase deficiency	5 mg tablets	56 tablets/28 days
		20 mg tablets	
		50 mg tablets	
		5 mg tablet taper pack	7 tablets/7 days*
		20 mg and 5 mg taper pack	14 tablets/14 days*
		50 mg and 20 mg taper pack	14 tablets/14 days*

**In patients established on treatment and are discontinuing treatment, one fill of one of the taper packs will be allowed.*

Initial Evaluation

I. **Mitapivat (Pyrukynd)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by a hematologist; **AND**
   C. A diagnosis of **pyruvate kinase deficiency (PKD)** when the following are met:
      1. Provider attestation to all of the following;
         i. Diagnosis is confirmed via genetic testing (documentation of results required); **AND**
         ii. Presence of two mutant alleles in the PKLR gene; **AND**
         iii. At least one missense mutation (i.e., presence of two non-missense mutations does not qualify for therapy); **AND**
         iv. Member is NOT homozygous for the R479H mutation; **AND**
      2. Hemoglobin level is less than 10 mg/dL, measured within the past three months; **AND**
      3. Documentation of baseline hemoglobin level (for renewal assessment); **AND**
      4. Member has symptoms of hemolytic anemia (e.g., fatigue, weakness, dizziness, jaundice) that negatively impact quality of life; **AND**
      5. The member has been regularly transfused or transfusion-dependent for at least 12 months (e.g., five or more blood transfusions over the past year); **OR**

i. The member is unable to tolerate blood transfusions and/or is not a candidate for blood transfusions. Documentation of rationale required.

II. Mitapivat (Pyrukynd) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Patients with pyruvate kinase deficiency that have two non-missense mutations or are homozygous for R479H mutation.
   B. Hemolytic anemia in patients with PKD that do not have symptoms or symptoms severe enough to impact quality of life.

III. Mitapivat (Pyrukynd) is considered investigational when used for all other conditions, including but not limited to:
   A. Pediatric patients with PKD
   B. Sickle cell disease
   C. Thalassemia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation that hemoglobin level (measured within the past three months) has increased compared to baseline; **AND**
IV. Documentation that the member's symptoms have improved compared to baseline.

Supporting Evidence

I. Mitapivat (Pyrukynd) is a pyruvate kinase (PK) activator for hemolytic anemia in adults with PKD. Safety and efficacy have not been established in pediatrics, but ongoing clinical trials are evaluating. Evidence for use is limited to a small adult-only population; it is unknown if the results are applicable to pediatrics. Pediatrics utilizing mitapivat (Pyrukynd) are best monitored under a clinical trial setting until therapy is FDA-approved for patients under the age of 18.
II. Individuals with PKD have two PKLR gene mutations, either homozygous for a single mutation or compound heterozygotes for two different mutations. Individuals with one mutation are generally not affected by PKD symptoms and do not require treatment. Mitapivat (Pyrukynd) has not been evaluated and has unknown clinical value in this population.
III. Diagnostics for PKD include biochemical measurement of red blood cell PK activity, and genetic testing. PKD is rare and may be misdiagnosed. Additionally, in clinical trials patients homozygous for R479H or those with two non-missense mutations did not respond to treatment. Thus, genetic testing is required to determine appropriate diagnosis with responsive mutations prior to coverage consideration. Agios Pharmaceuticals Inc. offers a complimentary genetic test.

Biochemical testing (e.g., PK activity, etc.) is insufficient to determine a diagnosis of PKD, and does not provide present mutations. Given the genetic, symptomatic, and management complexities of this condition, prescription by a specialist provider is required.

IV. PKD management is based on symptom severity, which varies between patients even when Hb levels are comparable. When patients are experiencing symptoms that impact quality of life (QOL), supportive management/treatment may be warranted. Management strategies include:
- Blood transfusions, often coupled with iron chelation therapy to prevent iron overload.
- Splenectomy, which may reduce transfusion burden and improve symptoms; however, is not curative. Optimal timing of splenectomy is between 5-18 years of age given risks.
- Folic acid may be administered in those with a deficiency.

V. The National Cancer Institute classified anemia into five grades: Grade 1 (mild): hemoglobin (Hb) of 10 g/dL to the lower limit of normal for member age and gender, Grade 2 (moderate): Hb between 8-10 g/dL, Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 is death. Mitapivat (Pyrukynd) was evaluated in patients with a Hb of 10 g/dL or less (i.e., at least moderate anemia), and this is the patient population expected to have symptoms that negatively impact QOL. Unmanaged patients with Hb above 10 g/dL are near normal levels and unlikely require treatment. A Hb level measured within the past three months is required to ensure treatment is appropriate. Documentation of baseline Hb is required upon initiation to determine objective therapeutic effect upon renewal. Not all patients in clinical trials responded to treatment. Additionally, documented symptom response is required given that PKD is managed/treated on the basis of symptoms and not target Hb levels, especially as positive long-term impact on the disease has not been demonstrated for this therapy. In absence of patient-reported symptom improvement, use of mitapivat (Pyrukynd) should not be continued.

VI. Mitapivat (Pyrukynd) was evaluated in two Phase 3 trials. Objective hematopoiesis measures and subjective patient reported outcomes (PROs) were evaluated. The Pyruvate Kinase Deficiency Diary (PKDD) and the Pyruvate Kinase Deficiency Impact assessment (PKDIA) measure daily signs of symptoms of PKD and impact on daily social and physical activities, respectively. Meaningful changes are predicted to be 5-8 points for PKDD and 6-10 points for PKDIA.
- ACTIVATE-T: Single-arm trial, over 24 weeks in regularly transfused patients (≥ 6/year). Baseline Hb: 9.1 g/dL. Outcomes: proportion of patients with transfusion response (33% reduction in transfusion burden), transfusion-free patients, and those achieving a normal Hb. Nine patients (33%) met transfusion response, 6 (22%) became transfusion-free, and 3 (11%) achieved normal Hb levels. Although not powered or evaluated for significance, the average PKDD average score decreased by -2.4 points (baseline was 51.9), and the PKDIA score decreased by -9.1 on average (baseline 52.6).
- ACTIVATE: An open-label, placebo-controlled trial over 12 weeks in patients not regularly transfused (≤ 4/year). Baseline Hb was 8.5-8.6 g/dL. Outcomes: Hb response (Hb change of ≥ 1.5 g/dL), and PROs. Hb response was seen in 16 (40%) of patients on mitapivat (Pyrukynd) vs. no patients in the placebo group, and the average change in Hb was +1.7 g/dL compared to -0.1 g/dL for the placebo group, both of which were statistically and clinically significant. The PKDD score at week 24 had decreased by 5.16 points on average compared to baseline for mitapivat (Pyrukynd) which was statistically significant over placebo. The PKDIA scores reached statistical superiority over placebo but did not meet clinically relevant thresholds.

VII. In ACTIVATE, serious adverse events (AE) occurred in 10% of patients on mitapivat (Pyrukynd), including atrial fibrillation, gastroenteritis, rib fracture, musculoskeletal pain. Common AE that occurred in at least 5% of patients and higher than placebo included decrease estrone (56%) and decreased estradiol (12%) in males only, increased urate, back pain, arthralgia, dyslipidemia, gastroenteritis, hot flush, oropharyngeal pain, hypertension, arrhythmia, breast discomfort, constipation, dry mouth and paresthesia. Around 155 patients have been treated with mitapivat (Pyrukynd) to date; thus, the full safety profile is likely not well understood.

VIII. Transfusions may place a high burden on patients. In the ASH publication, Management of Pyruvate Kinase Deficiency in Children and Adults (Grace, Barcellini, 2020), regularly transfused patients are those that receive six or more transfusions per year, where those that are not regularly transfused are those that have received four or fewer. Mitapivat (Pyrukynd) has shown to increase Hb levels and reduce transfusion burden, likely providing clinical value in those that have a high-transfusion burden, need treatment but are unable to tolerate transfusions (e.g., previous immune or hemolytic transfusion reaction), or where risks of transfusion outweigh the benefits. Long term implications on patient-perceived burden of disease, improved survival, positive impacts on bone mineral density, prevention of iron overload, etc. have not been shown. Furthermore, very few patients in the clinical trials were able to become transfusion-free. It is likely that transfusions will need to be continued in some capacity for most patients even after starting mitapivat (Pyrukynd). Mitapivat (Pyrukynd) has questionable value over transfusions in those that could be managed with transfusions intermittently. In the not regularly transfused population, improvement in markers of hemolysis and Hb were seen; however Hb level is not strongly correlated with symptom severity and thus need for treatment. The PKDD diary assessment met the minimally important clinical change; however, PKDIA scores, which measure QOL and physical functioning, did not meet clinically meaningful thresholds. In summary, mitapivat (Pyrukynd) may be a valuable therapy in those that are not candidates for current management strategies or where transfusion-burden is high. Therapy is determined as medically necessary in those beyond the definition of not regularly transfused (i.e., those eligible are those with five or more transfusions over the past year).

IX. In clinical trials, increases in Hb occurred rapidly in responders, with average increases in Hb by week eight of therapy. The max dose will be reached by the start of the third month; thus, a three-month initial duration of approval is sufficient to determine treatment response. Thereafter, Hb level within the past three months is required to confirm continued treatment benefit. In clinical trials not all patients responded to therapy or responded long-term. In the long-term extension trial, duration of response up to 19.5 months occurred in some patients, but many patients do not have extended duration of response. When subjective response or objective Hb response lapse, therapy should be discontinued.

Investigational or Not Medically Necessary Uses

I. Mitapivat (Pyrukynd) is considered not medically necessary:
   A. For patients with pyruvate kinase deficiency that have two non-missense mutations or are homozygous for R479H mutation. In a Phase 2, DRIVE-PK study of mitapivat (Pyrukynd) patients with these mutational characteristics were non-responders. Thus, the pivotal Phase 3 trials excluded these patients from enrollment.

B. For patients that are not experiencing symptoms severe enough to impact QOL. Decision to treat in PKD is based on symptom severity, rather than objective markers (e.g., Hb). The currently known value of mitapivat (Pyrukynd) is to improve symptoms of disease by increasing Hb. There are no data to show an impact on long-term outcomes of disease.

II. Mitapivat (Pyrukynd) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below. Clinical trials are underway to investigate:
   A. Pediatric patients with PKD
   B. Sickle cell disease
   C. Thalassemia

References

1. Grace RF, Rose C, Layton DM, et al. Safety and efficacy of mitapivat in pyruvate kinase deficiency. New England Journal of Medicine. 2019;381(10):933-944.
2. Pyrukynd [Prescribing Information]. Agios Pharmaceuticals Inc. Cambridge, MA. February 2022.
3. Agios Pharmaceuticals, Inc. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ag-348 in Not Regularly Transfused Adult Subjects with Pyruvate Kinase Deficiency. clinicaltrials.gov; 2020.
4. Agios Pharmaceuticals, Inc. An Open-Label Study to Evaluate the Efficacy and Safety of Ag-348 in Regularly Transfused Adult Subjects with Pyruvate Kinase (Pk) Deficiency. clinicaltrials.gov; 2021.
5. Grace RF, Barcellini W. Management of pyruvate kinase deficiency in children and adults. Blood. 2020;136(11):1241-1249.

Related Policies

There are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2022

Policy Type: PA/SP Pharmacy Coverage Policy: UMP242

Split Fill Management*

Description

mobocertinib (Exkivity) is an orally administered EGFR tyrosine kinase inhibitor.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
mobocertinib (Exkivity)	40 mg capsules	Metastatic non-small-cell lung cancer with exon 20 insertion mutation after progression on platinum-based chemotherapy	120 capsules/30 days

Initial Evaluation

I. Mobocertinib (Exkivity) is considered not medically necessary when used for all other conditions, including but not limited to non-small cell lung cancer (NSCLC).

Renewal Evaluation

I. N/A

Supporting Evidence

I. Mobocertinib (Exkivity) is an oral EGFR tyrosine kinase inhibitor (TKI) that is being evaluated for exon 20 insertion mutant-positive NSCLC (EGFRex20ins-NSCLC) in those that have had disease progression on platinum-based chemotherapy. This specific type of NSCLC is thought to account for 2-3% of NSCLC cases annually, and is more commonly seen in those that do not have a smoking history.

II. Mobocertinib (Exkivity) is the second therapy specifically FDA-approved for EGFRex20ins-NSCLC. Amivantamab-vmjw (Rybrevant), an IV human antibody, was FDA-approved in May 2021. Approval was based off of the Phase 1 CHYRSALIS trial, a single-arm, open-label trial in 81 patients that previously progressed on platinum chemotherapy.

III. Platinum-based chemotherapy is utilized first-line for this condition, and is considered standard of care. Mobocertinib (Exkivity) is the first TKI specifically FDA-approved for this mutation. Other EGFR TKIs (e.g., osimertinib [Tagrisso]) have been used in this setting off-label; however, most cases of EGFRex20ins-NSCLC are resistant to those therapies.

IV. Interim results of the Phase 1/2 trial are being used to support accelerated FDA-approval. Mobocertinib (Exkivity) was granted Priority Review, as well as Breakthrough Therapy, Fast

Track and Orphan Drug designations. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. Continued Phase 2, as well as Phase 3 trials are underway to assess safety and efficacy. Both of these therapies are expected to be utilized in the second-line treatment setting; however, given expected preference for the targeted indication – use in the first-line setting may appeal to patients and providers. Mobocertinib (Exkivity) is being evaluated in a Phase 3, open-label trial versus platinum-based chemotherapy in patients with advanced or metastatic EGFRex20ins-NSCLC. Per ClinicalTrials.gov, the study is recruiting; however, there have been potential pauses in recruitment due to futility analyses.

V. Mobocertinib (Exkivity) is being evaluated in a Phase 1/2, single-arm, open-label trial in 114 patients with metastatic EGFRex20ins-NSCLC that were previously treated with platinum chemotherapy. Interim results showed an overall response rate (ORR). Other trial outcomes include duration of response (DoR), and progression-free survival (PFS). The quality of the evidence is low given the open-label and single-arm trial design, and small sample size. True medication efficacy is unknown due to the observational nature of the data. Additionally, the endpoints evaluated have not been correlated with meaningful outcomes such as improved survival or quality of life. The results are similar to those seen for amivantamab-vmjw (Rybrevant). Use of this therapy in any treatment setting is considered experimental and investigational at this time given the unknown clinical benefit and ongoing clinical trials to evaluate safety and efficacy.

VI. The safety profile is based on the 114 patients that have received therapy to date. Treatment related adverse events (AE) occurred in 99% of patients. Common AE: diarrhea 91%, rash (45%), paronychia (38%), decreased appetite (35%), nausea (34%), dry skin (31%), vomiting (30%), increased creatinine (25%), stomatitis (24%), pruritus (21%). Grade 3-4 AE occurred in 47% and 49% of patients were documented to have serious AE. Dose reduction due to AE occurred in 25% of patients, and AE leading to treatment discontinued occurred in 17% of patients. One patient experienced cardiac failure, a TRAE leading to death. Given the observational nature of the data in a small population, the severity and extent of AE that are due to the drug versus the disease are unknown at this time.

VII. NCCN guidelines for advanced or metastatic EGFRex20ins-NSCLC recommend platinum-based combination chemotherapy for first-line treatment, this is a Category 1 recommendation. Mobocertinib (Exkivity) and amivantamab-vmjw (Rybrevant) have been added as subsequent therapy options (Category 2A recommendation). The recommendations are specific to patients with an ECOG score 0-2, and for those with PS 3-4, best supportive care is recommended (Category 2A recommendation). Clinical trials are highly encouraged for all settings. ASCO provides similar recommendations for platinum-based combination chemotherapy in the first-line setting; however, have not been updated to include the targeted therapies. Guidelines do not recommend conventional EGFR TKIs for this mutation, and ASCO recommends platinum chemotherapy after progression on a conventional EGFR TKI if one was utilized.

VIII. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for NSCLC notes that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC.

Investigational or Not Medically Necessary Uses

I. Mobocertinib (Exkivity) is being withdrawn from the market based on the outcome of the Phase 3 EXCLAIM-2 confirmatory trial in the setting of metastatic non-small-cell lung cancer with exon 20 insertion mutation after progression on platinum-based chemotherapy which did not meet its primary endpoint and thus did not fulfill the confirmatory data requirements of the Accelerated Approval granted by the U.S. FDA nor the conditional marketing approvals granted in other countries. Takeda is working with the FDA towards the withdrawal of Exkivity from the U.S. market and will also withdrawal Exkivity globally where approved.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Riely GJ, Neal JW, Camidge DR, et al. Activity and safety of mobocertinib (TAK-788) in previously treated non-small cell lung cancer with egfr exon 20 insertion mutations from a phase I/II trial. Cancer Discov. 2021;11(7):1688-1699.
2. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology, Non-Small Cell Lung cancer. V6.2021. Updated September 30,2021. Accessed October 6, 2021. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450
3. Hanna NH, Robinson AG, Temin S, et al. Therapy for stage iv non-small-cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. J Clin Oncol. 2021;39(9):1040-1091.
4. Rybrevant [Prescribing Information]. Janssen Pharmaceuticals. Horsham, PA. May 2021.
5. American Cancer Society. Treatment non-small cell lung cancer. Accessed August 23, 2021. https://www.cancer.org/cancer/lung-cancer/treating-non-small-cell.html.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated from E/I to not medically necessary following withdrawal from U.S. market	02/2024
Policy created	11/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP287

Split Fill Management*

Description

Momelotinib (Ojjaara) is an orally administered inhibitor of Janus Associated Kinase (JAK1 and JAK2) and Activin Type I receptor (ACVR1).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
momelotinib (Ojjaara)	Intermediate or high-risk myelofibrosis with anemia	200 mg tablets	30 tablets/30 days
		150 mg tablets	
		100 mg tablets	

Initial Evaluation

I. **Momelotinib (Ojjaara)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an oncologist, or hematologist; **AND**
   C. Medication will not be used in combination with another JAK inhibitor [e.g., ruxolitinib (Jakafi), fedratinib (Inrebic), pacritinib (Vonjo)]; **AND**
   D. A diagnosis of **myelofibrosis** (MF; including primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF) when the following are met:
      1. Member's condition is classified as intermediate (Int-1, Int-2) or high-risk myelofibrosis; **AND**
      2. Member is not a candidate for allogeneic hematopoietic cell transplant (HCT); **AND**
      3. Provider attests that the member has significant splenomegaly (increased spleen volume or size); **AND**
      4. Documentation of pre-treatment platelet counts showing that the member has a platelet count greater than or equal to 50 x 10^9 /L; **AND**
      5. Member has significant symptomatic anemia (defined as hemoglobin (Hgb) less than 10 g/dL); **AND**
      6. Treatment with a first-line JAK inhibitor [e.g., ruxolitinib (Jakafi), fedratinib (Inrebic)] led to the development of anemia (defined as hemoglobin (Hgb) less than 10 g/dL); **OR**

i. Treatment with a different JAK inhibitor [e.g., ruxolitinib (Jakafi), fedratinib (Inrebic)] has been deemed inappropriate due to pre-existing anemia (Hgb < 10 g/dL) prior to the initiation of therapy

II. Momelotinib (Ojjaara) is considered investigational when used for all other conditions, including but not limited to:
   A. Low-risk myelofibrosis
   B. Polycythemia vera
   C. Essential thrombocythemia
   D. Anemia correction in the setting of chronic kidney disease (CKD)
   E. Anemia correction in the setting of MDS or any other hematological condition
   F. Graft versus host disease
   G. Lymphoproliferative neoplasms
   H. Solid tumors (e.g., prostate, colorectal, lung)
   I. Acute myeloid leukemia (AML)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication will not be used in combination with another JAK inhibitor [e.g., ruxolitinib (Jakafi), fedratinib (Inrebic), pacritinib (Vonjo)]; **AND**
IV. Member has exhibited improvement or stability of disease symptoms [e.g., transfusion independence, improvement in total symptom score (TSS), correction of splenomegaly]

Supporting Evidence

I. Momelotinib (Ojjaara) is a Janus Kinase (JAK1, JAK2) and Activin Type I receptor (ACVR1) inhibitor, expected to be FDA-approved for adult patients with myelofibrosis (MF), who were previously treated with a JAK inhibitor and had hematologic suppression (anemia). It is orally administered at 200 mg once daily. Efficacy and safety of momelotinib (Ojjaara) has not been studied in pediatric population.
II. Myelofibrosis (MF) is a cancer of the bone marrow. It is a rare myeloproliferative neoplasm (MPN) where scar-like tissue replaces functional bone marrow, leading to abnormal blood cells. MF may progress to acute myeloid leukemia. The incidence of MF is 1/100,000 people per year, with roughly 21,000 cases in the US. An estimated 54% of these are anemic [hemoglobin (Hgb) <10 g/dL] requiring blood transfusions. At onset and throughout disease progression, MF may present high symptom burden with non-specific constitutional symptoms (e.g., fatigue, shortness of breath, bleeding, bone pain, abdominal pain) and splenomegaly. Over time MF may progress to acute myeloid leukemia (AML) and current incidence of such leukemic transformation is one in five patients (up to 20%).

III. There are five risk levels of disease that correlate with prognosis of MF, and treatment is based on risk stratification. When patients are not eligible for allogeneic stem cell transplant, symptom targeted therapy may be used in those with intermediate or higher risk MF. Treatment goals include reduction of spleen size and symptom burden. Symptomatic therapies include hydroxyurea and JAK inhibitors: ruxolitinib (Jakafi), fedratinib (Inrebic), pacritinib (Vonjo).

IV. JAK inhibitors have only been sufficiently evaluated in patients with at least intermediate-risk MF and have unknown clinical value for lower risk disease. JAK inhibitors do not reverse fibrosis or prolong survival but may reduce spleen size and improve disease-related symptoms. In absence of splenomegaly and symptoms, these medications have unknown application. Given the specialized diagnosis, treatment, and monitoring, prescribing by or in consultation with a specialist is required.

V. Notably, JAK inhibitor therapy may exacerbate anemia and thrombocytopenia. Pacritinib (Vonjo) is recommended as NCCN Category 1 recommended agent for patients with severe thrombocytopenia (platelets < $50x10^9$/L), while for those with anemia (Hgb <10 g/dL), erythropoietin alfa (Epogen), danazol, and lenalidomide (Revlimid) are guideline-directed therapies along with RBC transfusions. Notably, patients with erythropoietin (EPO) levels < 500 mU/mL may be good candidates for erythropoiesis stimulating agents (ESA, e.g., Retacrit, Procrit), while those with EPO> 500 mU/mL require therapy with danazol or lenalidomide.

VI. Momelotinib (Ojjaara) is the fourth JAK inhibitor in the MF therapy landscape, but the first agent with ACVR1 activity. It is expected to be specifically approved in those with severe anemia due to first-line therapies [e.g., HU, Jakafi, Inrebic], and may serve as an alternative to danazol and lenalidomide (Revlimid). It may also be considered a first-line agent for treatment-naïve MF patients with severe anemia at the onset. NCCN guidelines have not been updated to include momelotinib (Ojjaara).

VII. Momelotinib (Ojjaara) was studied in phase 3, randomized (2:1), double-blind, double-dummy clinical trial (MOMENTUM; N= 195) to assess the superiority of momelotinib (Ojjaara) versus danazol in symptomatic, anemic patients with a history of JAK inhibitor therapy. Patients: transplant-ineligible adults with intermediate or high-risk MF, palpable splenomegaly, JAK inhibitor therapy (≥ 90 days) complicated by anemia (Hgb ≤ 10 g/dL) and RBC transfusion ≥4 units in eight weeks; and mean (SD) Myelofibrosis Symptom Assessment Form- Total Symptom Score (MFSAF-TSS) of 25 (12.8).

VIII. The MOMENTUM clinical trial reported superiority of momelotinib (Ojjaara) to danazol with respect to TSS response rate showing a statistically significant treatment difference of 16% in favor of momelotinib (Ojjaara) (p 0.00095). Additionally, higher percentage of patients in momelotinib arm reported transfusion independence rates (13.58%, p0.0064, non-inferior to danazol). Additional secondary endpoints, namely, >25% splenic response rate (34% treatment difference, p<0.0001), mean (SD) absolute TSS change from baseline to week 24 (-6.5, p 0.0014), and rate of zero transfusion at week 24 (18% treatment difference, p 0.0012) were in favor of momelotinib (Ojjaara) versus danazol establishing statistically significant superiority in the clinical trial setting.

IX. Exploratory secondary endpoints of the MOMENTUM trial, overall survival, and leukemia-free survival were not statistically significant but showed numeric favorability to momelotinib (Ojjaara) with hazard ratios (HR) of 0.73 and 0.65, respectively. Additional phase 3 non-inferiority trials of momelotinib (Ojjaara): versus ruxolitinib (Jakafi) in JAK inhibitor-naïve anemic patients (SIMPLIFY-1; N= 432); and versus beast available therapy in JAK-inhibitor experienced patients (SIMPLIFY-2; N= 156) failed to achieve non-inferiority of momelotinib (Ojjaara) with the

comparator. However, participants in both trials achieved favorable transfusion independence for ≥ 12 weeks.

X. It should be noted that momelotinib (Ojjaara), when compared with ruxolitinib (Jakafi) in JAK inhibitor naïve population with MF (SIMPLIFY-1 clinical trial) did not exhibit statistically significant non-inferiority assessed via TSS response rate. At this time, magnitude of efficacy of momelotinib (Ojjaara) as a first-line therapy for MF in JAK-inhibitor naïve population, is unknown.

XI. MOMENTUM clinical program demonstrated the superiority of momelotinib (Ojjaara) versus danazol in JAK inhibitor refractory population across multiple key endpoints demonstrating disease morbidity advantage. TSS response rate is a validated measure of treatment response and reflects constitutional improvement in quality of life. Momelotinib (Ojjaara) therapy led to a higher transfusion independence rate and reduction in splenomegaly, which supports the clinical value of momelotinib (Ojjaara). At this time, the long-term efficacy of momelotinib (Ojjaara) in reducing leukemic transformation, improving overall survival, as well as achieving long-term disease stability – remains undetermined.

XII. During the MOMENTUM trial, the safety profile for momelotinib (Ojjaara) was comparable to that of danazol. Overall, severe (grade ≥3), adverse events (AEs) between arms were 53.8% and 64.6%, respectively. The most common hematological AE included anemia (99% vs 100%), thrombocytopenia (76% vs 61%), and neutropenia (29% vs 26%). Common AE for momelotinib versus danazol respectively, included diarrhea (22% vs 9%), nausea (16% vs 9%), asthenia (13% vs 9%), pruritis (11% for both arms), and acute kidney injury (4.6% vs 12%).

XIII. During the treatment phase, 23 (18%) patients in the momelotinib (Ojjaara) arm and 15 (23%) in the danazol arm discontinued therapy due to AE. The long-term safety of momelotinib (Ojjaara) remains undetermined.

XIV. Current clinical evidence for momelotinib (Ojjaara) provides indicators of efficacy and supports its place in therapy as an applicable therapeutic alternative in transplant-ineligible anemic patients with palpable splenomegaly when front-line JAK inhibitor therapy is complicated by anemia. The majority of patients, who are intolerant to first-line JAK inhibitors (e.g., ruxolitinib, fedratinib) due to the development of symptomatic anemia, may be candidates for second-line therapy with momelotinib (Ojjaara). Additionally, patients, who have pre-existing symptomatic anemia (Hgb < 10 g/dL) and for whom first-line JAK inhibitor therapy would be deemed inappropriate, may benefit from the anemia correction potential of this drug.

Investigational or Not Medically Necessary Uses

I. Momelotinib (Ojjaara) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Low-risk myelofibrosis
   B. Polycythemia vera
   C. Essential thrombocythemia
   D. Anemia correction in the setting of chronic kidney disease (CKD)
   E. Anemia correction in the setting of MDS or any other hematological condition
   F. Graft versus host disease
   G. Lymphoproliferative neoplasms
   H. Solid tumors (e.g., prostate, colorectal, lung)
   I. Acute myeloid leukemia (AML)

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Ojjaara [Prescribing Information]. GlaxoSmithKline, Durham, NC. September 2023.
2. Verstovsek S, Gerds AT, et al. Lancet. 2023 Jan 28;401(10373):269-280. Erratum in: Lancet. 2023 Apr 29;401(10386):1426.
3. Mesa RA, Kiladjian JJ, et al. J Clin Oncol. 2017 Dec 1;35(34):3844-3850.
4. Harrison CN, Vannucchi AM, et al. Lancet Haematol. 2018 Feb;5(2):e73-e81.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
fedratinib (Inrebic) Policy	Myelofibrosis
ruxolitinib (Jakafi, Opzelura)	Myelofibrosis, polycythemia vera, GVHD
pacritinib (Vonjo)	Myelofibrosis with severe thrombocytopenia (platelet count below 50 x 10^9/L

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	09/2023

Policy Type: PA/SP Pharmacy Coverage Policy: UMP047

Description
Medications included in this policy are subcutaneous and oral disease modifying therapies for the treatment of multiple sclerosis.

Length of Authorization
Cladribine (Mavenclad) only
- Initial: 12 months
- Renewal: Two months, maximum of one renewal per lifetime

All other agents
- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
cladribine (Mavenclad)	Relapsing forms of multiple sclerosis (MS)	10 mg tablets (box of 4 tablets)	1 box (4 tablets)/26 days*
		10 mg tablets (box of 5 tablets)	1 box (5 tablets)/26 days*
		10 mg tablets (box of 6 tablets)	1 box (6 tablets)/26 days*
		10 mg tablets (box of 7 tablets)	1 box (7 tablets)/26 days*
		10 mg tablets (box of 8 tablets)	1 box (8 tablets)/26 days*
		10 mg tablets (box of 9 tablets)	1 box (9 tablets)/26 days*
		10 mg tablets (box of 10 tablets)	1 box (10 tablets)/26 days*
daclizumab (Zinbryta)		150mg/mL single-dose PFS±	1 syringe/28 days
dimethyl fumarate (Tecfidera, dimethyl fumarate)		30 day starter pack	1 starter pack/30 days (60 capsules/30 days)
		120 mg capsule	60 capsules/30 days
		240 mg capsule	60 capsules/30 days
monomethyl fumarate (Bafiertam)		95 mg capsule	120 capsules/30 days

diroximel fumarate (Vumerity)	Relapsing forms of multiple sclerosis (MS)	231 mg capsule	120 capsules/30 days
fingolimod (Gilenya, fingolimod)		0.25 mg capsule	30 capsules/30 days
		0.5 mg capsule	30 capsules/30 days
fingolimod lauryl sulfate (Tascenso ODT)		0.25 mg tablet disintegrating	30 tablets/30 days
		5 mg tablet disintegrating	30 tablets/30 days
glatiramer acetate (Copaxone, Glatopa, glatiramer acetate)		20 mg/mL single dose PFS	30 syringes per/30 days
glatiramer acetate (Copaxone, Glatopa, glatiramer acetate)		40 mg/mL single dose PFS	12 syringes/28 days
interferon beta-1a (Avonex)		30 mcg/0.5mL PFS	4 syringes (1 kit)/28 days
		30 mcg/0.5mL pen	4 pens/28 days
interferon beta-1a (Plegridy)		Starter Pack – (Pen Injector or PFS)	1 starter pack/28 days
		125 mcg/0.5mL (Pen Injector or PFS)	2 pens (or PFS)/28 days
interferon beta-1a (Rebif)		22 mcg/0.5mL (Auto-injector or PFS)	12 syringes/28 days
		44 mcg/0.5mL (Auto-injector or PFS)	12 syringes/28 days
		Titration Pack (PFS or Solution)	1 pack (12 syringes)/28 days
interferon beta-1b (Betaseron)		0.3 mg powder for reconstitution	14 syringes/28 days
interferon beta-1b (Extavia)		0.3 mg powder for reconstitution	15 syringes/30 days
ofatumumab (Kesimpta)		20 mg/0.4mL Auto-injector	Initial: 3 pens/28 days Maintenance: 1 pen/28 days
ozanimod (Zeposia)	Relapsing forms of multiple sclerosis (MS); Ulcerative colitis**	7-Day Starter Pack (0.23 mg, 0.46 mg)	7 capsules/7 days
		Starter Kit (7-day starter pack and 0.92 mg 30-count bottle)	37 capsules/37 days
		Starter Kit (7-day starter pack and 0.92 mg 21-count bottle)	28 capsules/28 days
		0.92 mg capsules	30 tablets/30 days

ponesimod (Ponvory)	Relapsing forms of multiple sclerosis (MS)	2-10 mg starter pack	Initial: 14 tablets/14 days Maintenance: 30 tablets/30 days
		20 mg tablet	
siponimod (Mayzent)		0.25 mg starter pack (Titrate to 2 mg dose)	12 tablets/5 days
		0.25 mg tablets	28 tablets/28 days
		0.25 mg starter pack (Titrate to 1 mg dose)	7 tablets/4 days
		1 mg tablet	28 tablets/28 days
		2 mg tablets	30 tablets/30 days
teriflunomide (Aubagio, teriflunomide)		7 mg tablets	28 tablets/28 days
		14 mg tablets	28 tablets/28 days

**Maximum of 2 boxes/331 days*

‡PFS: Prefilled Syringe

***For ozanimod (Zeposia) in ulcerative colitis: Reference Chronic Inflammatory Disease policy*

Initial Evaluation

generic dimethyl fumarate, generic fingolimod, glatiramer acetate (Glatopa), generic glatiramer acetate, and generic teriflunomide are the preferred generic agents.

- There is no prior authorization* required on these preferred agents, unless requesting over the allowed quantity limits noted above.

interferon beta-1a (Avonex) and diroximel fumarate (Vumerity) are preferred agents.

- There is no prior authorization required on these preferred agents, unless requesting over the allowed quantity limits noted above. Step therapy may apply.

**Brand Aubagio, Copaxone, Gilenya, and Tecfidera are noncovered drugs given generic availability, nonformulary multi-source brand requirements apply*

I. **Cladribine (Mavenclad), daclizumab (Zinbryta), fingolimod lauryl sulfate (Tascenso ODT), interferon beta-1a (Plegridy), interferon beta-1a (Rebif), interferon beta-1b (Betaseron), interferon beta-1b (Extavia), monomethyl fumarate (Bafiertam), ofatumumab (Kesimpta), ozanimod (Zeposia), and ponesimod (Ponvory)** may be considered medically necessary when the following criteria below are met:

A. Medication is prescribed by, or in consultation with, a neurologist; **AND**

B. Medication will be used as monotherapy for multiple sclerosis; **AND**

C. Multiple sclerosis (MS) diagnosis is confirmed and documented by laboratory report (e.g. MRI); **AND**

D. A diagnosis of one of the following:

1. **Relapsing-Remitting MS (RRMS) or Clinically Isolated Syndrome (CIS)**; **OR**
2. **Active Secondary Progressive MS (SPMS)**; **AND**
   i. Active disease confirmed by clinical relapses or MRI evidence of contrast enhancing lesions and/or new or unequivocally enlarging T2 lesions; **AND**

E. Documentation of treatment with at least two of the following have been ineffective or not tolerated, or ALL are contraindicated: interferon beta-1a (Avonex), generic dimethyl

fumarate, generic fingolimod, glatiramer acetate/Glatopa, generic teriflunomide, or diroximel fumarate (Vumerity)

II. **Brand Aubagio, Brand Gilenya, Brand Tecfidera and Brand Copaxone** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(D) above are met; **AND**
   B. In the absence of a drug shortage, coverage of the multi-source brand drug is to be considered medically necessary when the prescriber is requesting the multi-source brand drug due to a documented adverse reaction to the generic equivalent; **AND**
   C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
      1. The prescriber must document one or more of the following, indicating that the reaction:
         i. Was life-threatening; **OR**
         ii. Required hospitalization; **OR**
         iii. Required intervention to prevent impairment or damage; **OR**
      2. The prescriber is requesting the brand name drug due to a documented allergy to the generic equivalent [i.e. skin rashes (particularly hives), itching, respiratory compilations and angioedema] that required medical intervention to prevent impairment or damage; **OR**
      3. The prescriber is requesting the brand name drug due to a documented intolerance to the generic equivalent which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
         i. More than one generic equivalent has been tried, or there is only one generic equivalent for the prescribed brand drug; **AND**
   D. **For Brand Aubagio:** Documentation of treatment with all five (1, 2, 3, 4, and 5) of the following have been ineffective, contraindicated, or not tolerated:
      1. interferon beta-1a (Avonex)
      2. glatiramer acetate (Glatopa) or generic glatiramer acetate
      3. generic dimethyl fumarate
      4. generic fingolimod
      5. diroximel fumarate (Vumerity); **OR**
   E. **For Brand Gilenya:** Documentation of treatment with all five (1, 2, 3, 4, and 5) of the following have been ineffective, contraindicated, or not tolerated:
      1. interferon beta-1a (Avonex)
      2. glatiramer acetate (Glatopa) or generic glatiramer acetate
      3. generic dimethyl fumarate
      4. generic teriflunomide
      5. diroximel fumarate (Vumerity); **OR**
   F. **For Brand Tecfidera:** Documentation of treatment with all five (1, 2, 3, 4, and 5) of the following have been ineffective, contraindicated, or not tolerated:
      1. interferon beta-1a (Avonex)
      2. generic fingolimod
      3. glatiramer acetate (Glatopa) or generic glatiramer acetate

4. generic teriflunomide
5. diroximel fumarate (Vumerity); **OR**

G. **For Brand Copaxone:** Documentation of treatment with all five (1, 2, 3, 4, and 5) of the following have been ineffective, contraindicated, or not tolerated:
   1. interferon beta-1a (Avonex)
   2. generic fingolimod
   3. generic dimethyl fumarate
   4. generic teriflunomide
   5. diroximel fumarate (Vumerity)

III. **Siponimod (Mayzent)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(E) above are met; **AND**
   B. CYP2C9 genotype has been confirmed; **AND**
   C. Member does not have a CYP2C9*3/*3 genotype

IV. **Interferon beta-1b (Extavia)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(E) above are met; **AND**
   B. Documentation of treatment with interferon beta-1b (Betaseron) has been ineffective, contraindicated, or not tolerated

V. Medications listed above are considered investigational when used for all other conditions, including but not limited to:
   A. Primary Progressive MS (PPMS)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescriber attestation that the patient has demonstrated a clinical benefit with therapy, as defined by no relapses, less than two unequivocally new MRI-detected lesions, or lack of increased disability on examination over a one-year period; **AND**
IV. If the request is **for Brand Aubagio, Brand Gilenya, Brand Tecfidera, or Copaxone:**
   A. In the absence of a drug shortage, coverage of the multi-source brand drug is to be considered medically necessary when the prescriber is requesting the multi-source brand drug due to a documented adverse reaction to the generic equivalent; **AND**
   B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

a. The prescriber must document one or more of the following, indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **OR**
b. The prescriber is requesting the brand name drug due to a documented allergy to the generic equivalent [i.e. skin rashes (particularly hives), itching, respiratory compilations and angioedema] that required medical intervention to prevent impairment or damage; **OR**
c. The prescriber is requesting the brand name drug due to a documented intolerance to the generic equivalent which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. More than one generic equivalent has been tried, or there is only one generic equivalent for the prescribed brand drug; **OR**

V. If the request is for **siponimod (Mayzent)** and treatment has been interrupted for four or more consecutive daily doses, a re-titration starter package is covered by the manufacturer

Supporting Evidence

I. **Siponimod (Mayzent):** Per the package label, if treatment with siponimod (Mayzent) is interrupted for FOUR or more consecutive daily doses after completion of initial titration, treatment should be reinitiated with Day 1 of the titration regimen, including first-dose monitoring when appropriate. Siponimod (Mayzent) manufacturer, Novartis, confirmed 5-day titration packs/starter pack will be shipped from HomeScripts mail order pharmacy at no charge to commercial plans. Even in cases where the member needs to re-titrate the starter pack is covered by Novartis via HomeScripts.
II. American Academy of Neurology (AAN) guidelines recommend clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity, guidelines do not contain treatment sequencing recommendations.
III. AAN guidelines recommend clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience one or more relapses, two or more unequivocally new MRI-detected lesions, or increased disability on examination over a one-year period of using a DMT.
IV. DMTs take a variable amount of time to become clinically active, and new lesion formation may occur after initiation but before the time of full efficacy, confounding interpretation of follow-up MRI scans. Consequently, many clinicians obtain new baseline MRI three to six months after initiating DMTs to monitor from a treated baseline. The optimal interval for ongoing monitoring is uncertain, as short-term stability as evidenced by clinical and MRI criteria may not consistently predict long-term stability.
V. Per Lublin, et al. 2014, disease activity is determined by clinical relapses assessed at least annually and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions).

VI. The FDA Summary Review for Regulatory Action on the NDA for siponimod (Mayzent) states the following: In the active secondary progressive phase of the disease, patients can accrue disability both from acute relapses and from the progressive component of the disease. Active secondary progressive disease and relapsing-remitting disease overlap in evolution. Categorization as secondary progressive disease is based on clinical judgment; there are no clinical findings or biomarkers that meaningfully define or predict the phenotypes of relapsing forms of MS. A continued progression of disability with no concurrent inflammatory activity and no clinical relapses is described a non-active secondary progressive MS. Importantly, to support an indication for the treatment of secondary progressive MS (as distinct from active secondary progressive MS), it is critical that efficacy be established in patients who have non-active secondary progressive MS (SPMS), and that the drug effect be clearly distinguished from an effect on inflammatory demyelination and clinical relapses that are present in patients with active SPMS (a relapsing form of MS). Multiple drugs have been approved for the treatment of relapsing forms of MS. Conversely, there is a significant unmet medical need for the treatment of non-active SPMS…… The indication supported by the submitted data is therefore for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. It must be emphasized that thirteen different therapies have been approved to treat relapsing forms of multiple sclerosis, and that the population for which siponimod will be indicated is the same as for those drugs. The siponimod labeling will be the first explicitly describing that relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, but all sponsors of the drugs approved for the treatment of relapsing forms of multiple sclerosis will be requested to update their indication statements to conform with this contemporary nomenclature.

VII. In the United States, the Office of Generic Drugs at the Food and Drug Administration (FDA) follows a rigorous review process to make sure that, compared to the brand name (or innovator) medications, the proposed generic medications:

- Contain the same active/key ingredient
- Have the same strength
- Use the same dosage form (for instance, a table, capsule, or liquid) and
- Use the same route of administration (for instance, oral, topical, or injectable)

VIII. The FDA's review process also ensures that generic medications perform the same way in the human body and have the same intended use as the name brand medication. Healthcare professionals and consumers can be assured that FDA-approved generic drug products have met the same rigid manufacturing standards as the innovator drug. In addition, FDA inspects facilities to make certain the generic manufacturing, packaging, and testing sites pass the same quality standards as those of brand-name drugs.

- Thus, when an adverse reaction or allergy occurs to any medication (brand or generic), it is important to report to MedWatch.
- In order to keep effective medical products available on the market, the FDA relies on the voluntary reporting of these events. This information is used to maintain safety surveillance and to monitor if modifications in use or design of the product are warranted to increase patient safety.

IX. It can be difficult to distinguish an allergy from a distinct adverse event related to the generic, therefore any event thought to be related to the medication should be reported to MedWatch.
- As defined by the American Academy of Allergy, Asthma, and Immunology, an allergic reaction occurs when the immune system overreacts to a substance, triggering an allergic reaction. Sensitivities to drugs may produce similar symptoms, but do not involve the immune system. Only 5-20% of adverse reactions to drugs are considered true allergic reactions. The chances of developing an allergy are higher when you take the medication frequently or when it is rubbed on the skin or given by injection, rather than taken by mouth. The most frequent types of allergic symptoms to medications include skin rashes (particularly hives), itching, respiratory complications and angioedema. The most severe form of immediate allergic reactions is anaphylaxis, and symptoms include hives, facial or throat swelling, wheezing, light-headedness, vomiting and shock.

X. Tools used in diagnosis of MS:

<table>
<tr><th colspan="2">MS with a relapsing-remitting course</th></tr>
<tr><td colspan="2">• Based upon two separate areas of damage (dissemination in space) in the CNS that have occurred at different points in time (dissemination in time). Unless contraindicated, MRI should be obtained.</td></tr>
<tr><th>Dissemination in <u>time</u>
(Development/appearance of new CNS lesions over time)</th><th>Dissemination in <u>space</u>
(Development of lesions in distinct anatomical locations within the CNS)</th></tr>
<tr><td>• ≥ 2 clinical attacks; OR
• 1 clinical attack AND one of the following:
○ MRI indicating simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI compared to baseline scan
○ CSF-specific oligoclonal bands</td><td>• ≥ 2 lesions; OR
• 1 lesion AND one of the following:
○ Clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location
○ MRI indicating ≥ 1 T2-hyperintense lesions characteristic of MS in ≥ 2 of 4 areas of the CNS (periventricular, cortical or juxtacortical, infratentorial, or spinal cord)</td></tr>
<tr><th colspan="2">Secondary progressive MS course</th></tr>
<tr><td colspan="2">• MS course characterized by steadily increasing objectively documented neurological disability independent of relapses. Fluctuations, periods of stability, and superimposed relapses might occur. Secondary progressive multiple sclerosis, is further distinguished as a progressive course following an initial relapsing-remitting course.
• Diagnosed retrospectively based on previous year's history.</td></tr>
</table>

Investigational Uses or Not Medically Necessary Uses

I. Primary Progressive MS
   A. All agents included in this policy have not been evaluated in or have not been found to have a positive effect on progression in the setting of PPMS.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Live 07/01/2023: Updated box around preferred agents not requiring prior authorization. Added new Zeposia formulations to QL table.	06/2023
Included new generic teriflunomide. Branded product updated to align with requirements for other multi-source brands (i.e., Gilenya Copaxone, Tecfidera).	03/2023

Added Tascenso ODT 5mg disintegrating tablet to QL table	01/2023
Effective 01/01/2023 - Updated diroximel fumarate (Vumerity) as a preferred product	12/2022
Included newly available generic fingolimod as preferred product, replacing brand formulation. Branded product updated to align with requirements for other multi-source brands (i.e., Copaxone, Tecfidera).	11/2022
Added Tascenso ODT to policy	09/2022
Added 0.25 (1mg) starter pack and 1 mg dose of Mayzent to policy	04/2022
Added renewal of brand Copaxone into policy aligning with requirements for brand Tecfidera requiring medical necessity for brand over generic; Updated teriflunomide (Aubagio) as a preferred product effective 1/1/2022.	11/2021
Update to initial requests for brand Tecfidera or brand Copaxone to require trial of Avonex, Gilenya, and glatiramer acetate (Glatopa)/generic glatiramer acetate for brand Tecfidera requests; and trial of Avonex, Gilenya, and generic dimethyl fumarate for brand Copaxone requests	05/2021
Adding loading dose to QL table for Kesimpta	02/2021
Addition of brand Copaxone into policy aligning with requirements for brand Tecfidera requiring medical necessity for brand over generic.	12/2020
Addition of ofatumumab (Kesimpta) and ponesimod to policy within non-preferred position. Addition of brand Tecfidera criteria requiring medical necessity for brand over generic.	11/2020
Updated preferred products to specify generic dimethyl fumarate upon new generic availability (effective 10/2020). Removed criteria specific to branded Copaxone. Addition of monomethyl fumarate (Bafiertam) to policy within non-preferred position.	09/2020
Updated to include ozanimod (Zeposia) as a non-preferred product	04/2020
Updated fingolimod (Gilenya) as a preferred product effective 4/1/2020 per WA PDL update	03/2020
Updated to add non-preferred Vumerity	11/2019
Updated to include box around preferred agents not requiring prior authorization	10/2019
Updated to new policy format. Added newly approved drugs Mayzent and Mavencald. Added question requiring diagnosis confirmed and documented by laboratory report (e.g., MRI).	08/2019
Policy created from criteria	11/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP166

Split Fill Management*

Description

Lenvatinib (Lenvima), pazopanib (Votrient), and sorafenib (Nexavar) are orally administered multi-tyrosine kinase inhibitors (multi-TKIs), which limit angiogenesis via the inhibition of the bindings of multiple tyrosine kinase enzymes to cell surface receptors (e.g., VEGF, FGFR, IL-2 receptor)

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
lenvatinib (Lenvima)	Unresectable Hepatocellular Carcinoma; Advanced Renal Cell Carcinoma; Recurrent, High-risk or Metastatic Endometrial Carcinoma; Locally Recurrent or Metastatic Progressive Thyroid Cancer	4 mg capsule therapy pack	30 capsules/30 days*
		10 mg capsule therapy pack	30 capsules/30 days*
		14 mg capsule therapy pack	60 capsules/30 days*
	Unresectable Hepatocellular Carcinoma	8 mg capsule therapy pack	60 capsules/30 days*
		12 mg capsule therapy pack	90 capsules/30 days*
	Advanced Renal Cell Carcinoma; Recurrent, High-risk or Metastatic Endometrial Carcinoma	18 mg capsule therapy pack	90 capsules/30 days*
		20 mg capsule therapy pack	60 capsules/30 days*
	Locally Recurrent or Metastatic Progressive Thyroid Cancer	24 mg capsule therapy pack	90 capsules/30 days*
pazopanib (Votrient)	Advanced Renal Cell Carcinoma; Advanced Soft Tissue Sarcoma	200 mg tablets	120 tablets/30 days
generic pazopanib			
sorafenib (Nexavar)	Desmoid Tumors	200 mg tablets	60 tablets/30 days
	Unresectable Liver Carcinoma; Advanced Renal Cell Carcinoma; Locally Recurrent or Metastatic Progressive Thyroid Cancer	200 mg tablets	120 tablets/30 days
generic sorafenib tosylate			
	Desmoid Tumors	200 mg tablets	60 tablets/30 days

Quantity limits are based on recommended daily dose of lenvatinib (Lenvima) for each indication; QL exceptions allowed only for dose reductions

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Initial Evaluation

I. **Lenvatinib (Lenvima), pazopanib (Votrient), generic pazopanib, sorafenib (Nexavar), or generic sorafenib tosylate** may be considered medically necessary when the following criteria are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. The member has not experienced disease progression while on other multi-TKIs [e.g., lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar)] unless outlined below (e.g., Renal Cell Carcinoma); **AND**
   D. A diagnosis of one of the following:
      1. **Renal Cell Carcinoma (RCC)**; **AND**
         i. The member has advanced (relapsed, stage III) or metastatic (stage IV) disease; **AND**
         ii. The request is for first-line systemic therapy; **AND**
            a. Lenvatinib (Lenvima) is being requested in combination with pembrolizumab (Keytruda); **OR**
         iii. The request is for subsequent-line systemic therapy; **AND**
            a. The member has had disease progression on, or intolerance to, **one** anti-angiogenic therapy unless all are contraindicated (e.g., axitinib [Inlyta], bevacizumab [Avastin], cabozantinib [Cabometyx]); **AND**
               i. The request is for Lenvatinib (Lenvima) in combination with everolimus (Afinitor); **OR**
               ii. The request is for monotherapy with pazopanib (Votrient); **AND**
                  1. Request is for generic pazopanib; **OR**
                     a. Treatment with generic pazopanib is contraindicated or was not tolerated; **OR**
               iii. The request is for monotherapy with generic sorafenib tosylate; **OR**
                  1. Request for brand sorafenib tosylate (Nexavar) and documentation of intolerance or contraindication to generic sorafenib tosylate; **OR**
      2. **Hepatocellular Carcinoma (HCC)**; **AND**
         i. The member has unresectable, advanced (stage III) or metastatic (stage IV) disease; **AND**
         ii. The medication will be used as monotherapy; **AND**
         iii. The request is for generic sorafenib tosylate; **AND**
            a. Provider attests the member is Child-Pugh Class A or Class B7; **OR**
         iv. Request for brand sorafenib tosylate (Nexavar) and documentation of intolerance or contraindication to generic sorafenib tosylate; **AND**
            a. Provider attests the member is Child-Pugh Class A or Class B7; **OR**
         v. The request is for lenvatinib (Lenvima); **AND**
            a. Provider attests the member has Child-Pugh Class A; **OR**
      3. **Thyroid Carcinoma; AND**
         i. The member has locally recurrent or metastatic (stage IV) disease; **AND**
         ii. The member has one of the following subtypes of differentiated thyroid carcinoma:

a. Papillary thyroid carcinoma; **OR**
b. Follicular thyroid carcinoma; **OR**
c. Hurthle cell thyroid carcinoma; **AND**

iii. The disease is refractory to radioactive iodine treatment (RAI)**; AND**
iv. The request is for monotherapy with lenvatinib (Lenvima); **OR**
v. The request is for monotherapy with generic sorafenib tosylate; **OR**
a. Request for brand sorafenib tosylate (Nexavar) and documentation of intolerance or contraindication to generic sorafenib tosylate; **OR**

4. **Soft Tissue Sarcoma (STS); AND**
i. The member has advanced (unresectable) or metastatic (stage IV) soft tissue sarcoma (STS); **AND**
ii. The diagnosis of soft tissue sarcoma (STS) does not include the following histological subtypes:
a. Gastrointestinal Stromal Tumors (GIST); **OR**
b. Adipocytic Sarcoma (Liposarcoma); **AND**
iii. The request is for pazopanib (Votrient); **AND**
a. The medication will be used as monotherapy; **AND**
b. The member has had disease progression on at least one anthracycline-based chemotherapy regimen unless all are contraindicated (e.g., doxorubicin, epirubicin, ifosfamide); **AND**
i. Request is for generic pazopanib; **OR**
1. Treatment with generic pazopanib has been ineffective, contraindicated, or not tolerated; **OR**

5. **Endometrial Carcinoma (EC); AND**
i. The member has advanced, or metastatic endometrial carcinoma (EC); **AND**
ii. The disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
iii. The member had disease progression on, or after, at least ONE platinum-based systemic chemotherapy in the first-line setting; **AND**
iv. The request is for lenvatinib (Lenvima); **AND**
a. Lenvatinib (Lenvima) will be used in combination with pembrolizumab (Keytruda); **OR**

6. **Desmoid Tumors (DT); AND**
i. The member has a diagnosis of desmoid tumors confirmed by:
a. An image-guided (CT or ultrasound) core needle or surgical biopsy of the tumor site; **AND**
b. Confirmation of diagnosis by a soft tissue pathologist; **AND**
c. Provider attestation that other germline mutation syndromes (i.e., familial adenomatous polyposis [FAP], Gardner syndrome) and/or myofibroblastic diseases (e.g., sarcoma, gastrointestinal stromal tumor, nodular fasciitis, leiomyoma) have been ruled out; **AND**
ii. The member has documentation of tumor progression within the last 6 months; **OR**
a. There is documentation of potential for morbidity (e.g., impairing, or threatening function, physical deformity); **OR**
b. There is documentation of significant symptoms (e.g., severe pain) **AND;**

iii. The medication is not used in combination with any other oncology therapy; **AND**
iv. The request is for generic sorafenib tosylate; **OR**
    a. Request for brand sorafenib tosylate (Nexavar) and there is documentation of intolerance or contraindication to generic sorafenib tosylate.

II. Sorafenib (Nexavar) is considered not medically necessary when criteria above are not met and/or when used for:
    A. Sorafenib (Nexavar) in combination with erlotinib for Hepatocellular Carcinoma

III. Lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar) are considered investigational when used for all other conditions, including but not limited to:
    A. Gastrointestinal Stromal Tumor
    B. Adipocytic Sarcoma/Liposarcoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or spread; **AND**
IV. For brand sorafenib tosylate (Nexavar): documentation of intolerance or contraindication to generic sorafenib tosylate; **OR**
V. For brand pazopanib (Votrient): documentation of intolerance or contraindication to generic pazopannib

Supporting Evidence

I. Multi-kinase inhibitors [lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar)] exert their actions by inhibiting activities of multiple tyrosine kinases by depriving access to the Cdc37-Hsp90 molecular chaperone unit. This inhibitory activity leads to limiting angiogenesis via various cell surface receptors (e.g., VEGF, FGFR, IL-2 receptor). Multi-kinase inhibitors (multi-TKI) listed under this policy have received FDA-approval for patients 18 years and older. Efficacy and safety of these agents have not been established in the pediatric population.
II. Many treatment options exist for the conditions listed in this policy (e.g., renal cell carcinoma, hepatocellular carcinoma, thyroid carcinoma and soft tissue carcinoma). Initial and further line therapies in these settings are contingent upon patient specific characteristics. Given the complexities surrounding diagnosis and treatment choices, targeted drug therapies such as multi-kinase inhibitors must be prescribed by, or in consultation with, an oncologist.

III. Multi-kinase inhibitors are considered medically necessary when used as monotherapy. Efficacy and safety of these agents has not been studied in combination with other agents, with the following exceptions: lenvatinib in combination with everolimus for the treatment of renal cell carcinoma, and lenvatinib in combination with pembrolizumab for the treatment of endometrial carcinoma and first-line therapy of renal cell carcinoma.

IV. **Renal Cell Carcinoma (RCC):**

- Sorafenib (Nexavar) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial and one randomized, Phase 2 discontinuation trial. The Phase 2 trial enrolled 202 patients with advanced RCC and included patients with no prior therapy and tumor histology other than clear cell carcinoma. Patients were on therapy for 12 weeks and then randomized to continue sorafenib (Nexavar) or switch to placebo. Sorafenib (Nexavar) had a progression free survival (PFS) of 163 days compared to 41 days for placebo (p=0.0001). The Phase 3 trial included 769 patients with advanced RCC who had received on prior systemic therapy. The primary endpoints included OS and PFS. The median PFS was 167 days for sorafenib (Nexavar) compared to 84 days for placebo with a HR of 0.44 (95% CI 0.35, 0.55).
- Recently, the NCCN guidelines have been updated to favor the use of multi-TKI in combination with immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab). Lenvatinib (Lenvima) in combination with pembrolizumab (Keytruda) was recently studied in a phase 3, randomized, open-label trial (CLEAR study, N=1069) in comparison with lenvatinib (Lenvima) + everolimus (Afinitor), and sunitinib (1:1:1 randomization). PFS was longer with lenvatinib plus pembrolizumab than with sunitinib (median, 23.9 vs. 9.2 months; HR 0.39; 95% CI, 0.32 to 0.49; P<0.001) and was longer with lenvatinib plus everolimus than with sunitinib (median, 14.7 vs. 9.2 months; HR 0.65). Additionally, overall survival (OS) was longer with lenvatinib plus pembrolizumab than with sunitinib (HR 0.66; 95% CI, 0.49 to 0.88; P = 0.005). However, OS was not statistically different in lenvatinib plus everolimus when compared to sunitinib (HR 1.15; 95% CI, 0.88 to 1.50; P = 0.30).
- Additionally, lenvatinib (Lenvima) was studied in combination with everolimus (Afinitor) as a second-line regimen in one randomized, open-label, active-controlled, multicenter, Phase 1b/2 trial with 153 patients with advanced or metastatic RCC who had previously received anti-angiogenic therapy. The PFS for lenvatinib (Lenvima) in combination with everolimus (Afinitor) was 14.6 months compared to 5.5 months for everolimus (Afinitor) alone with a HR of 0.37 (95% CI 0.22, 0.62).
- Current NCCN guideline recommends pazopanib (Votrient) as 'other recommended regimen' in the first-line treatment setting, while sorafenib (Nexavar) has moved to 'useful in certain circumstances' as a subsequent-line option only with a category 3 recommendation. Circumstances for the use of sorafenib (Nexavar) are not defined in the NCCN guideline. Meta-analysis of clinical trials involving head-to-head comparison between multi-TKI shows that newer multi-TKI have better efficacy profile compared to sorafenib (Nexavar). Clinical trial for sorafenib (Nexavar) included patients with previous trials of interferon or cytokine-based regimens only, which are no longer used in the first-line setting.

V. **Hepatocellular Carcinoma (HCC):**

- Sorafenib (Nexavar) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial in 602 patients with unresectable hepatocellular carcinoma (HCC). The primary endpoint was OS. Sorafenib (Nexavar) had an OS of 10.7 months compared to 7.9 months for placebo with a hazard ratio (HR) of 0.69 (95% CI 0.55, 0.87). The median time to progression was 5.5 months for sorafenib (Nexavar) and 2.8 months for placebo with a HR of 0.58 (95% CI 0.45, 0.74).
- Lenvatinib (Lenvima) was studied in one randomized, open-label, active-controlled, non-inferiority, Phase 3 trial in patients with previously untreated unresectable HCC (N=954). The primary efficacy endpoint was OS. Lenvatinib (Lenvima) had a median OS of 13.6 months compared to 12.3 months for sorafenib (Nexavar) with a HR of 0.92 (95% CI 0.79, 1.06). Lenvatinib (Lenvima) had a median PFS of 7.3 months compared to 3.6 months for sorafenib (Nexavar) with a HR of 0.64 (95% CI 0.55, 0.75).
- NCCN guideline for HCC was recently updated to include atezolizumab (Tecentriq) and bevacizumab (Avastin) as the preferred first-line therapy (category 1 recommendation). Sorafenib (Nexavar) and lenvatinib (Lenvima) are other recommended monotherapy options for first-line therapy (category 1) in patients with a Child-Pugh Class A score [or class A/ B7 for sorafenib (Nexavar)], and those who are treatment naïve in the first-line setting. Additionally, lenvatinib (Lenvima) and sorafenib (Nexavar) are also recommended as second-line agents with category 2A NCCN recommendations should there be progression on first-line therapy with atezolizumab (Tecentriq) and bevacizumab (Avastin). Additionally, it should be noted that incidence of hematological, respiratory, and hepatic adverse reactions is significant with a Tecentriq/Avastin regimen. In many situations, members discontinue the regimen due to adverse reactions and transition to multi-TKI agents without having progressed on the first-line therapy.
- NCCN guideline notes that sorafenib (Nexavar) may be used after disease progression on lenvatinib (Lenvima). However, there is no clinical data to support the use of lenvatinib (Lenvima) after disease progression with sorafenib (Nexavar). Neither of these therapies have been studied in large scale clinical trials to support the use after progression on the other. NCCN guidelines for HCC advise caution while using sorafenib (Nexavar) in patients with Child-Pugh Class B7. More than 95% of participants enrolled in the studies of sorafenib (Nexavar) as well as lenvatinib (Lenvima) had Child-Pugh score class A liver function. Safety data for patients with Child-Pugh score classes B or C are limited, and the recommended dose is uncertain. Additionally, in a systematic review meta-analysis of 8678 patients treated with first-line sorafenib therapy for advanced HCC, Child-Pugh B liver function was associated with a significantly worse OS compared with Child-Pugh A liver function (HR, 2.82 [95% CI, 2.04 to 3.92]; 4 studies). Estimated median OS was 7.2 months for the entire cohort, 8.8 months in patients with Child-Pugh A, and 4.6 months in patients with Child-Pugh B7.

VI. **Thyroid Carcinoma:**

- In the setting of thyroid carcinoma, sorafenib (Nexavar) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial with 417 patients, who had locally recurrent or metastatic, progressively differentiated thyroid carcinoma. All participants were refractory to radioactive iodine (RAI) regimen. The primary efficacy

outcome was PFS. Sorafenib (Nexavar) had a median PFS of 10.8 months compared to 5.8 months for placebo with a HR of 0.59 (95% CI 0.46, 0.76).

- Lenvatinib (Lenvima) was studied in one randomized, double-blind, placebo-controlled Phase 3 trial in patients with locally recurrent or metastatic differentiated thyroid cancer refractory to RAI (N=392). The primary efficacy endpoint was PFS. Lenvatinib (Lenvima) had a median PFS of 18.3 months compared to 3.6 months for placebo with a HR of 0.21 (95% CI 0.16, 0.28).
- NCCN guidelines recommend lenvatinib (Lenvima) as the preferred regimen and sorafenib (Nexavar) as other recommended regimen for advanced and metastatic thyroid carcinoma (category 2A recommendations). NCCN considers lenvatinib (Lenvima) to be the preferred agent due to its response rate of 65% compared to 12% for sorafenib (Nexavar), although these agents have never been compared in head-to-head trials. Additionally, lenvatinib (Lenvima) and sorafenib (Nexavar) have not been studied in the settings of medullary and anaplastic thyroid carcinomas.

VII. **Soft Tissue Sarcoma (STS):**

- Pazopanib (Votrient) was studied as a targeted therapy option for the treatment of advanced Soft Tissue Sarcoma (STS) in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial (N=369). Enrolled patients had metastatic STS who had failed at least one anthracycline-based chemotherapy regimen. Although patients with most histological subtypes of STS were included in this trial, patients with gastrointestinal stromal tumors (GIST) and adipocyte tumors (liposarcoma) were excluded (of note, there are around 50 histological subtypes of STS). Histological subtype patient distribution for this trial consisted of 47% leiomyosarcoma, 10% synovial sarcoma, and 47% other soft tissue sarcomas. The primary endpoint was PFS. Pazopanib (Votrient) significantly prolonged PFS at 4.6 months vs 1.6 months for placebo ($p<0.0001$). There was no statistical difference between pazopanib (Votrient) and placebo for OS. NCCN guidelines recommend pazopanib (Votrient) as an option for palliative therapy for patients with progressive, unresectable, or metastatic STS with a category 2A recommendation.

VIII. **Endometrial Carcinoma (EC):**

- Advanced endometrial carcinomas have a poor prognosis, continued annual increase in incidence and disease related mortality. Nearly 84% of patients with recurrent endometrial carcinoma (EC) have microsatellite stable (MSS) or microsatellite-indeterminate tumors. Based on historical clinical trial data, although pembrolizumab is effective for microsatellite instability-high (MSI-H) disease (objective response rate (ORR), 57.1%), it appears less effective for MSS disease (best response was PR, 2/18 patients). Similarly, in a phase II study of lenvatinib monotherapy for advanced, previously treated, endometrial cancer, the ORR was 14.3% and the median PFS was 5.4 months. Thus, as monotherapy, lenvatinib and pembrolizumab do not have substantial evidence of efficacy for advanced EC. However, a novel approach to use these two agents in combination has been considered. Subsequent to FDA-approval, NCCN guideline for uterine carcinoma has provided a category 2A recommendation to the use of above combination, for the treatment of recurrent, high-risk and metastatic EC as a subsequent-line treatment option.
- Surgery is often the initial treatment for early-stage endometrial cancer and consists of a hysterectomy, often along with a salpingo-oophorectomy, and removal of lymph nodes.

In some cases, depending on localized metastases, debulking may be required. Post-surgical adjuvant regimens may utilize radiation therapy and/ or platinum-based chemotherapy as preferred treatment options. For advanced stage (stage III or IV) EC, or when a member is not a candidate for surgery, systemic chemotherapy (platinum-based regimen preferred), and hormone therapy (e.g., tamoxifen, fulvestrant) are first-line treatment options.

- In a pivotal trial leading to US-FDA approval, Lenvatinib (Lenvima) was studied in combination with pembrolizumab (Keytruda) in a single-arm, open-label, Phase 1b/2 trial (Keynote146/ Study111; N=108) in patients with metastatic endometrial carcinoma after progression on at least one prior systemic therapy. All patients in this trial were exposed to platinum-based chemotherapy in the first-line setting. The primary efficacy outcome, ORR at week 24, was 38.3% (95% CI, 28.8, 47.8). Median duration of response (DoR) for responding participants was 21.2 months (95%CI; 7.6-NR). Additionally, a median PFS of 7.4 months (95% CI; 5.3-8.7) and a median OS of 16.7 months (95% CI; 15.0-NE) were reported. This led to an accelerated FDA approval of lenvatinib (Lenvima) for the treatment of EC in combination with pembrolizumab (Keytruda).
- As of August 2021, efficacy and safety outcomes from a follow-up single-arm, open-label, randomized, active-controlled phase 3 trial have been reported. Keynote-775 / Study 309 (N= 827) compared efficacy and safety of the combination therapy with lenvatinib (Lenvima) and pembrolizumab (LEN+Pembro), with a treatment of physician's choice (TPC; doxorubicin or paclitaxel) via a 1:1 randomization. Randomization was further stratified by DNA mismatch repair (MMR) status (i.e., pMMR versus dMMR) and microsatellite stability (MSI-H versus MSS). Primary efficacy outcomes were PFS and OS. All participants had prior progression on or after a platinum-based chemotherapy and no previous exposure to PD-1/ PD-L1 therapy. At median 12.2 months of follow-up, PFS was significantly improved with LEN + pembro versus TPC in pMMR advanced EC (median 6.6 vs 3.8 months: HR 0.60). OS in this population subset was significantly longer with LEN + pembro versus TPC (median 17.4 vs 12.0 months; HR 0.68). Additionally, efficacy outcomes in the overall trial population (both pMMR and dMMR EC) also favored LEN+ Pembro over TPC [median OS 18.3 vs 11.4 months (HR 0.62) and median PFS 7.2 vs 3.8 months (HR 0.56)]. However, given the majority participants in this clinical trial had MSS/pMMR EC (n=697 out of 827), the FDA approval is limited to the treatment of MSS/pMMR EC.

IX. **Desmoid Tumors (DT):**

- Desmoid tumors (DT) are rare, noncancerous growths, that are unable to metastasize and occur as a result of mutations in fibroblasts of connective tissue. DT can arise anywhere in the body, but most commonly appear in the abdominal/intra-abdominal area. The clinical course is variable, often with an initial growth phase followed by long periods of arrest and regression. Symptoms commonly include pain, fatigue, deformity, and functional impairment. Although non-malignant, DT can progress in size if left untreated and increase the risk of invasion into local organs.
- Sorafenib (Nexavar) for the treatment of DT was studied in one Phase 3, double-blind, placebo-controlled trial. Eligible patients were required to have newly diagnosed DT, or progressive DT and either had not received previous treatment for progressing DT that were not amenable to surgery or had refractory or recurrent DT after at least one line of

therapy. Median subject age was 37 years, majority female (69%), and extra-abdominal tumor-location (57%). Fifty four percent of the subjects in the sorafenib (Nexavar) group were newly diagnosed with DT, while the remaining 46% had recurrent disease after at least one form of previous treatment. The treatment experienced sofenib (Nexavar) group treatments included surgery (46%), radiation therapy (12%), and systemic therapy (36%). The primary outcome was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR) and overall survival (OS). Results showed a statistically significant 87% reduction of disease risk progression in subjects who received sorafenib (Nexavar) versus subjects who received placebo (hazard ratio [HR] = 0.13; p< 0.001).

- A definitive diagnosis of DT requires histopathologic analysis of a biopsy sample of the tumor which is examined for presence of desmoid cells. Both DTWG (2020) and NCCN soft tissue sarcoma (2023) guidelines recommend a histological diagnosis of DT via an image-guided (CT or ultrasound) core needle or surgical biopsy of the tumor site. Due to rarity of disease and association with other germline mutation syndromes (i.e., familial adenomatous polyposis [FAP], Gardner syndrome), it is essential to rule out potential for differential diagnosis without association to desmoid tumors (e.g., Gardner syndrome). DT also shares similarities with other myofibroblastic diseases (e.g., sarcoma, gastrointestinal stromal tumor, nodular fasciitis, leiomyoma) with 30% to 40% of DT cases reported to be misdiagnosed following histologic analysis. NCCN guidelines recommend evaluation and treatment by a multidisciplinary team with expertise and experience in desmoid tumors; however, DTWG guidelines require confirmation of diagnosis by a soft tissue pathologist.
- Both DTWG (2020) and NCCN (V 2.2023) guidelines recommend active surveillance/observation alone until the tumor has shown progression and is accompanied by significant symptom burden, at which point, active treatment is pursued. NCCN guidelines also recommend active treatment if progression of DT is accompanied by potential for morbidity. Guidelines recommend earlier active treatment in the case of nonprogressive DT in anatomical locations where progression of the tumor would be morbid. The Phase 3, placebo-controlled study included patients with either newly diagnosed or progressing desmoid tumors within 6 months of registration. Inclusion criteria encompassed patients who had symptomatic, progressive, or morbid disease unresectable to surgery. There is currently sufficient evidence to support the use of sorafenib (Nexavar) in subjects with nonprogressive DT.
- The use of sorafenib (Nexavar) has not been studied in combination with other chemotherapy agents (e.g., methotrexate and vinorelbine) or tyrosine kinase inhibitors (TKI's) such as pazopanib for use in desmoid tumors. Due to the lack of safety and efficacy data with a combination regimen, use of sorafenib (Nexavar) is not recommend with any other oncology therapy for the management of desmoid tumors.

Investigational or Not Medically Necessary Uses

I. Lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Gastrointestinal Stromal Tumor
   B. Adipocytic Sarcoma/Liposarcoma

i. Pazopanib (Votrient) was studied as a targeted therapy option for the treatment of advanced Soft Tissue Sarcoma (STS) in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial (N=369). Enrolled patients had metastatic STS who had failed at least one anthracycline-based chemotherapy regimen. Although patients with most histological subtypes of STS were included in this trial, patients with gastrointestinal stromal tumors (GIST) and adipocyte tumors (liposarcoma) were excluded.

C. Sorafenib (Nexavar) in combination with erlotinib for Hepatocellular Carcinoma
   i. Sorafenib (Nexavar) in combination with erlotinib, was studied in a randomized, placebo-controlled, Phase 3 trial in 720 patients with advanced HCC. Results found that the combination did not significantly improve survival relative to sorafenib (Nexavar) in combination with placebo. The combination had a significantly lower disease control rate (p=0.021) and a shorter treatment duration of 86 days compared to 123 days for sorafenib/erlotinib and sorafenib/placebo, respectively.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
cabozantinib (Cabometyx)	Differentiated Thyroid Carcinoma (DTC)
	Renal Cell Carcinoma (RCC)
	Hepatocellular Carcinoma (HCC)
everolimus (Afinitor, Afinitor Disperz)	Angiomyolipoma of the kidney, tuberous sclerosis syndrome
	Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole
	Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic
	Renal Cell Carcinoma (RCC)
	Subependymal giant cell astrocytoma
	Partial seizure, adjunct, tuberous sclerosis syndrome
fedratinib (Inrebic®) Policy	Myelofibrosis
nirogacestat (Ogsiveo™) Policy	Desmoid tumors
regorafenib (Stivarga)	Colorectal Cancer
	Gastrointestinal Stromal Tumor
	Hepatocellular Carcinoma
vandetanib (Caprelsa)	Locally advanced or metastatic medullary thyroid cancer
sunitinib (Sutent)	Gastrointestinal stromal tumor
	Renal Cell Carcinoma (RCC)
	Neuroendocrine pancreatic tumor

Policy Implementation/Update:

Action and Summary of Changes	Date
Added requirement to trial generic pazopanib prior to branded Votrient	11/2023
Added desmoid tumors as a covered indication to generic and brand sorafenib (Nexavar)	02/2024
Added requirement to trial generic pazopanib prior to branded Votrient	11/2023
Added requirement to trial generic sorafenib tosylate prior to branded Nexavar	06/2022
Rearranged and updated Lenvima dosing and quantity limits based on recommended maximum dose for each indication; QL exceptions would be allowed only for dose reductions	02/2022
Moved "Sorafenib (Nexavar) for the treatment of desmoid tumors (aggressive fibromatosis)" out of the "Not Medically Necessary" section to "Investagtional Use" section; Changed policy name from "lenvatinib (Lenvima™), pazopanib (Votrient®), sorafenib (Nexavar®)" to "Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)"	10/2021
Updated policy to include Lenvima and pembrolizumab combination therapy for endometrial carcinoma and as first-line therapy for RCC; In the HCC setting: removed criteria requiring member being treatment-naïve allowing coverage in first-line as well as 2nd-line settings, added requirement for Child-Pugh class A/B7. Updates to supporting evidence sections.	09/2021

Added clinical trial data for sorafenib (Nexavar) in the setting of desmoid tumors to the supporting evidence (investigational and not medically necessary uses: C.ii)	04/2021
Updated supporting evidence for investigational indication of endometrial carcinoma for Lenvima	12/2020
Transitioned criteria to policy format and merged into one policy; Updated criteria to include lenvatinib (Lenvima) requires failure of at least one anti-angiogenic therapy and combination therapy of lenvatinib (Lenvima) with everolimus (Afinitor); Updated disease staging requirements for most indications; Updated information on endometrial cancer for lenvatinib (Lenvima); Updated supporting evidence section	10/2020
Previous reviews • Lenvima: Updated indication to include advanced renal cell carcinoma (2017), updated indication to include unresectable hepatocellular carcinoma (2018) • Votrient: Updated to reflect FDA approved indications and quantity limits (2016) • Nexavar: Updated to reflect FDA approved indications (2016)	10/2018, 06/2017, 03/2016, 03/2016
Criteria created • Lenvima: 2015 • Votrient: 2012 • Nexavar: 2012	03/2015 02/2012 03/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP295

Description

Nedosiran (Rivfloza) is a subcutaneously injected *LDHA*-directed small interfering RNA indicated to lower urinary oxalate levels in those with primary hyperoxaluria type 1 (PH1).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
nedosiran (Rivfloza)	Primary hyperoxaluria type 1 (PH1) with relatively preserved kidney function (e.g., eGFR ≥ 30 mL/min/1.73 m^2)	80mg vial*	2 vials/28 days
		128mg pre-filled syringe*	1 pre-filled syringe/28 days
		160mg pre-filled syringe*	

**Dosing is based on member's weight. Please see appendix.*

Initial Evaluation

I. **Nedosiran (Rivfloza)** may be considered medically necessary when the following criteria are met:
   A. Member is 9 years of age or older; **AND**
   B. Documentation of member's weight; **AND**
   C. Medication is prescribed by, or in consultation with, a nephrologist, urologist, or medical geneticist; **AND**
   D. Medication will not be used in combination with lumasiran (Oxlumo); **AND**
   E. A diagnosis of **primary hyperoxaluria type 1 (PH1)** when the following are met:
      1. Diagnosis of PH1 confirmed with alanine glyoxylate aminotransferase (*AGXT*) mutation via genetic testing or liver enzyme analysis; **AND**
      2. Member has not undergone a liver transplant; **AND**
      3. Provider attestation that the member has an eGFR ≥30mL/min/1.73m^2; **AND**
      4. Documentation of baseline for one or more of the following:
         i. Urinary oxalate excretion level (corrected for BSA)
         ii. Spot urinary oxalate: creatinine ratio
         iii. Estimated glomerular filtration rate (eGFR)
         iv. Plasma oxalate level; **AND**
      5. Medication will be used in combination with pyridoxine; **OR**
         i. Member has been classified as a non-responder to pyridoxine after a three-month trial

II. Nedosiran (Rivfloza) is considered investigational when used for all other conditions, including but not limited to:

A. Primary hyperoxaluria type 2 (PH2)
B. Primary hyperoxaluria type 3 (PH3)
C. When used in combination with lumasiran (Oxlumo)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of member's weight; **AND**
IV. Medication will not be used in combination with lumasiran (Oxlumo); **AND**
V. Member has not undergone a liver transplant; **AND**
VI. Attestation member has an eGFR ≥30mL/min/1.73m2; **AND**
VII. Member has exhibited improvement or stability of disease symptoms as evidenced by <u>at least one</u> of the following:
   A. Decrease in urinary oxalate excretion from baseline
   B. Reduction in spot urinary oxalate: creatinine ratio from baseline
   C. Stabilization of glomerular filtration rate
   D. Decrease in plasma oxalate level from baseline; **AND**
VIII. Medication will be used in combination with pyridoxine; **OR**
   A. Member has been classified as a non-responder to pyridoxine after a three-month trial

Supporting Evidence

I. Nedosiran (Rivfloza) is a *LDHA*-directed small interfering RNA, FDA-approved to lower urinary oxalate levels in those nine years of age and older with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function (e.g., eGFR ≥ 30 mL/min/1.73 m^2). The efficacy and safety of nedosiran (Rivfloza) has not been established in patients under the age of nine. Dosing of nedosiran (Rivfloza) is based on actual body weight.
II. Primary hyperoxaluria (PH) is a group of autosomal recessive disorders of hepatic glyoxylate metabolism that cause the overproduction of endogenous oxalate — a redundant metabolic end product that is excreted primarily via the kidneys. Primary hyperoxaluria type 1 (PH1) is the most common and severe type of PH, due to mutations of the *AGXT* gene. Variants of this gene result in enhanced oxalate production. In high levels, oxalate forms crystals which can deposit in various parts of the body. As oxalate is typically excreted in the urine, the kidney is the prime target for oxalate deposition resulting in nephrocalcinosis, kidney stones, and end-stage kidney disease (ESKD). Some patients progress to systemic oxalosis when the GFR falls <30 to 40 mL/min per 1.73 m^2 which results in calcium oxalate deposits in the heart, blood vessels, joints, bones, and retinas.
III. PH1, which accounts for approximately 80% of PH cases, has an estimated prevalence of one to three per million in Europe and North America. Age at diagnosis varies, with some not being diagnosed until adulthood, and the median age at diagnosis is 5 years old. Those with more

severe disease present earlier in life with a diagnosis in infancy, accounting for approximately 26% of patients.

IV. Given the complexities related to diagnosis, treatment, and management of PH1, treatment in this disease space must be initiated by, or in consultation with, a specialist (e.g., nephrologist, urologist, or medical geneticist).

V. Nedosiran (Rivfloza) was studied in a Phase 2, multinational, double-blind, placebo-controlled trial (PHYOX2) of 35 patients with genetically confirmed PH1 (n=29) or PH2 (n=6). Participants also had to have a 24-hour urinary oxalate (Uox) excretion of ≥0.7 mmol and an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2. Patients were randomized 2:1 to receive nedosiran (Rivfloza) or placebo. All participants were instructed to continue their standard of care (conservative) therapies. Median age: 20 years (range: 9–46 years), 51% female, 71% White, 17% Asian. Baseline demographic and disease characteristics were generally balanced between the two treatment arms, with the exception of 24-hour Uox excretion at baseline, which was higher in the placebo arm (1.33 vs 1.96 mmol/24 hr). The primary efficacy outcome was the percent change from baseline in 24-hour Uox excretion, as assessed by area under the curve (AUC) from day 90 to day 180. Key secondary endpoints included the proportion of participants reaching normal or near-normal 24-hour Uox excretion on at least two consecutive visits, starting at day 90.

VI. The least-squares (LS) mean AUC 24-hour Uox was -3486 (95% CI: -5025, -1947) in the nedosiran (Rivfloza) group compared to 1490 (95% CI: 781, 3761) in the placebo group; a between group difference of 4976 (95% CI: 2803, 7149; p< 0.0001) was detected. The LS mean percent change from baseline in 24-hour urinary oxalate excretion (corrected for BSA in patients <18 years of age) averaged over Days 90, 120, 150 and 180, was -37% (95% CI: -53%, -21%) in the nedosiran (Rivfloza) group and 12% (95% CI: -12%, 36%) in the placebo group, for a between group difference of 49% (95% CI: 26%, 72%). Among patients with PH1, the between group difference was 56% (95% CI: 33%, 80%).

VII. While nedosiran (Rivfloza) demonstrated statistically significant results for the primary endpoint and this surrogate endpoint is accepted as a clinically meaningful endpoint by the FDA, the magnitude of AUC reduction correlating to a clinically significant impact is unclear at this time. The key secondary endpoint was only achieved in 48% of patients and was driven by patients who achieved a near-normalized 24-hour Uox, rather than those with normalized 24-hour Uox. Additionally, the secondary endpoint results may be difficult to reconcile as baseline characteristics between the treatment groups were unbalanced, and results may favor the study drug. Therefore, the quality of evidence is considered low.

VIII. Per the clinical practice recommendations for primary hyperoxaluria genetic testing is the gold standard for the diagnosis of all three types of PH. The consensus statement recommends that all patients who are suspected to have PH should undergo genetic assessment, as genetic confirmation of PH and typing are pivotal to the management of these patients. PH1 is due to mutations of the AGXT gene. Whereas PH2 is due to a deficiency in glyoxylate and hydroxypyruvate reductase (GRHPR) and PH3 is due to the loss of function of the mitochondrial enzyme 4-hydroxy-2-oxoglutarate adolase (HOGA). Biochemical assessment has an important role in the diagnostic workup of patients with symptoms suggestive of PH and can focus genetic testing. It can also be used as an indication of therapeutic response. However, measurement of

oxalate and relevant metabolites is not without difficulty, and one must interpret the results carefully, taking all potential flaws into account.

IX. Liver transplantation is the only curative intervention for PH1 as it corrects the underlying enzymatic defect due to mutations of the *AGXT* gene. Use and efficacy of nedosiran (Rivfloza) after transplant has not been evaluated in clinical trials.

IX. While the primary endpoint in clinical trials was 24-hour urinary oxalate excretion, it may be difficult for some patients to obtain a 24-hour urine collection in clinical practice. This can especially be noted in infants and small children who are not toilet trained, working adults, and school aged children. As a result, oxalate excretion can be evaluated by measuring the molar oxalate:creatinine ratio in spot urine samples. A 24-hour oxalate excretion does not correlate perfectly with oxalate-to-creatinine ratio, possibly as a consequence of imperfect urine collections and the effect of body size, which influences creatinine excretion and may therefore affect the oxalate-to-creatinine ratio. However, available evidence suggests that either measurement can be used to monitor response to treatment. Plasma oxalate can be a useful biomarker in PH1 as urinary oxalate measurements may be falsely low in patients with kidney insufficiency and progressive disease, which is common in patients with type 1 disease. In this setting, plasma oxalate levels may be useful, as there is an inverse relation between plasma oxalate and kidney function in children with early stages of chronic kidney disease where oxalate excretion has declined to such an extent that urine results are misleading. Lastly, estimated glomerular filtration rate can help to assess progression in ESKD in PH1 patients.

X. The efficacy and stability of symptoms can be assessed by multiple surrogate endpoints as compared to baseline (i.e., a decrease in urinary oxalate excretion from baseline, reduction in spot urinary oxalate: creatinine ratio from baseline, stabilization of glomerular filtration rate, decrease in plasma oxalate level from baseline). Therefore, improvement or stability in one metric provides enough evidence to support continuation of therapy.

X. Aside from drug therapies general measures used in all patients with PH1 include: hyperhydration, citrate and magnesium supplements to increase urinary oxalate solubility, and pyridoxine (vitamin B6). Pyridoxine is variably effective in some genotypes and is trialed for three to 6 months to see if the patient is a responder. Liver transplant is curative as it corrects the mutation in the AGXT gene but is associated with significant morbidity. Some patients may undergo sequential or isolated liver-kidney transplants.

Investigational or Not Medically Necessary Uses

I. Nedosiran (Rivfloza) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Primary hyperoxaluria type 2 (PH2)
      i. Only six patients diagnosed with PH2 were included in the nedosiran (Rivfloza) pivotal trial (PHYOX2). There was no consistent pattern observed for 24-hour Uox excretion in treated or untreated PH2 participants, thus the safety and efficacy of nedosiran (Rivfloza) in PH2 remains investigational.
   B. Primary hyperoxaluria type 3 (PH3)
      i. Nedosiran (Rivfloza) has not been FDA-approved, or sufficiently studied for safety and efficacy for PH3.
   C. When used in combination with lumasiran (Oxlumo)

i. On November 23, 2020, FDA approved lumasiran (Oxlumo) to lower urinary oxalate levels, a surrogate for kidney stones and loss of kidney function, in pediatric and adult patients with PH1 who have relatively preserved kidney function. Lumasiran (Oxlumo) is a small interfering ribonucleic acid (siRNA) that reduces levels of the glycolate oxidase enzyme by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes. On October 6, 2022, lumasiran (Oxlumo) was also approved to lower plasma oxalate, a surrogate for systemic manifestations of PH1, in patients with more advanced kidney disease. While both lumasiran (Oxlumo) and nedosiran (Rivfloza) are siRNA therapies approved for the treatment of PH1, their concurrent use has not been evaluated for safety or efficacy.

Appendix

Table 1: FDA approved dosing

Age	Body Weight	Dosing Regimen
Adults and adolescents 12 years and older	≥ 50 kg	160 mg once monthly (Pre-filled Syringe, 1mL)
	< 50 kg	128 mg once monthly (Pre-filled Syringe, 0.8mL)
Children 9 to 11 years	≥ 50 kg	160 mg once monthly (Pre-filled Syringe, 1mL)
	< 50 kg	3.3 mg/kg once monthly, not to exceed 128 mg (Vial, dose volume rounded to nearest 0.1 mL)

References

1. Rivfloza. Package Insert. Novo Nordisk Inc; September 2023.
2. Baum MA, Langman C, Cochat P, et al. PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2. Kidney Int. 2023;103(1):207-217.
3. Groothoff JW, Metry E, Deesker L, et al. Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. Nat Rev Nephrol. 2023;19(3):194-211.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created.	02/2024

Policy Type: PA/SP Pharmacy Coverage Policy: UMP077

Split Fill Management*

Description

Neratinib (Nerlynx) is an orally administered Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 and 4 (HER2, HER4) irreversible inhibitor.

Length of Authorization

- Initial:
  - i. Early stage breast cancer: 12 months
  - ii. Metastatic breast cancer: Six months
- Renewal:
  - i. Early stage breast cancer: Cannot be renewed
  - ii. Metastatic breast cancer: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
neratinib (Nerlynx)	40 mg tablets	Breast cancer, early stage, HER2-positive, following trastuzumab	180 tablets/30 days
		Breast cancer, advanced or metastatic HER2-positive	

Initial Evaluation

I. Neratinib (Nerlynx) may be considered medically necessary when the following criteria are met:
   A. Member is a female 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Neratinib (Nerlynx) will **not** be used in combination with another oncology therapy unless outlined below (e.g. in combination with capecitabine in metastatic disease); **AND**
   D. The member has **not** previously progressed on, or after, treatment with another tyrosine kinase inhibitor (e.g., lapatinib [Tykerb], tucatinib [Tukysa]); **AND**
   E. A diagnosis of one of the following:
      1. **Early stage (I-III) breast cancer**; **AND**
         i. Documentation is provided showing the disease is HER2-positive AND hormone receptor (HR)-positive; **AND**
         ii. The member has received adjuvant trastuzumab-based therapy (e.g., Herceptin, Trazimera, Kanjinti, etc.) within the past 12 months; **OR**
      2. **Advanced or metastatic breast cancer; AND**
         i. Documentation is provided showing the disease is HER2-positive; **AND**

ii. Member has received ≥2 prior anti-HER2-based regimens [e.g., trastuzumab (Herceptin), pertuzumab (Perjeta), trastuzumab emtansine (Kadcyla; TDM-1)] in the metastatic setting; **AND**
iii. Will be used in combination with capecitabine

II. Neratinib (Nerlynx) is considered not medically necessary when criteria above are not met and/or when used for:
A. Early stage breast cancer in members that have not received trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.) in the past 12 months
B. Early stage breast cancer that is not HR-positive
C. Early stage breast cancer in combination with trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.)

III. Neratinib (Nerlynx) is considered investigational when used for all other conditions, including but not limited to:
A. Triple negative breast cancer
B. Breast cancer that is HER-2 negative
C. Non-small cell lung cancer
D. Colorectal cancer
E. Head and neck cancer
F. Ovarian, endometrial, uterine cancer
G. Bladder or rectal cancer
H. Early stage breast cancer for greater than one year
I. Solid tumors, other than breast cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, an oncologist; **AND**
IV. A diagnosis of **advanced or metastatic breast cancer; AND**
- Will be used in combination with capecitabine; **AND**
- Will not be used with any other oncology therapy outside of capecitabine; **AND**
- Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

I. Neratinib (Nerlynx) was evaluated for safety and efficacy in the ExteNET trial; a randomized, double-blind, placebo-controlled trial in women who had been previously treated with trastuzumab therapy and had HER2-positive breast cancer.

II. Subjects included had early stage (I-III) disease and had completed trastuzumab within the past two years; however, the majority of subjects had received trastuzumab within the past year (81%). Notably, results were statistically significant in those that received trastuzumab within the past year and were not for those that had received treatment 1-2 years prior. The primary outcome was invasive disease-free survival (iDFS) defined as time between date of randomization to first occurrence of invasive recurrence. Results for the iDFS at 24 months was 94.2% for neratinib (Nerlynx) compared to 91.9% for placebo (HR 0.66 [0.49-0.90], p=0.008). Subgroup analyses showed a statistically significant result for those with HR-positive disease but did not for HR-negative disease. Additionally, results favored neratinib (Nerlynx) in those that used therapy after trastuzumab; however, were not significant for those concurrently receiving trastuzumab.

III. Neratinib (Nerlynx) has only been evaluated for safety and efficacy for up to one year of therapy in early stage disease; matching the prescribing information, which notes continuous dosing for one year in this setting.

IV. Neratinib (Nerlynx) was evaluated for safety and efficacy in the advanced or metastatic population in the NALA trial; a randomized, open label, trial evaluating neratinib (Nerlynx) plus capecitabine compared to lapatinib (Tykerb). Patients included in the trial had metastatic HER2-postive breast cancer and had received 2 or more prior anti-HER2 regimens [e.g., trastuzumab (Herceptin), pertuzumab (Perjeta), trastuzumab emtansine (Kadcyla; TDM-1)] in the metastatic setting. Median progression free survival (PFS) was 5.6 months with neratinib (Nerlynx) plus capecitabine and 5.5 months with lapatinib plus capecitabine (HR, 0.76; 95% [CI], 0.63 to 0.93; P=0.0059). Overall survival was 21.0 months with the neratinib (Nerlynx) arm and 18.7 months with the lapatinib arm; however, the between group difference was not statistically significant (HR, 0.88; 95% CI, 0.72 to 1.07; P=0.2086).

V. Patients in the NALA trial were excluded if they were previously treated with capecitabine, neratinib, lapatinib, or any other HER2 directed tyrosine kinase inhibitor. At this time, there is a lack of scientific evaluation for safety and efficacy of neratinib (Nerlynx) following progression on, or after, another tyrosine kinase inhibitor.

VI. In the NALA trial, 59% of patients were hormone receptor positive (HR+) and 41% were hormone receptor negative (HR-). Thus, coverage of neratinib (Nerlynx) is available regardless of hormone receptor status.

VII. ER testing should be used to determine if a patient is a candidate for endocrine therapies. Per NCCN guidelines, women with Stage IV or recurrent disease characterized by tumors that are HR-positive, HER2-positive tumors have the option of receiving HER2-directed therapy as a component of their treatment plan. Options include, treatment with a HER2-targeted therapy plus chemotherapy or endocrine therapy alone or in combination with HER2-targeted therapy. Endocrine therapy alone or in combination with HER2- targeted therapy is a less toxic approach compared with HER2-targeted therapy combined with chemotherapy. Premenopausal women treated with HER2-targeted therapy and endocrine therapy should receive ovarian suppression or ablation.

Investigational or Not Medically Necessary Uses

I. In the early stage breast cancer pivotal trial, ExteNET, subgroup analyses showed non statistically significant results for neratinib (Nerlynx) in the following populations:
   A. Breast cancer in members that have not received trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.) in the past 12 months
   B. Breast cancer that is not HR-positive
   C. Breast cancer in combination with trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.)

II. Neratinib (Nerlynx) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. Triple negative breast cancer
   B. Breast cancer that is HER-2 negative
   C. Non-small cell lung cancer
   D. Colorectal cancer
   E. Head and neck cancer
   F. Ovarian, endometrial, uterine cancer
   G. Bladder or rectal cancer
   H. Breast cancer for greater than one year
   I. Solid tumors, other than breast cancer

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. NCCN Clinical Practice Guideline in Oncology: Breast Cancer. Version 4.2020. National Comprehensive Cancer Network. Available at https://www.nccn.org/professionals/ physician_gls/pdf/breast.pdf. Updated May 8, 2020.
2. Nerlynx [Prescribing Information]. Los Angeles, CA. Puma Biotechnology, Inc. February 2020.
3. Chan PA, Delaloge S., Holmes FA. , et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2016;17(3): 367-377.
4. Puma Biotechnology, Inc. A study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ metastatic breast cancer who have received two or more prior HER2 directed regimens in the metastatic setting (NALA). Available from: http://www.clinicaltrials.gov/ct2/show/NCT01808573. NLM identifier: NCT01808573.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new indication for advanced or metastatic breast cancer. Addition of split fill management.	07/2020
Criteria transitioned to policy, with updates to newest format: inclusion of specialty provider, clarification on concurrent therapies, age requirement.	10/2019
Criteria created	09/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP136

Split Fill Management*

Description

Nilotinib (Tasigna) is a Bcr-Abl kinase inhibitor that binds to, and stabilizes, the inactive conformation of the kinase domain of the Abl protein.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
nilotinib (Tasigna)	50 mg capsules	Newly diagnosed OR resistant/intolerant Ph+ CML in chronic phase	112 capsules/28 days
	150 mg capsules	Newly diagnosed Ph+ CML in chronic phase	112 capsules/28 days
	200 mg capsules	Resistant or intolerant Ph+ CML Gastrointestinal Stromal Tumors (GIST)	112 capsules/28 days

Initial Evaluation

I. Nilotinib (Tasigna) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
   C. A diagnosis of one of the following:
      1. **Chronic myelogenous leukemia (CML)**; **AND**
         i. Member is newly diagnosed with Philadelphia chromosome-positive (Ph+) or BCR-ABL1 mutation positive CML in chronic phase; **OR**
         ii. Member is diagnosed with chronic OR accelerated phase Ph+ or BCR-ABL1 mutation positive CML; **AND**
            a. Member is 18 years of age or older; **AND**
            b. Treatment with a tyrosine kinase inhibitor [e.g. imatinib (Gleevec)] has been ineffective, contraindicated, or not tolerated; **OR**
         iii. Member is diagnosed with chronic phase Ph+ or BCR-ABL1 mutation positive CML; **AND**
            a. Member is one year of age or older; **AND**
            b. Treatment with a tyrosine kinase inhibitor [e.g. imatinib (Gleevec)] has been ineffective, contraindicated, or not tolerated; **OR**

2. **Gastrointestinal Stromal Tumors (GIST)**; **AND**
    i. Treatment with ALL the following have been ineffective, contraindicated, or not tolerated:
        a. imatinib (Gleevec)
        b. sunitinib (Sutent)
        c. regorafenib (Stivarga)

II. Nilotinib (Tasigna) is considered investigational when used for all other conditions, including but not limited to:
    A. CML without Philadelphia chromosome
    B. CML in the blast phase

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through use of samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Nilotinib (Tasigna) is prescribed by, or in consultation with, an oncologist; **AND**
IV. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
V. Clinical documentation of response to treatment, such as stabilization of disease or decrease in tumor size or spread is provided.

Supporting Evidence

I. Nilotinib (Tasigna) is FDA-approved for treatment of adult and pediatric patients greater than one year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase and is a NCCN Category 1.
II. Nilotinib (Tasigna) for the treatment Ph+ CML resistant to prior therapy is only FDA-approved for use in the pediatric population in patients with chronic phase Ph+CML.
III. Nilotinib (Tasigna) is FDA-approved for use in adult patients with chronic phase and accelerated phase Ph+ CML resistant to, or intolerant of, prior therapy that included imatinib.
IV. Payment considerations for nilotinib for the treatment of Gastrointestinal Stromal tumors is reserved for members who have tried and failed imatinib (Gleevec) and sunitinib (Sutent) for the treatment of GIST. This recommendation is reflective of NCCN guidelines. Much of the data comes from phase II studies and retrospective analyses involving a small number of patients. In a randomized phase 3 study of nilotinib as 3rd line therapy and best supportive care (with or without a TKI) in patients with GIST resistant to imatinib and sunitinib (n=248) the PFS on nilotinib (Tasigna) was not found to be superior to best supportive care (109 days vs 111 days; P=0.56). Additionally, regorafenib has FDA approval and NCCN category 1 designation for GIST in patients previously treated with imatinib and sunitinib.

Investigational or Not Medically Necessary Uses

I. Nilotinib (Tasigna) has not been sufficiently evaluated in the following settings. Limited evidence may be available;, however, safety and efficacy have not been established for:
   A. CML without Philadelphia chromosome
   B. CML in the blast phase

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Tasigna [Prescribing Information]. East Hanover, NJ: Novartis; September 2019.
2. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia – v.2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.
3. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma – v.3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf.

Policy Implementation/Update:

Date Created	February 2012
Date Effective	August 2010
Last Updated	December 2019
Last Reviewed	03/2012, 07/2012, 08/2012, 01/2013, 05/2018, 12/2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format. Expanded renewal duration from 6 months to 12 months for all indications. Required agent be used as monotherapy and not in combination with other oncolytics.	12/2019
Added new indication in pediatric patients one year of age or older with Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase (Ph+ CML-CP). Allowed for approval in the second line CML setting after being treated with a TKI (other than imatinib). For GIST off-label use, added a requirement to try/fail regorafenib as well as the existing agents (imatinib and sunitinib).	05/2018

Policy Type: PA Pharmacy Coverage Policy: UMP199

Description

Nilutamide (Nilandron) is an orally active first-generation nonsteroidal antiandrogen agent, which blocks effects of testosterone at the androgen receptor level, preventing androgen response.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Nilutamide (Nilandron)*	150 mg tablet	Metastatic prostate cancer	**Initial**: 60 tablets/ 30 days for one month **Maintenance**: 30 tablets/ 30 days

*Generic nilutamide is a formulary agent and does not require prior authorization

Initial Evaluation

I. Nilutamide (Nilandron) may be considered medically necessary when following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
   C. A diagnosis of **metastatic prostate cancer**; **AND**
   D. Treatment with generic nilutamide has been ineffective, contraindicated or not tolerated

II. Nilutamide (Nilandron) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member has absence of unacceptable toxicity from the medication; **AND**
III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Supporting Evidence

I. Nilutamide (Nilandron) is an orally active antiandrogen drug that works by blocking the effects of testosterone at the androgen receptor level thereby preventing an androgenic response. Nilandron interrupts the effect that testosterone has on the prostate and deprives it of signals typically responsible for growth and cell differentiation in the prostate.

II. Nilutamide (Nilandron) is FDA-approved for adult members (18 years and older) as a combination agent with surgical castration for the treatment of metastatic prostate cancer (Stage D2).

III. There are multiple treatment modalities for prostate cancer, wherein the choice of therapy depends on the manifestations of the disease. The initial and continued approach should be directed by a specialist due to the nuances of treatment, monitoring of disease, treatment safety, evaluation of efficacy, and consideration for patient specific goals. Therefore, nilutamide (Nilandron) should be prescribed by, or in consultation with, and oncologist or urologist.

IV. Coverage of brand name nilutamide (Nilandron) requires failure, intolerance or contraindication to generic nilutamide. Nilutamide is the AB-rated generic to nilutamide (Nilandron), and is deemed to be bioequivalent to the brand formulation; however, is a more cost-effective option.

References

1. Nilandron (nilutamide) [prescribing information]. St. Michael, Barbados: Concordia Pharmaceuticals; received May 2017.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	10/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP138

Split Fill Management*

Description

Nintedanib (Ofev) is an orally administered tyrosine kinase inhibitor.
Pirfenidone (Esbriet) is an orally administered pyridine that is thought to exert antifibrotic properties by decreasing fibroblast proliferation and the production of fibrosis associated proteins and cytokines.

Length of Authorization

- Initial:
  - Esbriet: 12 months
  - Ofev: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
nintedanib (Ofev)	Idiopathic pulmonary fibrosis (IPF); Systemic sclerosis-associated interstitial lung disease (SSc-ILD); Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype	100 mg capsules	60 capsules/30 days
		150 mg capsules	
pirfenidone (generic Esbriet)	Idiopathic Pulmonary Fibrosis (IPF)	267 mg capsules or tablets	270 capsules or tablets/ 30 days
		534 mg tablets	120 tablets/30 days
		801 mg tablets	90 tablets/30 days
pirfenidone (Esbriet)	Idiopathic Pulmonary Fibrosis (IPF)	267 mg capsules or tablets	270 capsules or tablets/ 30 days
		801 mg tablets	90 tablets/30 days

Initial Evaluation

I. **Nintedanib (Ofev) and prifenidone (Esbriet)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pulmonologist; **AND**

C. Nintedanib (Ofev) and prifenidone (Esbriet) will not be used in combination with each other; **AND**
D. Provider attests the member is currently abstaining from <u>any form of smoking</u>; **AND**
E. Documentation of baseline assessment [forced vital capacity (%FVC) **OR** carbon monoxide diffusing capacity (DLCO) **OR** six-minute walking distance (6MWD)]; **AND**
F. A diagnosis of one of the following:
    1. **Idiopathic pulmonary fibrosis (IPF); AND**
        i. Member has a usual interstitial pneumonia pattern (UIP) confirmed by a high resolution computed tomographic (HRCT) scan or surgical lung biopsy; **AND**
        ii. The request is for generic pirfenidone tablets; **OR**
            a. The request is for generic pirfenidone <u>capsules</u>, and treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **OR**
            b. The request is for brand Esbriet; **AND**
                i. Treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **AND**
                ii. Treatment with generic pirfenidone capsules has been ineffective, not tolerated, or contraindicated; **OR**
        iii. If the request is Nintedanib (Ofev), treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **OR**
    2. **Systemic sclerosis-associated interstitial lung disease (SSc-ILD); AND**
        i. Request is for nintedanib (Ofev); **AND**
        ii. The diagnosis confirmed by a high resolution computed tomographic (HRCT) scan; **OR**
    3. **Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype; AND**
        i. Request is for nintedanib (Ofev); **AND**
        ii. Member has fibrotic features in lungs confirmed by a high resolution computed tomographic (HRCT) scan; **AND**
        iii. Member has clinical signs of progression (eg. decline in %FVC with worsening respiratory symptoms **or** increasing extent of fibrotic changes on chest imaging)

II. Nintedanib (Ofev) and prifenidone (Esbriet) are considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
A. Bronchiolitis Obliterans Syndrome (BOS)
B. Lymphangioleiomyomatosis (LAM)
C. Non-Small Cell Lung Cancer (NSCLC)
D. Malignant Pleural Mesothelioma (MPM)
E. Esophagogastric Cancer
F. Thyroid Cancer
G. Breast Cancer
H. Ovarian Cancer

I. Pancreatic Cancer
J. Used in combination with other medications within this policy
K. Multiple Sclerosis
L. Chronic Lung Allograft Dysfunction
M. Radiation-induced Lung Injury
N. Diabetic nephropathy
O. Glomerulosclerosis
P. Cardiac Failure

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
II. The member is not continuing therapy based off established therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for continuation through this health plan; **AND**
III. Provider attests that member has exhibited improvement or stability of disease symptoms (e.g., increase in forced vital capacity (%FVC), carbon monoxide diffusing capacity (DLCO), or six-minute walking distance (6MWD) from baseline); **AND**
IV. Nintedanib (Ofev) and prifenidone (Esbriet) will not be used in combination with each other; **AND**
V. Provider attests that member is currently abstaining from any form of smoking; **AND**
VI. A diagnosis of one of the following:
    a. **Idiopathic pulmonary fibrosis (IPF); AND**
        1. The request is for nintedanib (Ofev); **OR**
        2. The request is for generic pirfenidone tablets; **OR**
            a. The request is for generic pirfenidone capsules, and treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **OR**
            b. The request is for brand Esbriet; **AND**
                i. Treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **AND**
                ii. Treatment with generic pirfenidone capsules has been ineffective, not tolerated, or contraindicated; **OR**
    b. **Systemic sclerosis-associated interstitial lung disease (SSc-ILD); AND**
        i. Request is for nintedanib (Ofev); **OR**
    c. **Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype; AND**
        i. Request is for nintedanib (Ofev)

Supporting Evidence

I. Nintedanib (Ofev) inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). It binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signaling 13 cascades.

II. Idiopathic pulmonary fibrosis (IPF) is an idiopathic chronic fibrosing interstitial pneumonia with a histopathologic or radiographic pattern of usual interstitial pneumonia (UIP).

III. High resolution computed tomography (HRCT) should be obtained in all patients suspected of having IPF. When the results of the HRCT cannot allow the clinician to make a confident diagnosis of IPF, surgical lung biopsy may be warranted. However, the decision requires assessment of the benefits of having a definitive diagnosis relative to the risks of the surgical procedure.

IV. For the treatment of IPF, nintedanib (Ofev) was studied in 1,066 patients with IPF in two Phase 3 trials (INPULSIS-1 and INPULSIS-2). These were randomized, double-blind, placebo-controlled studies comparing treatment with nintedanib (Ofev) 150 mg twice daily to placebo for 52 weeks.

- The primary outcome: The adjusted annual rate of change in FVC (in mL):
  i. INPULSIS-1: -114.7 mL per year in the nintedanib (Ofev) group and -239.9 mL per year in the placebo group over week 52 (absolute difference of 125.2 mL, 95% CI: 77.7, 172.8; $p<0.001$)
  ii. INPULSIS-2: -113.6 mL per year in the nintedanib (Ofev) group and -207.3 mL per year in the placebo group over week 52 (absolute difference of 93.7 mL, 95% CI: 44.8, 142.7; $p<0.001$)
- The secondary lung function outcomes:

	INPULSIS-1			INPULSIS-2		
End Points	**Nintedanib (N=307)**	**Placebo (N=204)**	**95% CI; *P* value**	**Nintedanib (N=327)**	**Placebo (N-217)**	**95% CI; *P* value**
Adjusted absolute mean change from baseline in FVC (mL)	-95.1	-205.0	109.9 (71.3, 148.6; *P*<0.001)	-95.3	-205.0	109.8 (70.9, 148.6; *P*<0.001)
Adjusted absolute mean change from baseline in FVC (% predicted)	-2.8%	-6.0%	3.2% (2.1, 4.3; *P*<0.001)	-3.1%	-6.2%	3.1% (1.9, 4.3; *P*<0.001)
FVC response at week 52 (%): FVC decline ≤ 5%	52.8%	38.2%	1.85% (1.28, 2.66; *p*=0.001)	53.2%	39.3%	1.79% (1.23, 2.55; *p*=0.001)
FVC response at week 52 (%): FVC decline ≤ 10%	70.6%	56.9%	1.91% (1.32, 2.79; *P*<0.001)	69.6%	63.9%	1.29% (0.89, 1.86; *p*=0.18)

V. The presence of SSc-ILD is defined by the identification of fibrotic features on HRCT scan. Surgical lung biopsy is seldom performed in SSc patients, unless the HRCT pattern is atypical, there is suspicion of a different diagnosis, or there is a complication such as cancer.

VI. Pulmonary function tests (PFT) in patients with SSc-ILD demonstrate a restrictive pattern, with FVC and diffusion capacity of the lung for carbon monoxide (DLCO). DLCO is a measure of the conductance of gas transfer from inspired gas to the red blood cells. A low DLCO combined with reduced lung volumes suggests interstitial lung disease (ILD).

VII. For systemic sclerosis-associated interstitial lung disease (SSc-ILD), nintedanib (Ofev) was studied in a Phase 3, randomized, double-blind, placebo-controlled trial (N=576) (SENSCIS trial). Patients received either nintedanib (Ofev) 150 mg twice daily (N=228) or placebo (N=288) for at least 52 weeks.

- The primary outcome: The adjusted annual rate of change in FVC (in mL): -52.4 mL per year in the nintedanib (Ofev) group and -93.3 mL per year in the placebo group over week 52 (absolute difference of 40.9 mL, 95% CI: 2.9, 79.0; $p=0.04$).

VIII. Safety and efficacy of nintedanib (Ofev) have not been established in pediatric patients.

IX. The safety and efficacy of pirfenidone (Esbriet) was studied in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in patients (40 to 80 years of age) with idiopathic pulmonary fibrosis (IPF) and a %FVC of at least 50%.
   A. Study One: 52-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=278) versus placebo (n=277). The primary efficacy outcome for the change in %FVC at week 52 demonstrated a statistically significant treatment effect with pirfenidone (Esbriet) when compared to placebo.
   B. Study Two: 72-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=174) or pirfenidone (Esbriet) 1197 mg/day (n=87) to placebo (n=174). The primary efficacy outcome for the change in %FVC at week 72 demonstrated a statistically significant treatment effect with pirfenidone (Esbriet) when compared to placebo.
   C. Study Three: 72-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=171) to placebo (n=173). In this study, there was no statistically significant difference at week 72 for the change in %FVC from baseline when compared to placebo.

X. The exact etiology of IPF is not known, but the associated risk factors include cigarette smoking, viral infection, environmental pollutants, chronic aspiration, genetic predisposition, and drugs.

XI. According to the American Thoracic Society guidelines, the diagnosis of IPF requires:
   A. Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
   B. The presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy.
   C. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

XII. The clinical efficacy of nitendanib (Ofev) has been studied in patients with chronic fibrosing ILDs with a progressive phenotype in a randomized, double-blind, placebo-controlled phase 3 trial (Study 5). A total of 663 patients were randomized in a 1:1 ratio to receive either nitendanib (Ofev) 150 mg twice daily or matching placebo for at least 52 weeks. Randomization was stratified based on high resolution computed tomography (HRCT) fibrotic pattern.
   A. The primary endpoint was the annual rate of decline in FVC (in mL) over 52 weeks. There was a statistically significant reduction by 107 mL in patients receiving OFEV compared to patients receiving placebo.

XIII. High-resolution computed tomography (HRCT) of the chest is mandatory in order to assess if ILD is present and, if so, to begin the differential diagnosis.

XIV. Progression of fibrosing ILDs is reflected in an increase in fibrosis evident on a computed tomography scan, a decline in FVC and gas exchange (DLCO), worsening of symptoms and exercise capacity (6MWD), and deterioration in health-related quality of life.
   A. There is no standardized definition of PF-ILD that clinicians and researchers have agreed upon. Several criteria have been used to define progression in patients with IPF, with most of these based on an absolute or relative decline in FVC and diffusing capacity of the lung for DLCO of greater than or equal to 5–10% or greater than or equal to 10–15%, a decline in 6MWD > 50 m, or worsening dyspnea and quality of life scores. FVC is a reliable, valid, and responsive measure of clinical status in patients, and a decline of 2-6%, although small, represents a clinically important difference. FVC is used as a surrogate marker of disease severity and progression. DLCO is considered a

standard predictor of survival. The distance walked in the 6MWT is used in a variety of pulmonary diseases and is predictive of mortality.

Investigational or Not Medically Necessary Uses

I. There is currently no evidence to suggest safety and/or efficacy with nitendanib (Ofev) or pirfenidone (Esbriet), when used for the treatment of bronchiolitis obliterans syndrome (BOS), lymphangioleiomyomatosis (LAM), non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), esophagogastric cancer, thyroid cancer, breast cancer, ovarian cancer, or pancreatic cancer. Further there is no evidence to support the use of nitendanib (Ofev) in combination with pirfenidone (Esbriet).

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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9. du Bois RM, Weycker D, Albera C, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med 2011; 184: 1382–1389.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Added step for branded Esbriet through both generic tablets and capsules prior to brand use; added step through generic tablets prior to use of generic capsules	01/2023
Added generic pirfenidone 534mg tablets to QL table	08/2022
Added new generic pirfenidone, requiring trial of generic pirfenidone prior to brand Esbriet	06/2022
• Added nintedanib (Ofev) to the Moda Split Fill program • Added criteria for nintedanib (Ofev) new indication Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype [request is for nintedanib (Ofev) and member has greater than 10% fibrotic features confirmed by a high resolution computed tomographic (HRCT) scan and clinical signs of progression (eg. decline in %FVC with worsening of respiratory symptoms, **or** increasing extent of fibrotic changes on chest imaging)]. • Added criteria for baseline assessment [eg. forced vital capacity (%FVC) or carbon monoxide diffusing capacity (DLCO) or six minute walking distance (6MWD)]	06/2020
Criteria updated to new policy format. Specific changes include: Updated idiopathic pulmonary fibrosis (IPF) initial evaluation. Combined policies with pirfenidone (Esbriet) for the indication of idiopathic pulmonary fibrosis (IPF). Added new indication of systemic sclerosis-associated interstitial lung disease (SSc-ILD), SSc-ILD initial evaluation, investigational use, and renewal evaluation. Added new supporting evidences and references.	12/2019
Policy created	10/2014

Policy Type: PA/SP Pharmacy Coverage Policy: UMP139

Split Fill Management*

Description

Niraparib (Zejula) is an orally administered poly (ADP-ribose) polymerase (PARP) inhibitor indicated for maintenance therapy, of ovarian, fallopian tube, or primary peritoneal cancer.
Niraparib-abiraterone acetate (Akeega) is a combination therapy containing abiraterone, an androgen biosynthesis inhibitor, indicated for prostate cancer.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
niraparib (Zejula)	Maintenance for: recurrent or advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer	100 mg capsules*	30 capsules/30 days
		100 mg tablet	30 tablets/30 days
		200 mg tablet	30 tablets/30 days
		300 mg tablet	30 tablets/30 days
niraparib-abiraterone acetate (Akeega)	Metastatic prostate cancer, Castration-resistant, deleterious or suspected deleterious BRCA-mutated	50 mg/500 mg	60 tablets/30 days
		100 mg/500 mg	60 tablets/30 days

* Capsule formulation is being withdrawn from the market by end of year 2023

Initial Evaluation

I. **Niraparib (Zejula), niraparib-abiraterone acetate (Akeega)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Medication will not be used in combination with any other oncolytic medication; **AND**
   D. Member has not progressed on prior PARP inhibitor therapy (e.g. olaparib [Lynparza], rucaparib [Rubraca], talazoparib [Talzenna]) therapy; **AND**
   E. The request is for niraparib (Zejula); **AND**
      1. A diagnosis of one of the following:
         i. **Advanced (stage III or IV) ovarian, fallopian tube, or primary peritoneal cancer**; **AND**
            a. Member has completed at least **one** prior platinum-based chemotherapy regimen (e.g. cisplatin, oxaliplatin, carboplatin); **AND**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

b. The member has **not** received bevacizumab (Avastin) in prior treatment; **AND**
c. Niraparib (Zejula) will **not** be used in combination with bevacizumab (Avastin); **OR**

ii. **Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer**; **AND**
a. Member has experienced disease progression on or after at least two or more prior platinum-based chemotherapy regimens (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
b. Member had complete or partial response to prior platinum-based chemotherapy (i.e., platinum-sensitive) (e.g. cisplatin, oxaliplatin, carboplatin); **AND**
c. Provider attests that member's epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based chemotherapy regimen (e.g. cisplatin, oxaliplatin, carboplatin); **OR**

F. The request is for niraparib-abiraterone (Akeega); **AND**
1. A diagnosis of **metastatic, castration-resistant prostate cancer** (**mCRPC**); **AND**
2. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) BRCA-mutation; **AND**
3. Evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or bilateral orchiectomy; **AND**
i. The member has not had disease progression on a second-generation antiandrogen agent (e.g. abiraterone, enzalutamide (Xtandi), apalutamide (Erleada), darolutamide (Nubeqa)); **AND**
4. Niraparib-abiraterone acetate (Akeega) will be used in combination with prednisone or prednisolone; **AND**
5. Documentation of clinical rationale why combination therapy, abiraterone and olaparib (Lynparza), would not be an effective regimen (use of generic abiraterone 250 mg tablets required)

II. Niraparib (Zejula) and niraparib-abiraterone acetate (Akeega) are considered investigational when used for all other conditions, including but not limited to:
A. Used in combination with other chemotherapy or targeted therapy regimen.
B. Breast Cancer
C. Lung Cancer
D. Advance Solid Tumors
E. Melanoma
F. Pancreatic cancer
G. Gastroesophageal cancer
H. Treatment of advanced ovarian cancer after 3 of more lines of therapy
I. High risk localized or locally advanced prostate cancer
J. Metastatic castration resistant prostate cancer with SPOP gene mutation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider attestation or clinical documentation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
    A. **Ovarian, fallopian tube, or primary peritoneal cancer; AND**
        1. Medication will not be used in combination with any other oncolytic medication; **OR**
    B. **Metastatic, castration-resistant, prostate cancer; AND**
        1. Niraparib-abiraterone (Akeega) will not be used in combination with other anti-cancer agents (outside of gonadotropin-releasing hormone agonist [e.g., leuprolide] or endocrine therapy [e.g., anastrozole, tamoxifen, fulvestrant] or bevacizumab or abiraterone); **AND**
        2. Niraparib-abiraterone acetate (Akeega) will be used in combination with prednisone or prednisolone

Supporting Evidence

Ovarian, fallopian tube, or primary peritoneal cancer

I. The safety and efficacy of niraparib (Zejula) in the setting of maintenance therapy for recurrent ovarian cancer was studied in a double-blind, placebo-controlled trial in adult patients with platinum-sensitive recurrent epithelial, ovarian fallopian tube, or primary peritoneal cancer. The patients were randomized 2:1 niraparib (Zejula) 300 mg orally daily or matched placebo within eight weeks of the last platinum-based chemotherapy regimen. The trial demonstrated a statistically significant improvement in progression free survival (PFS) for patients randomized to niraparib (Zejula) as compared with placebo in the gBRCAmut cohort and the non-gBRCAmut cohort.
    A. gBRCAmut Cohort: PFS in the niraparib (Zejula) arm was 21 and 5.5 in the placebo arm with a HR of 0.26 and 95% CI (0.17, 0.41).
    B. Non-gBRCAmut Cohort: PFS in the niraparib (Zejula) arm was 9.3 and 3.9 in the placebo arm with a HR of 0.45 and 95% CI (0.34, 0.61).
II. Therapy in the maintenance setting was initiated within eight weeks after completion of the last dose of platinum-based chemotherapy. Therefore, the inclusion of this as criteria (see above) is that treatment is started within a reasonable timeframe consistent with a maintenance treatment plan (i.e. as close to eight weeks as possible) while still recognizing that scheduling or other factors may impact the ability of a patient to start exactly within these first eight weeks.
III. Efficacy and safety of niraparib (Zejula) in the first-line maintenance treatment was assessed in a phase three, double-blind, randomized (PRIMA) clinical trial in patients with newly diagnosed advanced (stage III or IV) ovarian cancer. Seven hundred and thirty-three patients, who were in complete or partial response to first-line platinum-based chemotherapy, were randomized 2:1 to niraparib (Zejula) or matched placebo. Patients with and without homologous recombination

deficiency (HRD, e.g. gBRCA*m*) were included. At the end of treatment period, niraparib (Zejula) treatment arm showed a statistically significant improvement in median progression free survival (PFS) as compared to placebo arm.

A. Homologous recombination deficiency (HRD; e.g. gBRCA*m*) cohort: median PFS was 21.9 months in niraparib (Zejula) arm and 10.4 months in placebo arm (hazard ratio 0.43; 95% CI, 0.31 to 0.59; P<0.001)
B. Overall population (without HRD; gBRCA*m*) cohort: median PFS was 13.8 months in niraparib (Zejula) arm and 8.2 months in placebo arm (HR 0.62; 95% CI, 0.5 to 0.76; *p*<0.001).

None of the treated patients had a history of taking bevacizumab (Avastin). Therefore, efficacy and safety of niraparib (Zejula) after first-line therapy with bevacizumab (Avastin), or in combination with, bevacizumab (Avastin) is not supported.

IV. During PRIMA trial, serious adverse events occurred in 98.8% (N=478) patients in the treatment arm with 70.5% being grade ≥ 3. These numbers were 91.8% (N=224) and 46%, respectively in the placebo arm. Serious adverse events led to 79.5% dose interruption rates, 70.9% dose reduction rates, and 12% treatment discontinuation in the treatment group vs. 18%, 8.2%, and 2.5%, respectively, in the placebo group.
V. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy to support the use of a subsequent PARP inhibitor following progression of disease on another PARP inhibitor.

Prostate cancer

I. Niraparib-abiraterone acetate (Akeega) is FDA approved for the treatment of metastatic castration resistant prostate cancer (mCRPC) with *BRCA1/2* mutation.
II. The safety and efficacy of Niraparib/abiraterone acetate (Akeega) is demonstrated in the MAGNITUDE trial, which is a randomized, double blind, placebo-controlled, phase 3 trial. A total of 423 adult patients were randomized 1:1 to either receive abiraterone/prednisone in combination with niraparib or placebo. The primary outcome was radiographic progression free survival (rPFS) assessed by blinded independent central review per RECIST 1.1 (soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease). Treatment with niraparib-abiraterone resulted in a 45% lower risk of radiographic progression or death compared to the placebo/abiraterone arm (HR 0.55 95% CI 0.39-0.78, P = 0.0007). An overall survival benefit was also seen in the *BRCA* subgroup in a prespecified IPCW analysis (HR 0.54, 95% CI 0.33-0.90, P=0.0181). The most common adverse effects in the treatment group were anemia (50%), hypertension (33%), and constipation (33%). Treatment-emergent adverse events leading to dose interruption, dose reduction, or discontinuation of niraparib occurred in 49.7%, 20.3%, and 15.1% of patients in the active arm respectively. Niraparib/abiraterone for *BRCA mutation* is listed as a Category 1 recommendation per NCCN guidelines.
III. One of the key inclusion criteria in MAGNITUDE was bilateral orchiectomy or ongoing androgen deprivation therapy (ADT) with a GnRH agonist/antagonist. ADT was required to be continued throughout the study for patients who had not undergone bilateral orchiectomy. The safety and efficacy of Akeega in patients with prior treatment and progression on a second-generation AR inhibitor (i.e., enzalutamide, apalutamide and darolutamide) has not been established as these patients were excluded from the trial.

IV. The PROPel trial investigating olaparib (Lynparza) versus placebo in combination with abiraterone targeted a similar patient population as MAGNITUDE, men with metastatic castration resistant prostate cancer with HRR related mutations. The treatment group demonstrated a reduced risk of disease progression or death by 34% versus abiraterone alone (HR 0.66; 95% CI 0.54-0.81; p<0.0001). As of November 2023, head-to-head trials have not been conducted to suggest superiority of one regimen over the other. Abiraterone is currently available as a generic formulation.

Investigational or Not Medically Necessary Uses

I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the use of niraparib (Zejula) in the following settings listed below:
   A. Used in combination with other chemotherapy or targeted therapy regimen.
   B. Breast Cancer
   C. Prostate Cancer
   D. Lung Cancer
   E. Advance Solid Tumors
   F. Melanoma
   G. Pancreatic cancer
   H. Gastroesophageal cancer
   I. Treatment of advanced ovarian cancer after 3 of more lines of therapy
      i. Niraparib (Zejula) was studied in the QUADRA trial, evaluating niraparib (Zejula) for the treatment of advanced ovarian cancer after three or more chemotherapies. This was a single arm trial with investigator assessment of objective response rate (ORR) as the efficacy outcome measure. Given the setting of the QUADRA trial (single arm, uncontrolled nature), no comparative overall survival information can be obtained from the study, and it is difficult to assess any potential effect of niraparib (Zejula) on time to event endpoints.
      ii. In September 2022, the manufacturer of niraparib (Zejula) voluntarily withdrew the indication for treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens. This withdrawal was based on a totality of information from PARP inhibitors in the late line treatment setting in ovarian cancer. A potential detrimental effect on overall survival was observed with two different PARP inhibitors in two independent randomized, active-controlled clinical trials conducted in a BRCA mutant 3L+ advanced ovarian cancer population.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Olaparib (Lynparza) Policy	Breast cancer, metastatic, HER2-negative, germline BRCA-mutated (gBRCAm)
	Prostate cancer, metastatic castration-resistant (mCRPC)
Talazoparib (Talzenna) Policy	Breast cancer, locally advanced or metastatic, BRCA-mutated
	Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated
Second Generation Anti-Androgen Agents	Prostate cancer

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated renewal to allow provider attestation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression).	02/2024
Updated Zejula policy to include Akeega based on expanded indication in metastatic castration resistant prostate cancer (mCRPC). Updated QL table, general formatting, verbiage to align with current policies, and supporting evidence.	12/2023
Add 100, 200, and 300 mg tablets to the QL table with a 30/30 QL; reducing the QL from 90/30 due to the manufacturer's website promoting conversion to the once daily tablet (regardless of dose), rather than taking 1 to 3 capsules daily.	08/2023
Removal of ovarian cancer indication in the late line (3+) treatment setting following voluntarily withdrawal of the indication by the manufacturer.	09/2022
Addition of new indication and supporting evidence for first-line maintenance therapy in women with advanced ovarian cancer; Updated policy format to categorize recommendation for niraparib (Zejula) based treatment OR maintenance therapy; added split fill management	09/2020
Criteria transition into policy with the following updates made: addition of supporting evidence and investigation section, broke out the different indications (treatment versus maintenance therapy) due to the newly approved indication for late-line treatment in women with recurrent ovarian cancer, included	11/2019

mutation status for the treatment of recurrent ovarian cancer, included criterion around prior PARP inhibitor use, increase initial approval duration from three months to six months to be consistent with other payers, included age criterion per label, and removed the 8 weeks criterion around most recent platinum-based therapy in the setting of maintenance therapy in recurrent ovarian cancer; in place of the 8 weeks criterion, provider attestation and documentation is required instead.	
Criteria created	08/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP296

Split Fill Management*

Description

Nirogacestat (Ogsiveo) is a gamma secretase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
nirogacestat (Ogsiveo)	Desmoid Tumors	50 mg tablets	168 tablets /28 days

Initial Evaluation

I. **Nirogacestat (Osgiveo)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist **AND**
   C. Medication is not used in combination with any other oncology therapy; **AND**
   D. A diagnosis of **desmoid tumors** confirmed by:
      1. An image-guided (CT or ultrasound) core needle or surgical biopsy of the tumor site; **AND**
      2. Confirmation of diagnosis by a soft tissue pathologist; **AND**
      3. Provider attestation that other germline mutation syndromes (i.e., familial adenomatous polyposis [FAP], Gardner syndrome) and/or myofibroblastic diseases (e.g., sarcoma, gastrointestinal stromal tumor, nodular fasciitis, leiomyoma) have been ruled out; **AND**
   E. Documentation of tumor progression within the last 12 months; **AND**
      1. Documentation of significant symptoms (e.g., severe pain); **OR**
      2. Documentation of potential for morbidity (e.g., impairing, or threatening function, physical deformity).

II. Nirogacestat (Ogsiveo) is considered investigational when used for all other conditions, including but not limited to:
   A. Treatment of multiple myeloma
   B. Treatment of ovarian cancer
   C. Treatment in pediatrics and adolescents under the age of 18 years of age
   D. Use of nirogacestat (Ogsiveo) in combination with other oncology therapy

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g., tumor shrinkage, decreased morbidity, evidence of quality of life, symptoms, and/or functionality improvements)

Supporting Evidence

I. Desmoid tumors (DT), are rare, noncancerous growths, that are unable to metastasize and occur as a result of mutations in fibroblasts of connective tissue. DT can arise anywhere in the body, but most commonly appear in the abdominal/intra-abdominal area. The clinical course is variable, often with an initial growth phase followed by long periods of arrest and regression. Symptoms commonly include pain, fatigue, deformity, and functional impairment. Although non-malignant, DT can progress in size if left untreated and increase the risk of invasion into local organs.
II. The safety profile of nirogacestat (Ogsiveo) was reviewed in one Phase 3, international, double-blind, randomized, placebo controlled (DeFi) trial. Nirogacestat (Ogsiveo) was found to have a less favorable safety profile and resulted in significantly more side effects that led to dose reductions and permanent discontinuations compared to placebo. The nirogacestat (Ogsiveo) arm had a 42% dose reduction and 20% permanent discontinuation rate (versus 0% and 1% in the placebo arm, respectively) due to intolerable adverse events (AE). Split fill management is therefore recommended to reduce waste of unused medication due to a high risk of AE incidence, dose reduction, or permanent discontinuation with nirogacestat (Ogsiveo).
III. Safety and efficacy for an increased dosing frequency above the FDA-approved dose of 150mg twice daily has not been studied nor well-established.
IV. Safety and efficacy of nirogacestat (Ogsiveo) use in patients under the age of 18 has not been well-established. A Phase 2, interventional study to evaluate the efficacy and safety of nirogacestat (Ogsiveo) in pediatric patients 12 months to 18 years of age is expected to be completed by December of 2024. However, there is currently a lack of sufficient evidence or additional scientific literature to support the use of nirogacestat (Ogsiveo) in members <18 years of age.
V. Due to rarity of disease and association with other germline mutation syndromes (i.e., familial adenomatous polyposis [FAP], Gardner syndrome), it is essential to rule out potential for differential diagnosis without association to desmoid tumors (e.g., Gardner syndrome). DT also shares similarities with other myofibroblastic diseases (e.g., sarcoma, gastrointestinal stromal tumor, nodular fasciitis, leiomyoma) with 30% to 40% of DT cases reported to be misdiagnosed following histologic analysis.
VI. The use of nirogacestat (Ogsiveo) has not been studied in combination with other chemotherapy agents (e.g., methotrexate and vinorelbine) or tyrosine kinase inhibitors (TKI's) such as sorafenib. Due to the lack of safety and efficacy data with a combination regimen, use of nirogacestat (Ogsiveo) is not recommend with any other oncology therapy.

VII. A definitive diagnosis of DT requires histopathologic analysis of a biopsy sample of the tumor which is examined for presence of desmoid cells. Both DTWG (2020) and NCCN soft tissue sarcoma (2023) guidelines recommend a histological diagnosis of DT via an image-guided (CT or ultrasound) core needle or surgical biopsy of the tumor site. Due to rarity of disease and association with other germline mutation syndromes (i.e., familial adenomatous polyposis [FAP], Gardner syndrome), it is essential to rule out potential for differential diagnosis without association to desmoid tumors (e.g., Gardner syndrome). Desmoid Tumors also shares similarities with other myofibroblastic diseases (e.g., sarcoma, gastrointestinal stromal tumor, nodular fasciitis, leiomyoma) with 30% to 40% of DT cases reported to be misdiagnosed following histologic analysis. NCCN guidelines recommend evaluation and treatment by a multidisciplinary team with expertise and experience in desmoid tumors; however, DTWG guidelines require confirmation of diagnosis by a soft tissue pathologist.

VIII. Both DTWG (2020) and NCCN (V 2.2023) guidelines recommend active surveillance/observation alone until the tumor has shown progression and is accompanied by significant symptom burden, at which point, active treatment is pursued. NCCN guidelines also recommend active treatment if progression of DT is accompanied by potential for morbidity. The FDA-approved indication of nirogacestat (Ogsiveo) is specific to adult patients with progressing desmoid tumors. This indication is supported by the DeFi clinical trial which included patients with histologically confirmed diagnosis of progressing desmoid tumors within 12 months before screening. There is insufficient evidence to support the use of nirogacestat (Ogsiveo) in patients with nonprogressive DT at this time. Although guidelines also recommend earlier active treatment in the case of nonprogressive DT in anatomical locations where progression of the tumor would be morbid, there's insufficient evidence to support nirogacestat (Ogsiveo) as the treatment of choice in this scenario.

IX. In the Phase 3, international, double-blind randomized, placebo controlled (DeFi) trial, eligible patients were required to have progressing DT and either had not received previous treatment for progressing DT that were not amenable to surgery or had refractory or recurrent DT after at least one line of therapy. Median subject age was 34 years, majority female (64%), with *CTNNB1* genetic mutation (61%), and extra-abdominal tumor-location (76%). The majority had received previous treatment (74%) with a median of two lines of previous therapy. Treatments included surgery (44%), radiation therapy (23%), chemotherapy (34%), and TKIs (33%) with sorafenib being the most common TKI received (24%). The primary outcome was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR) and patient-reported outcomes. Results showed a statistically significant 71% reduction of disease risk progression in subjects who received nirogacestat (Ogsiveo) in 28-day cycles versus subjects who received placebo (hazard ratio [HR] = 0.29; $p < 0.001$). However, data is of low/uncertain value for clinical decision-making, as the primary and objective secondary outcomes are surrogate endpoints and are not validated to correlate with morbidity, mortality, quality of life, symptom, or functionality improvements. Although the study found statistically and clinically significant differences in favor of nirogacestat (Ogsiveo) compared to placebo in patient-reported outcomes at cycle 10, there remains uncertainty in whether clinically meaningful results were attained throughout the course of treatment as only cycle 10 data is reported.

Investigational or Not Medically Necessary Uses

I. Nirogacestat (Ogsiveo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Multiple myeloma
      i. A phase 1b interventional study of belantamab mafodotin in combination with nirogacestat (Ogsiveo) and pomalidomide in patients with multiple myeloma is currently in the recruitment phase and is estimated to be completed by October of 2026. There is currently a lack of sufficient evidence or additional scientific literature to support the use of nirogacestat (Ogsiveo) in multiple myeloma.
   B. Ovarian Cancer
      i. A phase 2 interventional study of nirogacestat (Ogsiveo) in ovarian granulosa cell tumors is currently in the active phase and is expected to be completed by July of 2026. There is currently a lack of sufficient evidence or additional scientific literature to support the use of nirogacestat (Ogsiveo) in ovarian cancer.
   C. Pediatrics and adolescents under the age of 18 years old
      i. A phase 2 interventional study to evaluate the efficacy and safety of nirogacestat (Ogsiveo) in pediatric patients >12 months to 18 years of age is currently in the active phase and is expected to be completed by December of 2024. There is currently a lack of sufficient evidence or additional scientific literature to support the use of nirogacestat (Ogsiveo) in members <18 years of age.
   D. Use of nirogacestat (Ogsiveo) in combination with other oncology therapy
      i. There are currently no ongoing or active trials to study the use of nirogacestat (Ogsiveo) in combination with other oncology therapy. There is currently a lack of additional scientific literature to support the use of nirogacestat (Ogsiveo) in combination with other chemotherapy agents.

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References

1. OGSIVEO. Prescribing Information. SpringWorks Therapeutics, Inc; 2023
2. Unapproved nirogacestat (Ogsiveo) Dossier. SpringWorks Therapeutics. May, 2023
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4. National Comprehensive Cancer Network. Soft Tissue Sarcoma (Version 3.2023). NCCN. Updated December 12, 2023. Accessed December 18, 2023. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
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8. Children's Oncology Group. A Study of a New Drug, Nirogacestat, for Treating Desmoid Tumors That Cannot be Removed by Surgery. Clinicaltrial.gov. December 11, 2019. Updated November 11, 2023. Accessed December 19, 2023. https://clinicaltrials.gov/study/NCT04195399

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy name	Disease State
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Desmoid Tumor

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed mutational analysis requirement from diagnosis of desmoid tumors	03/2024
Policy created	02/2024

Policy Type: PA/SP Pharmacy Coverage Policy: UMP140

Description

Nitisinone (Nityr; Orfadin) competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase (4HPPD), an enzyme present early in the tyrosine degradation pathway, thereby preventing the accumulation of toxic metabolites.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
nitisinone (nitisinone)	2 mg capsule	Hereditary tyrosinemia type 1	2 mg/kg/day
	5 mg capsule		
	10 mg capsule		
nitisinone (Nityr)	2 mg tablet		
	5 mg tablet		
	10 mg tablet		
nitisinone (Orfadin)	2 mg capsule		
	5 mg capsule		
	10 mg capsule		
	20 mg capsule		
	4 mg/mL suspension		

Initial Evaluation

I. Nitisinone (Nityr; Orfadin) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a provider who specializes in the treatment of genetic or metabolic disorders; **AND**
   B. A diagnosis of **hereditary tyrosinemia type 1 (HT-1)** when the following are met:
      1. Elevated succinylacetone (SA); **AND**
      2. Documentation of baseline plasma tyrosine level; **AND**
      3. Treatment will be used in conjunction with a diet restricted in tyrosine and phenylalanine

II. Nitisinone (Nityr; Orfadin) is considered investigational when used for all other conditions, including but not limited to:
   A. Alkaptonuria

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not established on therapy through the use of samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g. biochemical and/or clinical response).

Supporting Evidence

I. In patients with HT-1, tyrosine metabolism is interrupted due to a lack of the enzyme (fumarylacetoacetate hydrolase) needed in the last step of tyrosine degradation. Toxic metabolites of tyrosine, succinylacetoacetate (SAA) and succinylacetone (SA), accumulate and cause liver and kidney toxicity. Nitisinone (Nityr; Orfadin) competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase (4HPPD), an enzyme present early in the tyrosine degradation pathway, thereby preventing the build-up of the toxic metabolites SAA and SA.
II. Nitisinone (Nityr; Orfadin) must be used in conjunction with a diet restricted in tyrosine and phenylalanine to prevent further increased tyrosine levels. Dose is titrated as needed based on biochemical and/or clinical response. If the biochemical response is satisfactory, the dosage should be adjusted only according to body weight gain. Dose should not be adjusted according to tyrosine concentration.
III. Nitisinone (Nityr; Orfadin) should be started as early as possible (i.e. immediately after diagnosis of HT1 by blood or urine measurement of SA).
IV. If the biochemical parameters (except plasma SA) have not normalized within one month of starting therapy, the dose should be increased to 1.5 mg/kg/day. The dose of nitisinone should be adjusted to completely suppress excretion of SA; however, it may take as long as three months for complete suppression of SA to occur. A dose of 2 mg/kg/day may be needed, especially in infants; although, this dose should be considered maximal. Monitoring of the nitisinone blood levels is recommended for dose adjustment and also to check adherence.

Investigational or Not Medically Necessary Uses

I. Nitisinone (Nityr; Orfadin) has not been sufficiently evaluated in the following settings. Limited evidence is available; however, safety and efficacy have not been established for:
    A. Alkaptonuria

References

1. Orfadin [Prescribing Information]. Waltham, MA: Sobi, Inc; May 2019.
2. Nityr [Prescribing Information]. Cambridge, United Kingdom: Cycle Pharmaceuticals Ltd.; November 2018.
3. UpToDate, Inc. Disorders of tyrosine metabolism. UpToDate [database online]. Waltham, MA. Last updated August 08, 2019 Available at: http://www.uptodate.com/home/index.html.

Policy Implementation/Update:

Date Created	December 2019
Date Effective	December 2019
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date

Policy Type: PA/SP Pharmacy Coverage Policy: UMP141

Description

Obeticholic acid (Ocaliva) is a Farnesoid X Receptor (FXR) agonist that works by suppressing bile acid synthesis and increasing bile acid transport out of the hepatocytes, thus reducing overall hepatic exposure to toxic levels of bile acids.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
obeticholic acid (Ocaliva)	5 mg tablets	Primary Biliary Cholangitis (PBC)	30 tablets/30 days
	10 mg tablets		

Initial Evaluation

I. **Obeticholic acid (Ocaliva)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a gastroenterologist or hepatologist; **AND**
   B. A diagnosis of **Primary Biliary Cholangitis (PBC)** [i.e. primary biliary cirrhosis]; **AND**
      1. Diagnosis confirmed by **TWO** of the following:
         i. Alkalaine phosphate (e.g. ALP) level at least 1.5 times the upper limit of normal
         ii. Positive antimitochondrial antibodies (AMA) test
         iii. Histopathologic evidence (i.e. nonsuppurative cholangitis and destruction of small or medium-sized bile ducts); **AND**
      2. Treatment with ursodeoxycholic acid (e.g. Urso, Ursodiol) has been ineffective, contraindicated, or not tolerated; **AND**
         i. Inadequate response is defined as an alkaline phosphate level greater than 1.67 times the upper limit of normal after one year of treatment with ursodeoxycholic acid; **AND**
      3. Member has compensated liver disease (Child-Pugh A)

II. Obeticholic acid (Ocaliva) is considered investigational when used for all other conditions, including but not limited to:
   A. Non-alcoholic steatohepatitis (NASH)
   B. Non-alcoholic fatty liver disease (NAFLD)

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

C. Familial partial lipodystrophy
D. Obesity
E. Digestive system disease/symptoms (bile acid diarrhea, unspecified diarrhea, gallstones, primary sclerosing cholangitis, biliary atresia, etc.)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has a diagnosis of **Primary Biliary Cholangitis (PBC)** [i.e. primary biliary cirrhosis]; **AND**
    A. Member has compensated liver disease (Child-Pugh A); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g. reduction of pruritus, reduced fatigue, or decrease in alkaline phosphate levels)

Supporting Evidence

I. Obeticholic acid (Ocaliva) is FDA-approved for the treatment of primary biliary cholangitis (PBC) when used in combination with ursodeoxycholic acid (UDCA) in adults with inadequate response to UDCA; or, as monotherapy in adults unable to tolerate UDCA.
II. Per the American Association for the Study of Liver Diseases (AASLD) guidelines, UDCA at a dose of 13 to 15 mg/kg/day is the first-line therapy for PBC. However, about 45% of patients receiving UDCA have shown an inadequate response to or are intolerant to UDCA. Obeticholic acid (Ocaliva) is listed as a second-line therapy.
III. Treatment response in PBC is monitored using liver biochemical values - specifically, serum ALP and total bilirubin. Improvements in liver tests are typically seen within a few weeks, with the majority of liver test improvements occurring within 6 to 9 months. About 20% of patients will have normalization of liver biochemistries after two years.
IV. Per guidelines, the benefit of obeticholic acid (Ocaliva) in patients with decompensated liver disease is unestablished. In September 2017, the FDA issued a black box warning regarding inappropriate dosing of obeticholic acid (Ocaliva) in patients with moderate to severe liver impairment (Child-Pugh-Turcotte B and C), which was associated with worsening PBC and death. Therefore, the use of obeticholic acid (Ocaliva) in patients with decompensated PBC is not recommended.
V. Approval for obeticholic acid (Ocaliva) for PBC was based on data reported from the phase 3 POISE trial, that showed that obeticholic acid (Ocaliva) at 5mg and 10mg doses was statistically superior to placebo in meeting the primary endpoint of a reduction in ALP to <1.67 times the ULN, with a ≥15% reduction from baseline, and a total bilirubin level at or below the ULN after 12 months of treatment. Real-world data from the POISE OLE trial showed that during the 6-year follow-up, patients taking obeticholic acid (Ocaliva) had an approximately 70% lower relative risk of death or liver transplant compared to external control groups.

Investigational or Not Medically Necessary Uses

I. Obeticholic acid (Ocaliva) has not been sufficiently evaluated in the following settings:
   A. Non-alcoholic steatohepatitis (NASH)
      1. Regulatory:
         a. In June 2020, the manufacturer of obeticholic acid (Ocaliva) received a complete response letter (CRL) from the FDA stating that the NDA for obeticholic acid (Ocaliva) for the treatment of liver fibrosis due to NASH could not be approved based on prespecified 18-month interim data. The CRL indicated that the predicted benefit of obeticholic acid (Ocaliva) based on a surrogate histopathologic endpoint remained uncertain and did not sufficiently outweigh the potential risks to support accelerated approval for the treatment of patients with liver fibrosis due to NASH.
         b. In July 2022, the NDA was resubmitted after releasing a second interim analysis. In September 2022, the manufacturer released disappointing results from a study evaluating obeticholic acid (Ocaliva) in patients with pre-cirrhotic liver fibrosis due to NASH (REVERSE study). However, the manufacturer plans to pursue an NDA for the treatment of fibrosis due to NASH based on the REGENERATE study results.
         c. In May 2023, the FDA's gastrointestinal drugs advisory committee recommended 15 to 1 to reject the NDA for accelerated approval and wait until the full data of the REGENERATE trial are available, which is estimated to take 3 more years. Similar to its first CRL, the FDA's primary concern was related to the potential adverse events of obeticholic acid (Ocaliva).
      2. Clinical review:
         a. Obeticholic acid (Ocaliva) is being evaluated in an ongoing clinical trial (REGENERATE) adult patients with NASH and fibrosis stages F2-F3 or F1 with at least one comorbidity were randomized to receive obeticholic acid (Ocaliva) 10 mg, obeticholic acid (Ocaliva) 25 mg, or placebo. The primary endpoint of fibrosis improvement was achieved in 18% of patients in the obeticholic acid (Ocaliva) 10-mg group, 23% in the obeticholic acid (Ocaliva) 25-mg group, and 12% in the placebo group. The primary endpoint of NASH resolution (based on no hepatocellular ballooning and no residual lobular inflammation) with no worsening of fibrosis **did not** meet statistical significance (8% placebo vs 11% 10 mg group [p=0.18] and 12% in the 25 mg group [p=0.13]).
         b. The release of its second interim analysis of the REGENERATE study, demonstrated that 22% of patients receiving obeticholic acid (Ocaliva) 25 mg met the primary endpoint of achieving at least one stage of fibrosis improvement with no worsening of NASH by 18 months on liver biopsy compared with 10% of patients receiving placebo (P <0.0001). The 10-mg obeticholic acid (Ocaliva) dose did not show statistically significant improvements compared to placebo. Additional analysis showed the effect of obeticholic acid (Ocaliva) was more pronounced in individuals

with advanced fibrosis without cirrhosis (F3) at baseline, with 25% of these patients in the obeticholic acid (Ocaliva) 25-mg group demonstrating an improvement in fibrosis by at least one stage without worsening of NASH as compared to 10% in the placebo group (P = 0.0001). In contrast, 19% of patients with F2 fibrosis at baseline saw an improvement in fibrosis by at least one stage without worsening of NASH in the obeticholic acid (Ocaliva) 25-mg group, as compared to 10% in the placebo group (P <0.04).

c. There were significant concerns related to the tolerability of obeticholic acid (Ocaliva) as 55% of patients in the obeticholic acid (Ocaliva) group experienced pruritus compared to 24% in the placebo group, which was the most common cause for treatment discontinuation.
d. The REVERSE trial (n=919) evaluated whether obeticholic acid (Ocaliva) can lead to histological improvement in fibrosis with no worsening of NASH in adults with compensated cirrhosis due to NASH. The trial did not meet its primary endpoint; only 11% of patients treated with once-daily obeticholic acid (Ocaliva) 10 mg and 12% receiving 25 mg achieved a ≥1-stage improvement in fibrosis with no worsening of NASH after up to 18 months of treatment, compared with 10% of patients who received placebo. In the obeticholic acid (Ocaliva) group, 40-60% of participants reported pruritis, and higher incidence of gallstones in subjects taking up to 25mg obeticholic acid (Ocaliva).

3. According to the practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association first line treatment for NASH is weight loss as it generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation. As of June 2023, the AASLD guidelines did not recommend the off-label use of obeticholic acid (Ocaliva) to treat NASH until further safety and efficacy data becomes available.
4. Based on the data reviewed to date, the predicted benefit of obeticholic acid (Ocaliva) based on a surrogate histopathologic endpoint remains uncertain and does not sufficiently outweigh the potential risks for the treatment of patients with liver fibrosis due to NASH. Additional efficacy and safety data are needed to support its use in NASH.
5. The Institute for Clinical and Economic Review (ICER) released a Final Evidence Report assessing the comparative clinical effectiveness and value of obeticholic acid for NASH in May 2023. The report states that the current evidence is not adequate to demonstrate a net health benefit for obeticholic acid when compared to lifestyle management alone, in addition to significant safety concerns.

B. Non-alcoholic fatty liver disease (NAFLD)
C. Familial partial lipodystrophy
D. Obesity

E. Digestive system disease/symptoms (bile acid diarrhea, unspecified diarrhea, gallstones, primary sclerosing cholangitis, biliary atresia, etc.)
    i. Several phase II trials are evaluating obeticholic acid (Ocaliva) for various digestive system diseases and symptoms. At this time, safety, and efficacy of obeticholic acid (Ocaliva) in these indications is not established and therefore considered investigational.

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Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Removed generic obeticholic acid from policy until available on the market	02/2024
Added E/I supporting evidence for NASH indication and digestive system disease/symptoms. Updated supporting evidence for PBC. Updated references. Added related policies.	06/2023
Added generic obeticholic acid to policy QL table, require use of generic prior to brand	05/2023
Added supporting evidence for the investigational use in NASH	07/2020

Prior authorization criteria transitioned to policy format. Updated initial and renewal durations. Addition of specialist requirements. Addition of confirmed diagnosis and Child Pugh A classification. Further clarification of characteristics of inadequate response to ursodeoxycholic acid. Addition of renewal criteria.	12/2019
Policy created	06/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP142

Description
Octreotide acetate (Sandostatin, Bynfezia Pen, Mycapssa) works by suppressing LH response to GnRH, decreasing splanchnic blood flow, and inhibiting the release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
octreotide acetate (generic, Sandostatin)	50 mcg/mL ampule, vial, syringe	Acromegaly	90 ampules, vials, syringes/30 days
		Metastatic carcinoid tumor	
		Vasoactive intestinal peptide tumor (VIPoma)	
	100 mcg/mL ampule, vial, syringe	Acromegaly	
		Metastatic carcinoid tumor	
		Vasoactive intestinal peptide tumor (VIPoma)	
	500 mcg/mL ampule, vial, syringe	Acromegaly	
		Metastatic carcinoid tumor	
		Vasoactive intestinal peptide tumor (VIPoma)	
	1000mcg/5mL (200 mcg/mL) vial	Acromegaly	9 vials/30 days
		Metastatic carcinoid tumor	23 vials/30 days
		Vasoactive intestinal peptide tumor (VIPoma)	14 vials/30 days
	5000mcg/5mL (1000 mcg/mL) vial	Acromegaly	2 vials/30 days
		Metastatic carcinoid tumor	5 vials/30 days
		Vasoactive intestinal peptide tumor (VIPoma)	3 vials/30 days
octreotide acetate (Bynfezia Pen)	7000mcg/2.8mL (2500 mcg/mL) prefilled injection pen	Acromegaly	2 pens/30 days
		Metastatic carcinoid tumor	4 pens/30 days
		Vasoactive intestinal peptide tumor (VIPoma)	2 pens/30 days
octreotide acetate (Mycapssa)	20 mg capsule	Acromegaly	112 capsules/28 days
Provider Administered Agents*			

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

octreotide acetate, mi-spheres (Sandostatin LAR)	10 mg vial	Acromegaly; Metastatic carcinoid tumor; Vasoactive intestinal peptide tumor (VIPoma)	N/A
	20 mg vial		
	30 mg vial		

**Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit.*

Initial Evaluation

I. **Octreotide acetate (Sandostatin, Bynfezia Pen, Mycapssa) and generic octreotide acetate** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. If requesting injectable brand octreotide acetate (Sandostatin, Bynfezia Pen): Treatment with generic octreotide has been ineffective, not tolerated, or is contraindicated; **AND**
   C. A diagnosis of one of the following:
      1. Acromegaly; AND
         i. Member has had inadequate response to, or cannot be treated with surgical resection and pituitary irradiation; **AND**
         ii. If requesting oral octreotide acetate (Mycapssa): member has a documented response and tolerability to treatment with long-acting octreotide injection (Sandostatin LAR) OR lanreotide (Somatuline Depot) injection; **AND**
            a. Provider rationale as to why continuation of therapy with long-acting octreotide injection (Sandostatin LAR) OR lanreotide (Somatuline Depot) injection is not appropriate (i.e., there is medical necessity for change outside of patient preference); **OR**
      2. **Metastatic carcinoid tumor; AND**
         i. Use is intended for the symptomatic management of severe diarrhea and/or flushing episodes; **AND**
         ii. The request is for injectable octreotide (e.g. generic octreotide acetate, Sandostatin, Bynfezia Pen); **OR**
      3. Vasoactive intestinal peptide tumors (VIPomas) [pancreatic neuroendocrine (islet cell) tumor, insulinoma, glucagonoma, somatostatinoma, and gastrinoma]; **AND**
         i. Use is intended for the symptomatic management of profuse watery diarrhea; **AND**
         ii. The request is for injectable octreotide (e.g. generic octreotide acetate, Sandostatin, Bynfezia Pen); **AND**

II. Octreotide (Sandostatin, Sandostatin LAR, Bynfezia Pen) is considered investigational when used for all other conditions.

III. Octreotide oral capsules (Mycapssa) are considered investigational when used for all other conditions, including but not limited to, metastatic carcinoid tumor and vasoactive intestinal peptide tumors (VIPomas).
   A. Octreotide capsules (Mycapssa) have only been studied and FDA-approved in the setting of long-term maintenance of acromegaly symptoms and is therefore considered

investigational when used for all other indications, including metastatic carcinoid tumors and VIPomas.

Renewal Evaluation

I. Disease response with improvement in patient's symptoms including reduction in symptomatic episodes (such as diarrhea, rapid gastric dumping, flushing), and/or stabilization of glucose levels, and/or decrease in size of tumor or tumor spread; **OR**

II. For **acromegaly** ONLY: Disease response as indicated by an improvement in signs and symptoms compared to baseline; **AND**

    1. Age-adjusted normalization of serum IGF-1; **OR**
    2. Reduction of growth hormone (GH) by random testing to < 1.0 mcg/L

Supporting Evidence

I. The 2014 Endocrine Society Practice Guidelines for Acromegaly recommend transsphenoidal surgery/surgical resection/debulking as primary therapy for Acromegaly patients, followed by radiation therapy for residual tumor mass following surgery. In patients with persistent disease following surgery, guidelines recommend use of somatostatin receptor ligands (SRLs) or pegvisomant as the initial adjuvant medical therapy.

II. Bynfezia Pen was approved via the 505 (b)(2) pathway and relies on the FDA's finding of safety and effectiveness for the previously approved drug Sandostatin (octreotide acetate injection). The FDA has found that Bynfezia Pen and Sandostatin are pharmacokinetically bioequivalent based on data from the comparative PK study submitted with the NDA. The FDA expects the benefits and risks of Bynfezia pen used at the proposed doses will be similar to the benefits and risks associated with Sandostatin for the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIPoma) secreting tumors.

III. Octreotide acetate oral capsules (Mycapssa) was approved for the treatment of Acromegaly ONLY by the FDA based on data from the randomized, double-blind, placebo controlled, phase 3 CHIASMA OPTIMAL study in Acromegaly patients who were previously treated with stable doses of long-acting SRLs (octreotide or lanreotide). The primary endpoint was the proportion of patients maintaining biochemical response, defined as IGF-1 ≤ 1.0 x ULN, studied in a population of adult patients age 18 and older who had evidence of active acromegaly disease and had an average IGF-1 of ≤ 1.0 x ULN on a stable dose of injectable octreotide or lanreotide. The primary endpoint was met, as 58% of patients receiving oral octreotide capsules maintained IGF-1 response versus the 19% receiving placebo (P=0.008). Octreotide acetate oral capsules (Mycapssa) were safe and well tolerated. No new or unexpected significant safety signals were observed during the trial. In the absence of head to head studies, long acting injectables remain the best value treatment for acromegaly and are preferred unless there is medical necessity for the oral product.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added Bynfezia Pen to policy with requirement for inadequate response to generic octreotide, unless not tolerated or contraindicated. Mycapssa capsules added in the setting of acromegaly requiring response with long acting octreotide injection or lanreotide (Somatuline Depot) injection; and requiring rationale for use of oral formulation over continuation of injectable long acting product. Removed trial and failure of bromocriptine from requirements for approval of injectable octreotide for acromegaly. Updated quantity limits of all products to align with diagnosis.	9/2020
Transitioned to policy format and updated the following: • Added age requirement of 18 years or older • For octreotide (Sandostatin), added requirement for inadequate response to generic octreotide, unless not tolerated or contraindicated • Removed octreotide (Sandostatin LAR) from the policy as it is excluded from coverage under the pharmacy benefit	12/2019
Previous review	10/2017
Criteria created	10/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP243

Description

Odevixibat (Bylvay) is an orally administered reversible ileal bile acid transporter (IBAT) inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: Six months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
odevixibat (Bylvay)	Pruritis in patients three months of age and older with progressive familial intrahepatic cholestasis (PFIC); Cholestatic pruritis in patients 12 months of age and older with Alagille Syndrome (ALGS)	200 mcg pellets	Monthly quantity to allow for a maximum of 120 mcg/kg per day
		600 mcg pellets	
		400 mcg capsules	
		1200 mcg capsules	

Initial Evaluation

I. **Odevixibat (Bylvay)** may be considered medically necessary when the following criteria are met:
   A. Documentation of member's weight, measured within past three months, is provided; **AND**
   B. Medication is prescribed by, or in consultation with, a hepatologist or gastroenterologist; **AND**
   C. A diagnosis of **progressive familial cholestasis (PFIC)** or **Alagille Syndrome (ALGS)** when the following are met:
      1. The request is for the treatment of progressive familial cholestasis (PFIC); **AND**
         i. Diagnosis is confirmed by a molecular generic test; **AND**
         ii. Member does not have PFIC type 2 with ABCB11 variant resulting in nonfunctional or absent bile salt export pump protein (BSEP-3) as confirmed by a molecular genetic test; **AND**
         iii. Member is three months of age or older; **OR**
      2. The request is for the treatment of Alagille Syndrome (ALGS); **AND**
         i. Diagnosis is confirmed by a molecular generic test; **OR**
            a. Diagnosis is confirmed by evidence of bile duct paucity on liver biopsy; **AND**
            b. Provider attestation Alagille Syndrome (ALGS) is present in a first degree relative; **OR**
               i. Provider attestation member has presence of 3 or more clinical features of the disease (e.g., cholestasis, consistent cardiac, renal, ocular disease, butterfly vertebrae, or characteristic Alagille facies); **AND**

ii. Treatment with maralixibat (Livmarli) has been ineffective, not tolerated, or is contraindicated; **AND**

D. Provider attestation member has cholestasis including at least one of the following:
   1. Total serum bile acids greater than three times the upper limit of normal for age; **OR**
   2. Conjugated bilirubin greater than 1 mg/dL; **OR**
   3. Unexplained fat-soluble vitamin deficiency; **OR**
   4. Gamma glutamyl transferase (GGT) greater than three times the upper limit of normal for age; **OR**
   5. Intractable pruritis explainable only by liver disease; **AND**

E. Other causes of cholestasis have been ruled out (e.g., drug toxicity, hepatitis A, sclerosing cholangitis); **AND**

F. Member does not have decompensated cirrhosis or prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy); **AND**

G. Provider attestation of presence of moderate to severe pruritis; **AND**

H. Treatment with <u>all</u> the following has been ineffective, contraindicated, or not tolerated:
   1. Ursodiol; **AND**
   2. Bile acid sequestrant (e.g., cholestyramine, colesevelam); **AND**
   3. Rifampin; **AND**
   4. Opioid antagonist (e.g., naltrexone); **AND**
   5. Serotonin inhibitor (e.g., sertraline, ondansetron)

I. Odevixibat (Bylvay) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Benign recurrent intrahepatic cholestasis (BRIC) 1 and 2
   B. Primary sclerosing cholangitis
   C. Biliary Atresia

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Member has exhibited improvement or stability of disease symptoms [e.g., improvement in pruritis, quality of sleep] **AND**

IV. Documentation of member's weight, taken within past three months, is provided; **AND**

V. Member has not had a liver transplant since the last prior authorization period; **AND**

VI. Member has not progressed to decompensated cirrhosis or experience hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy)

Supporting Evidence

Progressive familial intrahepatic cholestasis (PFIC)

I. Progressive familial intrahepatic cholestasis (PFIC) is a group of rare genetic cholestatic diseases which may start early after birth or at a young age and may rapidly progress to end-stage disease. The disease is commonly classified as one of three PFIC 1-3 types depending on the genetic defect, although there may be up to six types. PFIC1 occurs due to mutations on the *ATP8B1* gene. This gene is also expressed in small intestine, kidney, and pancreas, which explains certain extrahepatic manifestations (e.g., sensorineural deafness). PFIC2 occurs due to mutations on the *ABCB11* gene and PFIC3 is due to reduced expression of multidrug resistance MDR3, which is encoded by *ABCB4* gene.

II. Patients often present with symptoms of cholestasis, growth retardation, increased serum bile acid (BA) blood and liver concentration, jaundice, and pruritis. Cholestasis is an impairment of bile formation and/or bile flow and is caused by absence of transport proteins in PFIC. The most sensitive test to confirm cholestasis is via elevations in fasting serum bile acids (normal levels depend on age but are usually <20 umol/L); however, this may not be readily available. Other biomarkers that can be used to confirm cholestasis are elevated gamma glutamyl transferase (GGT) levels (normal levels depend on age but are usually <200 IU/L) and conjugated/direct serum bilirubin levels (normal levels are usually less than 0.3 mg/dL). Additionally, cholestasis may be suspected in patients experiencing unexplained fat-soluble vitamin deficiency or intractable pruritis explainable only by liver disease.

III. Pruritis is often described as unrelenting and debilitating, leading to cutaneous wounds and sleep disturbances and is one of the primary causes for surgical treatments and liver transplant. Pruritis is described as mild to moderate in intensity in patients with PFIC3 and as moderate to severe in patients with PFIC1-2. If left untreated, the disease rapidly progresses to liver failure and is associated with early mortality.

IV. Odevixibat (Bylvay) is FDA-approved for the treatment of pruritis associated with PFIC in patients three months of age and older. Age of PFIC onset varies by subtypes where PFIC1 and PFIC2 usually develop during infancy, and PFIC3 develops during late infancy to early adulthood. Symptoms of pruritis may present as early as three months of age.

V. PFIC should be considered in patients with cholestasis after ruling out more common causes such as biliary atresia, Alagille syndrome, alpha-1 antitrypsin deficiency, cystic fibrosis, drug toxicity, hepatitis A, sclerosing cholangitis and extrahepatic bile duct obstruction. Diagnosis takes into account clinical, biochemical, radiological, and histological approaches. Genetic testing may be utilized for supporting a diagnosis of PFIC; however, the clinical phenotype is not always confirmed by genetic testing. This is likely due to other causative genes and/or non-coding regions of known PFIC genes that may contribute to disease manifestation. Approximately one-third of individuals with normal-GGT PFIC lack mutations in *ATP8B1* or *ABCB11* and mutations in *TJP2* explain all of the remaining patients. Additionally, in some patients only one allele of *ATP8B1* or *ABCB11* are detected, making it difficult to distinguish as disease-causing mutations or rare normal variants.

VI. Odevixibat (Bylvay) is not recommended in patients with BSEP3 variants (subpopulation within PFIC2). Pivotal trials excluded patients with BSEP3 variants as these patients lack a functional BSEP in canalicular member to export bile salts to bile for enterohepatic circulation via biliary

excretion. Therefore, the pharmacological effects of odevixibat (Bylvay) to inhibit the reabsorption of bile salts in the gastrointestinal tract cannot be expected.

VII. Majority of patients with PFIC receive liver transplantation before they reach adulthood. Intractable pruritis is a reason for evaluation for liver transplantation and placement on transplant list, regardless of the extent of direct liver involvement from PFIC. Majority of liver transplants in PFIC are considered successful with most patients alive without a need for re-transplantation. It is considered a curative treatment for the symptoms of pruritis. Therefore, odevixibat (Bylvay) is not expected to be medically necessary in patients with liver transplants as these patients would likely be cured of pruritis.

VIII. Odevixibat (Bylvay) was not studied in patients with decompensated cirrhosis or in patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy). Odevixibat (Bylvay) should be permanently discontinued if patients progress to portal hypertension or experiences a hepatic decompensation event. Close monitoring and caution is warranted when initiating treatment in patients with liver disease.

IX. According to systematic reviews, around 80% of patients with PFIC have pruritis graded as severe and mild pruritis presentation is less common. PEDFIC1 pivotal trial population consisted of patients with a mean pruritis score of around 3 (a lot of scratching) on a scale from 0 (no scratching) to 4 (worst possible scratching). Additionally, PEDFIC1 inclusion criteria required patients to have history of significant pruritis and patients were included in the trial if the average scratching score was greater than or equal to 2 (medium scratching) in the 2 weeks prior to baseline. Therefore, the value of odevixibat (Bylvay) in patients with mild pruritis has not been established and the drug may be medically necessary only in patients with history of significant scratching or medium scratching at baseline, consistent with moderate to severe pruritis presentation.

X. Initial treatment of PFIC addresses nutritional problems and pruritis caused by cholestasis. Treatment response is often unpredictable; however, depending on the degree of pruritis and PFIC type, some patients may respond to pharmacological therapy with standard of care agents. There is lack of randomized controlled studies of standard of care agents in the treatment of PFIC; however, evidence related to pruritis is available from studies in other cholestatic disease states, retrospective PFIC cohort studies, and historical treatment experience with the drugs.

- **Ursodiol** - commonly used as the first-line treatment option due to its anti-cholestatic properties which are exerted by improved hepatobiliary secretory function and reduced bile toxicity. It is the only medication that may affect liver disease progression and is recommended by the European Association for the Study of the Liver (EASL) guidelines as the initial pharmacological treatment in PFIC3. However, several rare disease organizations and expert reviews recommend ursodiol regardless of PFIC type. The effect of ursodiol on pruritis is an area that requires more research; however, several open-label and retrospective cohort studies note positive treatment response in pediatric patients with PFIC and other intrahepatic liver diseases (Narkewicz, 1998; Dinler, 1999; Wanty, 2004).
- Subsequent treatment options are aimed at reducing symptoms of pruritis. Pruritis can be a feature of any cholestatic disease, thus there are many treatment options available with variable evidence.

- **Bile acid sequestrants** - cholestyramine is FDA-approved for the treatment of pruritis associated with cholestasis in adults and is often used as one of the first-line treatment options for pediatric patients with pruritis associated with cholestasis. Despite limited evidence base, cholestyramine is listed as a treatment option for PFIC by the Children's Liver Disease Foundation and is recommended first-line by EASL guidelines for the treatment of pruritis associated with cholestasis. The lack of evidence is largely because the agent entered widespread use before the era of evidence-based medicine. Additionally, colestipol and colesevelam have also been evaluated in the treatment of pruritis and are generally better tolerated than cholestyramine (Cies, 2007).
- **Rifampin** - is commonly used after treatment failure with ursodiol/cholestyramine and is recommended for the treatment of pruritis in pediatric patients with PFIC by EASL guidelines. Additionally, there are various reports in literature showing positive results on pruritis due to chronic cholestasis, including retrospective, case controlled, and prospective trials. One meta-analysis of five randomized prospective controlled trials in adults and children concluded that rifampin is safe and effective for treatment of pruritis in patients with cholestasis associated with chronic liver diseases (Khurana, 2006).
- **Opioid antagonist** - naltrexone is recommended for the treatment of pruritis associated with cholestatic liver disease by the EASL guidelines as a subsequent option for patients failing cholestyramine and rifampin. Efficacy is supported by a meta-analysis which concluded that opioid antagonists significantly reduced cholestasis-related pruritis (Tandon 2007). Safety and efficacy of naltrexone in children is scarce; however, naltrexone can be safely used by pediatric patients with cholestatic liver disease and its use has been described in case reports and case series (Zellos, 2010; Mozer-Glassberg, 2011; Chang 2008).
- **Serotonin Inhibitors** - EASL guidelines recommended sertraline as a fourth-line treatment option for patients with cholestatic pruritis. Efficacy and safety are supported by one randomized double-blind, placebo-controlled study in patients with pruritis due to liver disease (Mayo, 2007) and one prospective multicenter study in children with refractory cholestatic pruritis related to PFIC and Alagille syndrome (Thebaut, 2017). Ondansetron has been studied in several cholestatic liver diseases with mixed results. One placebo-controlled trial studied intravenous ondansetron in adult patients with cholestatic pruritis and showed improvement in itch intensity by 50%. Another randomized, double-blind cross over study determined there was significant but moderate reduction in visual analogue scale (VAS) score when ondansetron was compared to placebo in patients with chronic liver disease. Another study showed that ondansetron therapy effectively reduced pruritis in 5 out of 13 patients, however, the reduction in itch intensity did not correlate to substantial decrease in objective scratching activity. A fourth clinical trial compared ondansetron to placebo and found no significant differences in pruritis scores or scratching activity (Ebhohon, 2023).

XI. Odevixibat (Bylvay) was studied in PEDFIC1, a Phase 3 double-blind, placebo-controlled, randomized, 24-week trial followed by PEDFIC2, an open-label extension study. PEDIFC1 was

conducted in 62 patients with pruritus, aged six months to 17 years, in patients with molecularly confirmed PFIC types 1 and 2. Patients received 40 mcg/kg or 120 mcg/kg odevixibat (Bylvay) dose and were allowed to continue on background treatment (e.g., ursodiol, rifampicin, antihistamines, naltrexone). The primary endpoint was the proportion of positive pruritis assessments (PPAs) as measured by the single-item observer-reported outcome instrument (ObsRo). Secondary endpoint was the change in serum BA from baseline. Both endpoints met statistical significance. Reduction in proportion of pruritis assessments to a score of 0 (no scratching) or 1 (little scratching) from baseline is also deemed clinically meaningful in a patient population refractory to standard of care.

Endpoints	Placebo (n=20)	Odevixibat 40 µg/kg/day (n=23)	Odevixibat 120 µg/kg/day (n=19)	All odevixibat (n=42)
LS Mean (SE) proportion of PPAs, %	30.1	58.3	51.8	55.1
LS mean Δ, (95% CI) [p-value]	-	**28.2 (9.8-46.6) [0.003]**	**21.7 (1.9-41.5) [0.033]**	**25.0 (8.5-41.5) [0.004]**
Patients with sBA response, %	0	**43.5**	**21.1**	**33.3**
Proportion Δ in sBA, (95% CI) [p-value]	-	0.435 (0.22-0.66) [0.001]	0.211 (0.02-0.46) [0.035]	0.333 (0.09-0.050) [0.003]

XII. The safety data for odevixibat (Bylvay) is available for 69 patients. In PEDFIC1, adverse events (AEs) reported in ≥ 2% of patients at a rate greater than placebo included diarrhea, increased bilirubin and transaminases, vomiting, abdominal pain, and fat-soluble vitamin deficiency. Drug related and liver related AEs occurred at a higher frequency in odevixibat (Bylvay) treated patients than in placebo and included increased ALT (9.5% vs 5%), AST (7.1% vs 5%), bilirubin (9.5% vs 5%), and diarrhea (9.5% vs 5%). No differences in serious AEs were recorded in PEDFIC1. Interim analysis of PEDFIC2 trial show a similar trend with four additional patients reporting serious AEs of cholestasis, acute pancreatitis, splenomegaly, jaundice, hypophagia, and weight decrease. The rate of discontinuation due to adverse events was low.

Alagille Syndrome (ALGS)

XIII. Alagille Syndrome (ALGS) is a rare, genetic, autosomal dominant disorder, caused by mutations in the genes encoding jagged1 (JAG1) or neurogenic locus notch homolog protein 2 (NOTCH2), both involved in the Notch signaling pathway. It is a multisystem disorder affecting the liver, cardiovascular system, skeleton, face, and eyes. Phenotypic presentation of the disease is variable; however, complications can include cholestasis, pruritis, progressive liver disease, failure to thrive, and xanthomas, all of which lead to liver transplantation. Pruritis is the hallmark symptom of this disease and is thought to be caused by a buildup of pruritogens that accompany bile acids. Bile acid buildup occurs due to impaired development of bile ducts leading to bile duct paucity (reduction of interlobular bile ducts).

XIV. Odevixibat (Bylvay) is FDA-approved for the treatment of cholestatic pruritis associated with ALGS in patients 12 months of age and older. The age of presentation ranges from 16 weeks to 10 years and most patients are diagnosed in the first year of life. The odevixibat (Bylvay) clinical trial program did not evaluate patients <12 months of age; therefore, drug safety and efficacy in this population has not been established.

XV. Diagnosis of ALGS is based on a combination of clinical features of the disease, lab findings, imaging, genetic testing, and liver biopsy. Clinical features include hepatic manifestations such as chronic cholestasis and bile duct paucity, characteristic facial features (deep-set eyes and a flat nasal bridge), ophthalmic abnormalities, skeletal involvement, cardiovascular, and renal abnormalities. Cholestasis occurs in 87-100% of patients but may present as mild or not clinically identifiable in certain cases of ALGS. The most sensitive test to confirm cholestasis is via

elevations in fasting serum bile acids (normal levels depend on age but are usually <20 umol/L); however, this may not be readily available. Other biomarkers that can be used to confirm cholestasis are elevated gamma glutamyl transferase (GGT) levels (normal levels depend on age but are usually < 200 IU/L) and conjugated/direct serum bilirubin levels (normal levels are usually less than 0.3 mg/dL). Additionally, cholestasis may be suspected in patients experiencing unexplained fat-soluble vitamin deficiency or intractable pruritis explainable only by liver disease. Patients affected with ALGS often present with multiple elevated biomarkers of cholestasis and peak values include bile acid levels> 100 times normal, total bilirubin > 20 mg/dL, and GGT > 2,000 U/L.

XVI. Molecular generic test is considered confirmatory for ALGS syndrome. Majority of patients have mutations in JAG1 (94%) with only a small subset (<1%) having mutations in NOTCH2. Additionally, mutations that are variants of unknown significance can also cause ALGS. Genetic evaluation for JAG1 and NOTCH2 mutations is currently available on a commercial basis, though screening for NOTCH2 is limited to a small number of locations at this time.

XVII. If patients are not screened for ALGS using a genetic test or if JAG1 or NOTCH2 mutations are not identified, patients may be diagnosed using a combination of clinical criteria, liver biopsy which screens for bile duct paucity, and presence of ALGS in first degree relatives. Bile duct paucity is one of the most common characteristics of ALGS and occurs in 90% of patients; however, it may not be present in many patients younger than six months of age and may not be present in mild disease presentation. Bile duct paucity is determined using a ratio of bile ducts to portal tracts of less than 0.5 in a liver biopsy with an adequate number (10) of portal tracts present. The normal number of bile ducts in a portal tract increases throughout the first years of life, reaching a normal ratio of nearly 2 by adolescence.

XVIII. Diagnostic Criteria for Alagille Syndrome:

ALGS in a first degree relative	Paucity	JAG1 or NOTCH2 mutation*	Number of criteria needed**
Present or absent	Present	Identified	Any or no features
None (proband)	Present	Not identified	3 or more features
None (proband)	Absent or unknown	Not identified	4 or more features
None (proband)	Absent or unknown	Identified	1 or more features
Present	Present	Not identified	1 or more features
Present	Absent or unknown	Not identified	2 or more features
Present	Absent or unknown	Identified	Any or no features

*Not identified = not identified on mutation screening, or not screened for

** Major clinical criteria include cholestasis, consistent cardiac, renal, ocular disease, butterfly vertebrae, or characteristic Alagille facies of childhood or adulthood

XIX. Odevixibat (Bylvay) was not studied in patients with decompensated cirrhosis or in patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy). Due to unknown safety and efficacy in this population, odevixibat (Bylvay) should be permanently discontinued if patients progress to portal hypertension or experience a hepatic decompensation event. Additionally, odevixibat (Bylvay) is associated with causing liver test abnormalities and may or may not exacerbate liver injury in patients with severe liver disease (e.g., decompensated cirrhosis, portal hypertension). More studies are needed in this setting to confirm drug safety in significant liver disease.

XX. Severe cholestatic pruritis occurs in up to 45% of patients with ALGS and has negative impacts on quality of life. Itching is often described as the most burdensome symptom of ALGS. According to one study evaluating the burden of ALGS and pruritis among 26 patients and 24 caregivers, 15% of patients experienced severe itching, 31% experienced moderate itching, 24% experienced mild itching, and 27% experienced very mild itching. Pivotal trial evaluating odevixibat (Bylvay) studied patients with moderate to severe pruritis at baseline as measured by the PRUCISION observer-reported outcome (ObsRO) caregiver instrument. The value of odevixibat (Bylvay) in patients with mild pruritis has not been established and the drug may be medically necessary only in patients with history of significant scratching or medium scratching at baseline, consistent with moderate to severe pruritis presentation.

XXI. Treatment of ALGS is aimed at maintaining optimal nutrition, preventing fat-soluble vitamin deficiencies, addressing pruritis, improving bile flow, and treating any extrahepatic features. Maralixibat (Livmarli) is another FDA approved agent for pruritis associated with ALGS. In addition, there are agents that are commonly used off-label. For relief of pruritis unresponsive to antihistamines, ursodeoxycholic acid, rifampin, bile-acid sequestrants, naltrexone, and sertraline may be used. Antihistamines should not be exclusive therapy but can be dosed at night when pruritis interferes with sleep. Treatment response to pharmacological agents is often unpredictable; however, depending on the degree of pruritis, some experience relief of pruritis symptoms. Patients refractory to pharmacological therapy may undergo partial external biliary diversion or ileal exclusion surgery to remove excess bile prior to liver transplantation.

XXII. There is lack of robust studies of standard of care agents (ursodiol, bile acid sequestrants, rifampin, naltrexone, sertraline) in the treatment of ALGS; however, evidence related to pruritis is available from studies in other cholestatic disease states, retrospective and open-label ALGS studies, and historical treatment experience with the drugs. Maralixibat (Livmarli) is a newer agent approved for the treatment of ALGS. There is no direct comparative evidence demonstrating superiority of one agent over the other. Trial of all standard of care agents including maralixibat (Livmarli) prior to odevixibat (Bylvay) is both a cost effective and clinically appropriate strategy as each drug exerts effects on pruritis via distinct therapeutic pathways and inefficacy with one or more agent(s) does not confer inefficacy with subsequent drugs.

- **Maralixibat (Livmarli)** - was studied in a pivotal Phase 2b, double-blind, placebo-controlled, randomized drug withdrawal (RWD) trial ICONIC, two randomized, double-blind, placebo-controlled Phase 2 trials ITCH and IMAGO, as well as ongoing open-label trial MERGE. The pivotal study included 31 pediatric patients (median age: 5.4 years) with ALGS (JAG1 mutation: 100%), native liver, elevated serum bile acids (mean: 283umol/L), and moderate to severe pruritis (mean weekly average ItchRO(Obs) score: 2.9). At baseline, patients were treated with standard of care agents (ursodeoxycholic acid: 81%; rifampin 74%; naltrexone: 3%; sertraline: 3%) that were continued during the trial. Patients were excluded if they had prior surgical interruption of the enterohepatic circulation, liver transplantation, and decompensated cirrhosis. The primary endpoints were the least square (LS) mean change in serum bile acid (sBA) levels and LS mean difference in pruritis severity as measured by the ItchRO(Obs) score between maralixibat (Livmarli) and placebo during the RWD period. Both endpoints met statistical significance and it was

determined that there were substantial number of patients experiencing clinically meaningful change in pruritis scores while on treatment with maralixibat (Livmarli).

- Pooled safety data is available in 86 patients with ALGS with median duration of exposure of 32.3 months. Most common (≥5%) any grade adverse events (AE) included diarrhea (55.8%), abdominal pain (53.5%), vomiting (40.7%), fat-soluble vitamin deficiency (25.6%), transaminases increased (18.6%), gastrointestinal bleeding (10.4%), bone fractures (9.3%), and nausea (8.1%). Three patients experienced vomiting as a serious AE requiring hospitalization or intravenous fluid administration. Treatment interruptions or dose reduction occurred in 5 (6%) patients due to diarrhea, abdominal pain, or vomiting. Seven (8.1%) patients discontinued due to ALT increase. There are no black box warnings or contraindications at this time. Warnings and precautions include liver test abnormalities, gastrointestinal adverse reactions, and fat-soluble vitamin deficiency.
- **Ursodiol** - commonly used as the first-line treatment option due to its anti-cholestatic properties which are exerted by improved hepatobiliary secretory function and reduced bile toxicity. It is the only medication that may affect liver disease progression and is recommended by the European Association for the Study of the Liver (EASL) guidelines as the initial pharmacological treatment for cholestatic pruritis. Additionally, several rare disease organizations such as The Childhood Liver Disease Research Network and National Organization for Rare Disorders (NORD) and expert reviews recommend ursodiol as first line in patients with ALGS. The effect of ursodiol on pruritis is an area that requires more research; however, an open-label study, retrospective cohort study, and case reports note positive treatment response in pediatric patients with ALGS and other intrahepatic liver diseases (Kronsten, 2013; Narkewicz, 1998;).
- Subsequent treatment options are aimed at reducing symptoms of pruritis. Pruritis can be a feature of any cholestatic disease, thus there are many treatment options available with variable evidence.
- **Bile acid sequestrant** - cholestyramine is FDA-approved for the treatment of pruritis associated with cholestasis in adults and is often used as one of the first-line treatment options for pediatric patients with pruritis associated with cholestasis. Despite a limited evidence base, cholestyramine is listed as a treatment option for ALGS by The Childhood Liver Disease Research Network and NORD and is recommended first-line by EASL guidelines for the treatment of pruritis associated with cholestasis. There is additionally one retrospective study indicating efficacy in some patients. The lack of evidence is largely because the agent entered widespread use before the era of evidence-based medicine. Additionally, colestipol and colesevelam have also been evaluated in the treatment of pruritis and are generally better tolerated than cholestyramine (Cies, 2007; Kronsten, 2013).
- **Rifampin** - commonly used after treatment failure with ursodiol/cholestyramine and is recommended for the treatment of cholestatic pruritis by EASL guidelines, rare disease organizations, and expert reviews. Additionally, there are various reports in literature showing positive results on pruritis due to chronic cholestasis, including retrospective, case controlled, and prospective trials in other cholestatic diseases in

children and adults. For example, one meta-analysis of five randomized prospective controlled trials in adults and children concluded that rifampin is safe and effective for treatment of pruritis in patients with cholestasis associated with chronic liver diseases (majority of patients had primary biliary cirrhosis). Additionally, one prospective study, one retrospective study, and cases reports are also available in patients with ALGS (Khurana, 2006; Yerushalmi, 1999; Kronsten, 2013).

- **Opioid antagonist** - naltrexone is recommended for the treatment of pruritis associated with cholestatic liver disease by the EASL guidelines as a subsequent option for patients failing cholestyramine and rifampin and is mentioned by expert reviews and rare disease organizations (NORD). Efficacy is supported by a meta-analysis which concluded that opioid antagonists significantly reduced cholestasis-related pruritis (Tandon, 2007). Safety and efficacy of naltrexone in children is scarce; however, naltrexone can be safely used by pediatric patients with cholestatic liver disease and its use has been described in a retrospective study, case reports and case series in patients with ALGS (Kronsten, 2013; Zellos, 2010; Mozer-Glassberg, 2011).
- **Serotonin Inhibitors** - EASL guidelines recommended sertraline as a fourth-line treatment option for patients with cholestatic pruritis. Efficacy and safety are supported by one randomized double-blind, placebo-controlled study in patients with pruritis due to liver disease (Mayo, 2007) and one prospective multicenter study in children with refractory cholestatic pruritis related to PFIC and Alagille syndrome (Thebaut, 2017). Ondansetron has been studied in several cholestatic liver diseases with mixed results. One placebo-controlled trial studied intravenous ondansetron in adult patients with cholestatic pruritis and showed improvement in itch intensity by 50%. Another randomized, double-blind cross over study determined there was significant but moderate reduction in visual analogue scale (VAS) score when ondansetron was compared to placebo in patients with chronic liver disease. Another study showed that ondansetron therapy effectively reduced pruritis in 5 out of 13 patients, however, the reduction in itch intensity did not correlate to substantial decrease in objective scratching activity. A fourth clinical trial compared ondansetron to placebo and found no significant differences in pruritis scores or scratching activity (Ebhohon, 2023).

XXIII. Odevixibat (Bylvay) was studied in one pivotal Phase 3 double-blind, placebo-controlled, trial ASSERT. The pivotal study included 52 pediatric patients (median age: 4.0 years) with ALGS (JAG1 mutation: 92%; NOTCH2 mutation 8%), native liver, elevated serum bile acids (mean: 240 umol/L), and moderate to severe pruritis (mean ObsRO score: 2.9). At baseline, patients were treated with standard of care agents (ursodeoxycholic acid: 89%; other anti-pruritis medication: 98%) that were continued during the trial. Other anti-pruritic drugs included rifampicin, naltrexone, antihistamines, steroids, gabapentin, ondansetron. Patients were excluded if they had prior surgical interruption of the enterohepatic circulation, liver transplantation, and decompensated cirrhosis. The primary endpoint was the least square (LS) mean change from baseline to month six in scratching score as measured by the PRUCISION observer-reported outcome (ObsRO) caregiver instrument. The secondary endpoints were change from baseline in serum bile acids (sBA) and change from baseline in caregiver-reported sleep parameters. All

endpoints met statistical significance and it was determined that there were substantial number of patients experiencing clinically meaningful change in pruritis scores while on treatment with odevixibat (Bylvay).

XXIV. Safety data is available from 35 patients treated with odevixibat (Bylvay) during the Phase 3 clinical trial ASSERT. Any treatment emergent adverse event rate was 74% in odevixibat (Bylvay) arm compared to 71% in placebo. Drug-related adverse events occurred more frequently in odevixibat (Bylvay) arm compared to placebo (23% vs 18%). Serious adverse events, and drug-related serious adverse events occurred at a similar frequency in both treatment arms. Most common drug related treatment emergent adverse events in the odevixibat (Bylvay) vs placebo arms, respectively, were diarrhea (11% vs 6%), vomiting (6% vs 0%), abdominal pain (3% vs 0%), hepatic enzyme increased (3% vs 1%), INR increased (3% vs 1%), frequent bowel movements (3% vs 0%), hematemesis (3% vs 0%), nausea (3% vs 0%), blood triglyceride increased (3% vs 0%), and weight decreased (3% vs 0%).

Investigational or Not Medically Necessary Uses

I. Odevixibat (Bylvay) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. BRIC1 and BRIC2
      i. BRIC1 and BRIC2 are milder versions of PFIC1 and PFIC2. BRIC1 and 2 occur on the same genes as PFIC1 and 2, respectively. However, cholestatic events are described as recurrent and unpredictable. Cholestatic episodes often last for a couple of weeks, vary in severity and duration and do not progress to liver failure. Therefore, there is uncertainty whether the duration of disease would offset treatment benefit. Further research and collection of evidence in patients with BRIC1 and BRIC2 is warranted at this time.
   B. Primary sclerosing cholangitis, biliary atresia
      i. Odevixibat (Bylvay) was studied in one Phase 2, open-label, single-arm study in pediatric patients with diagnosis of pruritis due to cholestatic disease (including but not limited to PFIC, Alagille syndrome, primary sclerosing cholangitis, and biliary atresia). Most patients experienced reductions in serum bile acid levels which correlated with improvements in pruritis and sleep disturbance scores. The quality of evidence is low at this time and phase 3 randomized controlled studies are warranted to confirm treatment benefit.
      ii. Phase 3, double-blind, randomized controlled trials in patients with biliary atresia (NCT04336722).

Appendix

I. Odevixibat (Bylvay) oral pellets are intended for us by patients weighing less than 19.5 kg and capsules are intended for use by patients weighing 19.5 kg or above.

II. Table 1: Recommended Dosage for 40mcg/kg/day

Body weight (kg)	Total Daily Dose (mcg)
7.4 and below	200

7.5 to 12.4	400
12.5 to 17.4	600
17.5 to 25.4	800
25.5 to 35.4	1200
35.5 to 45.4	1600
55.5 and above	2400

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease State
Maralixibat (Livmarli™)	Alagille Syndrome (ALGS)

Policy Implementation/Update:

Action and Summary of Changes	Date
Maralixibat (Livmarli) has been added as a step requirement for odevixibat (Bylvay) when the request is for ALGS.	11/2023
New indication Alagille Syndrome added; renewal evaluation changed from 12 to six months; added ondansetron as an example of accepted medications in serotonin inhibitor class, updated supportive evidence section, added related policies section.	07/2023
Policy created	11/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP048

Split Fill Management*

Description

Olaparib (Lynparza) is an orally administered poly (ADP-ribose) polymerase (PARP) enzymes inhibitor including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair.

Length of Authorization

- Initial:
  - i. Early, high-risk breast cancer: 12 months
  - ii. All other indications: 3 months
- Renewal:
  - i. Early, high-risk breast cancer: no renewals allowed
  - ii. All other indications: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
olaparib (Lynparza)	Breast cancer, early, high-risk, HER2-negative, germline BRCA-mutated (gBRCAm), after neoadjuvant or adjuvant chemotherapy; Breast cancer, metastatic, HER2-negative, gBRCAm with prior chemotherapy in the metastatic setting; Ovarian, fallopian tube, or primary peritoneal cancer; advanced, homologous recombination deficient (HRD)-positive status; after complete or partial response to first-line platinum chemotherapy, in combination with bevacizumab; maintenance therapy;	100 mg tablets	120 tablets/30 days

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

	Ovarian, fallopian tube, or primary peritoneal cancer; gBRCAm or sBRCAm, after first-line platinum-based chemotherapy, first-line maintenance therapy; Ovarian, fallopian tube, or primary peritoneal cancer; recurrent after complete or partial response to platinum-based chemotherapy; maintenance therapy Pancreatic adenocarcinoma, metastatic gBRCAm or sBRCAm; first-line maintenance therapy in those who have not progressed on at least 16 weeks of first-line platinum-based chemotherapy; Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated Prostate cancer, metastatic castration-resistant, deleterious or suspected deleterious BRCA-mutated (BRCAm)	150 mg tablets	120 tablets/30 days

Initial Evaluation

I. **Olaparib (Lynparza)** may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in consultation with, a specialist in oncology; **AND**
   B. The patient has <u>not</u> progressed on or after prior PARP inhibitor therapy (e.g., olaparib [Lynparza], niraparib [Zejula], rucaparib [Rubraca], talazoparib [Talzenna]); **AND**
   C. A diagnosis of one of the following:
      1. **Ovarian cancer (including fallopian tube and primary peritoneal cancer)**; **AND**
         i. The member has advanced or metastatic (Stage III-IV) disease; **AND**
         ii. Request is for <u>maintenance therapy</u>**; AND**
            a. Member has completed a prior platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
            b. The tumor is platinum-sensitive (i.e., the patient is in complete or partial response to their most recent platinum-based regimen); **AND**
            c. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) BRCA mutations (gBRCAm or sBRCAm); **AND**
               i. For <u>first-line maintenance therapy</u>:
                  1. Olaparib (Lynparza) will be used as monotherapy; **AND**
                     a. Member has not received prior treatment with bevacizumab; **OR**

2. Member has received, and currently has a positive response to bevacizumab treatment; **AND**
    a. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) homologous recombination deficient-positive mutation (gHRDm); **AND**
    b. Olaparib (Lynparza) will continue to be used in combination with bevacizumab; **OR**

ii. Request is for maintenance therapy for recurrent disease after at least two prior lines of platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) chemotherapy regimens

2. **Breast cancer, early, high-risk or metastatic; AND**
    i. Member has a diagnosis of HER2-negative breast cancer; **AND**
    ii. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gBRCAm; **AND**
    iii. Diagnosis of early (stage II-III) breast cancer; **AND**
        a. Provider attestation that member is at high risk of disease recurrence; **AND**
        b. Has required surgical intervention; **AND**
        c. Has received prior adjuvant or neoadjuvant therapy with a taxane (e.g., docetaxel), an anthracycline (e.g., doxorubicin), or platinum-based chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
        d. Olaparib (Lynparza) will be used as monotherapy or in combination with endocrine therapy (e.g., anastrozole, tamoxifen, fulvestrant); **OR**
    iv. Diagnosis of metastatic (stage IV) breast cancer; **AND**
        a. Has received prior treatment with an anthracycline (e.g., doxorubicin); **AND**
        b. Has received prior treatment with a taxane (e.g., paclitaxel); **AND**
        c. Member has disease progression on at least one prior endocrine therapy; **OR**
            i. Endocrine therapy has been deemed inappropriate by the treating healthcare provider; **AND**
        d. Medication will not be used in combination with other anti-cancer agents; **OR**
3. **Pancreatic cancer, First-line Maintenance; AND**
    i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gBRCAm; **AND**
    ii. Diagnosis of metastatic pancreatic adenocarcinoma; **AND**
    iii. The member has received at least 16 weeks of continuous treatment with a platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin) that was administered as first-line therapy; **AND**

iv. Provider attests that the disease has not progressed while on first-line platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin); **AND**

v. Medication will not be used in combination with other anti-cancer agents; **OR**

4. **Prostate cancer, metastatic, castration-resistant (mCRPC); AND**

i. Documentation of metastatic disease (i.e., stage IV); **AND**

ii. Disease is castration-resistant, defined by disease progression despite ongoing therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; **AND**

iii. The request is for olaparib (Lynparza) in combination with abiraterone (Zytiga, Yonsa) and prednisone or prednisolone (Note: the plan's preferred therapy is generic abiraterone unless contraindicated or not tolerated); **AND**

a. The member has not had disease progression on a second-generation antiandrogen agent (e.g., abiraterone (Zytiga, Yonsa), enzalutamide (Xtandi), apalutamide (Erleada), darolutamide (Nubeqa)); **AND**

b. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gBRCAm; **OR**

iv. The request is olaparib (Lynparza) monotherapy; **AND**

a. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) alteration in at least **one** of the following HRR genes: ATM, BRCA1, BRCA2; **AND**

b. Disease has progressed on prior enzalutamide (Xtandi) or abiraterone (Zytiga, Yonsa) treatment.

II. Olaparib (Lynparza) is considered investigational when used for all other conditions, including but not limited to:

A. Early breast cancer with low-moderate-risk without metastasis, and/or HER2-positive, and/or breast cancer without gBRCAm

B. Treatment of early, high-risk breast cancer for > 12 months

C. Pancreatic cancer without metastasis, and without gBRCAm

D. Metastatic, gBRCAm pancreatic cancer that has progressed on first line platinum-based chemotherapy

E. Metastatic, castration-resistant prostate cancer with a tumor mutation NOT listed above (including BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L) when used as a subsequent-line treatment

F. Use after disease progression on or after prior PARP inhibitor therapy

G. Treatment of advanced ovarian cancer after 3 or more lines of therapy

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Olaparib (Lynparza) will not be used in combination with other anti-cancer agents (outside of gonadotropin-releasing hormone agonist [e.g., leuprolide] or endocrine therapy [e.g., anastrozole, tamoxifen, fulvestrant] or bevacizumab or abiraterone); **AND**
IV. Clinical documentation of response to treatment (e.g., stabilization of disease or decrease in tumor size, or tumor spread).

Supporting Evidence

I. Many treatment options exist for ovarian, breast, pancreatic, and prostate cancer. Initial and subsequent therapies in this setting are contingent upon patient-specific characteristics. Given the complexities surrounding the diagnosis and treatment options, targeted drug therapies, such as PARP inhibitors, should be prescribed by, or in consultation with, an oncologist.
II. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy to support the use of a subsequent PARP inhibitor following the progression of disease on another PARP inhibitor.
III. **Treatment of Ovarian Cancer:**
    - In the pivotal trials for maintenance treatment of recurrent ovarian cancer and first-line maintenance therapy for ovarian cancer with gBRCAm or sBRCAm, eligible patients had completed at least ONE course of platinum-based chemotherapy. In the pivotal trials for first-line maintenance therapy for ovarian cancer with gBRCAm or sBRCAm non-eligible patients included: patients with early-stage disease (FIGO State I, IIA, IIB, or IIC) and patients with prior bevacizumab treatment. Subjects were randomized to treatment allocation within eight weeks after completion of the last dose of platinum-based chemotherapy. The intent is that treatment is started within a reasonable timeframe consistent with a maintenance treatment plan (i.e., as close to eight weeks as possible), to ensure the member is platinum-sensitive.
    - PAOLA-1, the Phase 3 trial that studied olaparib (Lynparza) as dual therapy with bevacizumab for maintenance therapy for advanced ovarian cancer, was a double-blind, randomized, placebo-controlled trial with the primary endpoint of progression free survival (PFS). The primary endpoint results of the predefined subgroups of HRD-positive, HRD-negative, or unknown found only a statistically significant difference in PFS in the HRD-positive subjects (HR: 0.33, 95% CI: 0.25, 0.45) and not the HRD-negative or unknown patients (HR: 0.92, 95% CI: 0.72, 1.17). Subjects enrolled in the trial had Stage III or IV disease and had a successful response to prior taxane-based chemotherapy.
    - The NCCN guideline for the treatment of ovarian cancers, recommends pathological staging followed by cytoreductive surgery as the preferred first-line treatment option for early-stage non-metastatic ovarian cancer. For patients who are poor candidates for surgery or

have a low likelihood of optimal cytoreduction, a neoadjuvant systemic therapy (e.g., paclitaxel and platinum-based chemotherapy, bevacizumab) may be required. Similarly, these chemotherapy regimens may be applicable as adjuvant therapy following cytoreductive surgery (for stage II-IV disease). Post-primary treatment, a first-maintenance therapy with PARP inhibitors (e.g., niraparib, olaparib) may be utilized to extend remission. For a disease that recurs after first-maintenance, recurrence therapy with platinum-based chemotherapy regimens followed by a PARP inhibitor for maintenance (also known as recurrent maintenance) may be warranted. Use of olaparib (Lynparza) for recurrent-maintenance is recommended only for patients, who have not previously been treated with a PARP inhibitor.

IV. **Treatment of Breast Cancer:**

- OlympiA was a 12-month phase 3, double-blinded, randomized, placebo-controlled trial that investigated the use of olaparib in patients with early, high-risk, non-metastatic breast cancer with documented germline BRCA mutations (gBRCAm) that is predicted to be deleterious or suspected deleterious without disease progression after neoadjuvant or adjuvant treatment with anthracycline, taxane, or platinum agents. Additional oncology therapy was not permitted, but concomitant endocrine therapy was allowed. High-risk patients were defined by residual invasive disease after neoadjuvant therapy, or positive histopathological tests showing affected axillary or lymph nodes after adjuvant therapy. The primary end point was invasive disease-free survival (IDFS), defined as time to first invasive breast tumor, invasive disease, disease recurrence, second primary invasive cancer, or death from any cause. Three-year IDFS was present in 85.9% of the olaparib arm and 77.1% in the placebo arm (HR = 0.58, [95% CI 0.41, 0.82], p=0.001). Overall survival was greater in the olaparib group by 32% compared to placebo (HR = 0.68, [98.5% CI 0.47-0.97], p=0.009). Distant disease–free survival was significantly longer among patients assigned to receive olaparib than placebo: 87.5% vs 80.4% (HR = 0.57, [99.5% CI, 0.39 to 0.83], P<0.001).
    i. In line with the duration of the OlympiA trial, the FDA approved olaparib for treatment of HER2-negative high-risk, early breast cancer for up to 12 months, or until disease recurrence, or unacceptable toxicity. NCCN guidelines similarly recommend olaparib be used for up to 12 months.
    ii. Since the publication of the OlympiA trial, capecitabine has been added as another guideline-directed adjuvant therapy option for HER2-negative, triple negative breast cancer (TNBC). Other guideline recommended adjuvant therapy options include olaparib (Lynparza) and pembrolizumab. Currently, there are no data to guide selection or sequencing of adjuvant therapy (olaparib or capecitabine) in HER2-negative TNBC. However, selection of therapy is based on patient specific factors (e.g., presence of gBRCAm for Lynparza). Current utilizers of capecitabine as an adjuvant therapy may be expected to transition to Lynparza based on presence of high-risk breast cancer, gBRCAm, and patient-specific factors including tolerability and toxicity. Additionally, the OlympiAD trial for metastatic breast cancer supported the efficacy of Lynparza versus chemotherapy (45% of patients received capecitabine) via improved surrogate outcomes of PFS.

- In the pivotal trial for breast cancer with metastatic, HER2-negative and gBRCAm, eligible patients had received neoadjuvant, adjuvant, or treatment for metastatic disease with an anthracycline (unless it was contraindicated) and a taxane. Approximately 70% of patients had received treatment in the metastatic setting; with 27% of patients having progressed after two lines of systemic therapies in the metastatic setting. 33% had no prior systemic therapy for metastatic disease. Eligible patients in this trial could have hormone-receptor positive metastatic breast cancer (i.e., estrogen-receptor positive, progesterone-receptor positive, or both) or triple negative metastatic breast cancer. Patients with hormone-receptor positive disease had received at least one endocrine therapy (adjuvant therapy or therapy for metastatic disease) and had disease progression during therapy, unless they had disease for which endocrine therapy was considered to be inappropriate.

V. **Treatment of Pancreatic Cancer:**

- The pivotal trial (POLO) is a Phase 3 trial that studied metastatic, gBRCAm pancreatic cancer; eligible patients had received a minimum of 16 weeks of first-line platinum-based chemotherapy (cisplatin, carboplatin, or oxaliplatin) and had not progressed while on the first-line platinum-based chemotherapy. The patients were randomized in a 3:2 ratio to receive maintenance olaparib (Lynparza) or placebo with the primary end point progression-free survival. The median progression-free survival was statistically significant, 7.4 months in the olaparib (Lynparza) arm compared to 3.8 months in the placebo arm (HR 0.53 [95% CI, 0.35-0.81], p=0.0035). The interim analysis of overall survival showed no difference between groups (median, 18.9 months vs. 18.1 months; hazard ratio for death, 0.91; 95% CI, 0.56 to 1.46; P=0.68). Additionally, there was no significant between-group differences in health-related quality of life.
- Limited exception should be granted to those who do not meet the criteria for metastatic, gBRCAm pancreatic cancer as stated in this policy, given the current lack of data to support an improvement in survival or quality of life even in the evaluated population.
- The preferred systemic regimens for metastatic, gBRCAm pancreatic cancer include:
    i. FOLFIRINOX or modified FOLFIRINOX ± subsequent chemoradiation
    ii. Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation

VI. **Treatment of Prostate Cancer:**

- PROfound, the Phase 3 trial that studied olaparib (Lynparza) in metastatic castration-resistant prostate cancer, enrolled men with homologous recombination repair (HRR) gene mutations in at least one of 15 prespecified HRR genes. Eligible patients had either a history of bilateral orchiectomy or were using luteinizing hormone-releasing hormone (LHRH) analog therapy and had progressed on enzalutamide or abiraterone acetate or both and were randomized (2:1) to receive either olaparib (Lynparza) or investigator's choice of enzalutamide or abiraterone acetate. Subjects were assigned cohorts based on HRR mutation (Cohort A: ATM, BRCA1, BRCA2; Cohort B: BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L). The primary endpoint was PFS in Cohort A and was significant between the treatment groups (HR: 0.34, 95% CI: 0.25, 0.47; p<0.001). Additionally, OS in Cohort A was significantly different between treatment groups (HR: 0.69, 95% CI: 0.50, 0.97; p=0.0175). PFS and OS were studied in Cohort B as exploratory endpoints and the results were not statistically significant and did not suggest improved outcomes with olaparib (Lynparza) over abiraterone or enzalutamide in those patients.

- In a randomized, double-blind, Phase 3 clinical trial (PROpel), the efficacy, safety, and tolerability of olaparib (Lynparza) was assessed versus placebo when given in addition to abiraterone in men with metastatic castration-resistant prostate cancer (mCRPC), who had not received prior chemotherapy or novel hormonal agents (NHAs; e.g., enzalutamide, apalutamide, abiraterone) in the 1st-line metastatic setting. Previous therapy with docetaxel in the neoadjuvant or adjuvant setting, as well as first-generation antiandrogen agents (e.g., bicalutamide, nilutamide) were permitted; however, were not required as part of the inclusion criteria. The primary endpoint, radiographic progression-free survival (rPFS), and secondary endpoints included OS and time to first subsequent anticancer therapy or death. In a predefined interim analysis (as of July 2022), olaparib (Lynparza) in combination with abiraterone reduced the risk of disease progression or death by 34% versus abiraterone alone (based on a hazard ratio [HR] of 0.66; 95% confidence interval [CI] 0.54-0.81; p<0.0001). Median rPFS was 24.8 months for olaparib (Lynparza) plus abiraterone versus 16.6 months for abiraterone alone.

Investigational or Not Medically Necessary Uses

I. Early breast cancer with low to moderate-risk without metastasis, and/or HER2-positive, and/or breast cancer without gBRCAm, and/or use of Lynparza >1 year for early, high-risk breast cancer
   A. Safety and efficacy have only been established in patients with high-risk, non-metastatic HER2-negative, gBRCAm breast cancer treated with olaparib for a maximum duration of 12 months.

II. Pancreatic cancer without metastasis, and without gBRCAm
   A. The safety and efficacy of olaparib in the pancreatic cancer setting have only been established in patients with metastatic disease with gBRCAm who has not progressed on the first-line platinum-based chemotherapy.

III. Metastatic, gBRCAm pancreatic cancer that has progressed on first-line platinum-based chemotherapy
   A. The safety and efficacy of olaparib in the pancreatic cancer setting have only been established in patients with metastatic disease with gBRCAm who has not progressed on the first-line platinum-based chemotherapy.

IV. Use after disease progression on, or after, prior PARP inhibitor therapy
   A. There is no evidence to support the use of a subsequent PARP inhibitor following the progression of disease on another PARP inhibitor.

V. Metastatic castration-resistant prostate cancer with other tumor mutations (including BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L)
   A. The phase 3 trial PROfound studied olaparib (Lynparza) versus enzalutamide or abiraterone in Cohort A (ATM, BRCA1, BRCA2) and Cohort B (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L). While statistically significant differences in PFS and overall survival (OS) were found in treatment with olaparib (Lynparza) in Cohort A and pooled Cohort A+B, the same was not found in Cohort B alone. Exploratory endpoints found PFS in Cohort B (HR: 0.88; 95% CI: 0.58, 1.36) and OS in Cohort B (HR: 0.73; 95% CI: 0.45, 1.23) not to be

statistically significant and does not indicate improved patient outcomes with use of olaparib (Lynparza) over enzalutamide or abiraterone in these patients.

VI. Treatment of advanced ovarian cancer after 3 or more lines of therapy

A. The manufacturer of olaparib (Lynparza) voluntarily withdrew the indication for treatment of adult patients with advanced ovarian cancer who have been treated with 3 or more prior chemotherapy regimens. This withdrawal was based on a totality of information from PARP inhibitors in the late line treatment setting in ovarian cancer. Including, a subgroup analysis indicating a potential detrimental effect on overall survival (OS) for Lynparza compared to the chemotherapy control arm in the subgroup of patients who had received three or more prior lines of chemotherapy corresponding to the scope of the treatment indication for Lynparza in the randomized Phase III study, SOLO3 (NCT02282020).

B. SOLO3 was requested by the FDA to confirm the clinical benefit of Lynparza in the above indication. SOLO3 is a Phase III, open-label, randomized, controlled, multi-center study to assess the efficacy and safety of single agent Lynparza vs standard of care, based on physician's choice of single agent chemotherapy (i.e., weekly paclitaxel, topotecan, pegylated liposomal doxorubicin [PLD], or gemcitabine) in patients with platinum-sensitive relapsed (PSR) ovarian cancer who had received at least 2 prior lines of platinum-based chemotherapy, and who carried a germline deleterious or suspected deleterious breast cancer susceptibility gene (BRCA1/2) mutation. SOLO3 met its primary endpoint of ORR and the key secondary endpoint of progression-free survival (PFS). The final OS analysis subsequently occurred in 2021. In a OS subgroup analysis, a potential survival detriment was observed in the subgroup of patients treated with 3 or more prior lines of chemotherapy.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month*

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy	Disease State
Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors	Breast cancer
Talazoparib (Talzenna)	Breast cancer
Niraparib (Zejula)	Ovarian Cancer
Rucaparib (Rubraca)	Ovarian Cancer
Gonadotropin-releasing hormone (GnRH)	Advanced prostate cancer
	Advanced breast cancer in premenopausal women
	Reduction of endometrial thickness prior to endometrial ablation
	Gender dysphoria
	Central Precocious Puberty (CPP)
	Uterine leiomyoma (fibroids)
	Endometriosis
darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), abiraterone (Zytiga, Yonsa)	Prostate cancer

Policy Implementation/Update:

Action and Summary of Changes	Date
Removal of ovarian cancer indication in the late line (3+) treatment setting following voluntarily withdraw of the indication by the manufacturer. Added requirement of deleterious or suspected deleterious BRCA-mutated (BRCAm) for the treatment of mCRPC in combination with abiraterone.	09/2023
Added expanded indication for the treatment of mCRPC in combination with abiraterone; updated supporting evidence	06/2023
Removal of ovarian cancer indication in the late line (3+) treatment setting following voluntarily withdraw of the indication by the manufacturer.	09/2022
Defined castration resistant disease in setting of prostate cancer. Updated ovarian cancer criteria to align with FDA approved indications and to remove redundancies in coverage requirements; updated breast cancer criteria to remove requirement of 'no more than 2 therapies in metastatic setting'; updated supporting evidence	08/2022

Added new FDA expanded indication as an adjuvant therapy in early, high-risk, non-metastatic breast cancer. Combined criteria for metastatic and early, high-risk breast cancer. Updated investigational section and supporting evidence. Added criteria to disallow use after progression on another PARP inhibitor to align with other PARP inhibitor policies. Added renewal criteria to disallow combination therapy to align with initial criteria. Added related policies table.	06/2022
Included new FDA expanded indications as first-line maintenance therapy in advanced HRD-positive ovarian cancer in combination with bevacizumab and metastatic castration-resistant prostate cancer with certain HRR mutations. Supporting evidence has been included in the policy.	10/2020
Included new FDA expanded indication as first-line maintenance therapy in pancreatic adenocarcinoma with metastasis, gBRCAm, and patients whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. The criteria for approval in the pancreatic adenocarcinoma setting is to label, and the supporting evidence has been included in this policy. Advanced ovarian cancer without gBRCAm has been removed from the investigational and experimental section since olaparib (Lynparza) is approved in ovarian cancer without gBRCAm or sBRCAm. Pancreatic cancer without gBRCAm, and pancreatic cancer that has progressed on platinum-based chemotherapy have been added to the investigational and experimental section with supporting evidence. To improve clarity, for all the indications in this policy, the mutation documentation and the specific diagnoses have been separated out into individual criterion. Removal of toxicity question upon renewal as this is managed by the provider.	02/2020
Removal of DDID to reflect the most updated template version, removed the 8 weeks criterion around most recent platinum-based therapy in the setting of maintenance therapy in ovarian cancer; in place of the 8 weeks criterion, provider attestation and documentation is required instead.	12/2019
Criteria transitioned to policy format with the following additional updates: Included new FDA expanded indication as first-line maintenance therapy in ovarian cancer with gBRCAm or sBRCAm after complete or partial response to platinum-based chemotherapy. Additionally, a question was added to the renewal portion of this policy to assess for toxicity. Capsule formulation is no longer available; therefore, it has been removed from policy. Lastly, NCCN recognizes the term “deleterious” as pathogenic in the setting of gBRCAm OR sBRCAm; therefore, the policy has been updated to include the term “pathogenic” and “likely pathogenic” in parentheses next to the terms “deleterious” and “suspected deleterious” respectively.	03/2019
Criteria update: Added coverage criteria for ovarian cancer maintenance and metastatic breast cancer	02/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP143

Description

Omacetaxine mepesuccinate (Synribo) is a reversible protein synthesis inhibitor which binds to the A-site cleft of the ribosomal subunit to interfere with chain elongation and inhibit protein synthesis. It acts independently of BCR-ABL1 kinase-binding activity, and has demonstrated activity against tyrosine kinase inhibitor-resistant BCR-ABL mutations.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
omacetaxine mepesuccinate (Synribo)	3.5 mg vial	Chronic or accelerated phase CML	Initial: 28 vials/28 days Maintenance: 14 vials/28 days

Initial Evaluation

I. Omacetaxine mepesuccinate (Synribo) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
   C. A diagnosis of **chronic myelogenous leukemia (CML)** when the following are met:
      1. CML is in chronic or accelerated phase; **AND**
      2. Member has a complete blood count preformed routinely during treatment; **AND**
      3. Treatment with at least TWO of the below tyrosine kinase inhibitors (TKI) has been ineffective, contraindicated, or not tolerated:
         i. imatinib (Gleevec)
         ii. bosutinib (Bosulif)
         iii. nilotinib (Tasigna)
         iv. dasatinib (Sprycel)

II. Omacetaxine mepesuccinate (Synribo) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
IV. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
V. Clinical documentation of response to treatment, such as stabilization of disease or decrease in tumor size or spread is provided.

Supporting Evidence

I. Omacetaxine mepesuccinate (Synribo) is indicated for the treatment of chronic or accelerated phase CML in patients resistant and/or intolerant to at least two tyrosine kinase inhibitors.
II. Myelosuppression with Grade 3/4 neutropenia, thrombocytopenia, and anemia commonly occur; generally reversible, although may require treatment delay and/or a reduction in the number of treatment days with future cycles. Myelosuppression may rarely be fatal. Blood counts should be monitored in induction and maintenance cycles.
III. Non-hematologic toxicities include Grade 3 or 4 hyperglycemia. Avoid use of omacetaxine mepesuccinate (Synribo) in the setting of poorly controlled diabetes.
IV. Within the pivotal trial, disease progression was defined as reduction of cells expressing Philadelphia chromosome mutation, normalization of white blood cells, or until patient is no longer achieving clinical treatment benefit.
V. Dosing with omacetaxine mepesuccinate (Synribo) in the initial phase is 1.25 mg/m2 subcutaneously twice daily for 14 consecutive days every 28 days, over a 28-day cycle. This cycle is repeated at this dosing every 28 days until patients achieve a hematologic response. Following hematologic response, the maintenance dosing regimen is initiated, which is 1.25 mg/m2 subcutaneously twice daily for 7 consecutive days every 28 days, over a 28-day cycle.

Investigational or Not Medically Necessary Uses

I. There is limited to no evidence to support the use of omacetaxine mepesuccinate (Synribo) in any other condition.

References

1. Synribo [Prescribing Information]. North Wales, PA: Teva Pharmaceuticals USA Inc; November 2019.
2. Nicolini FE, Lipton JH, Kantarjian H, et al. Subcutaneous omacetaxine mepesuccinate in patients with chronic phase (CP) or accelerated phase (AP) chronic myeloid leukemia (CML) resistant/intolerant to two or three approved tyrosine-kinase inhibitors (TKIs) [abstract]. J Clin Oncol. 2012;30(suppl):abstract 6513.
3. Cortes J, Digumarti R, Parikh PM, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors. Am J Hematol. 2013;88(5):350-4.
4. NCCN Clinical Practice Guideline in Oncology: Chronic Myeloid Leukemia. Version 2.2020. National Comprehensive Cancer Network. Available at https://www.nccn.org/professionals/physician_gls/PDF/cml.pdf. Updated September 25, 2019.

Policy Implementation/Update:

Date Created	February 2013
Date Effective	February 2013
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Extend approval duration to six months for initial approvals and 12 months for renewals. Required agent be used as monotherapy and not in combination with other oncologic medications.	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP175

Description

Omalizumab (Xolair) is a subcutaneously administered monoclonal antibody that binds to IgE causing the IgE receptors to downregulate and limit the degree of release of the mediators of allergic response.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product name	Indication*	Dosage form	Quantity limit
omalizumab (Xolair)	Chronic idiopathic urticaria (CIU)	150 mg*	2 vials/28 days (1.2ml/28 days)
		150 mg/1 mL prefilled syringe/autoinjector	1/28 (1ml/28 days)
		300 mg/2 mL prefilled syringe/autoinjector	1/28 (2ml/28 days)
	Allergic asthma**	150 mg vial*	2 vials/28 days (1.2ml/28 days)
		75 mg/0.5 mL prefilled syringe/autoinjector	2/28 (1ml/28 days)
		150 mg/1 mL prefilled syringe/autoinjector	2/28 (2ml/28 days)
		300 mg/2 mL prefilled syringe/autoinjector	2/28 (4ml/28 days)
	Chronic rhinosinusitis with nasal polyposis (CRSwNP)**	150 mg vial*	8 vials/28 days (9.6ml/28 days)
		75 mg/0.5 mL prefilled syringe/autoinjector	2/28 (1ml/28 days)
		150 mg/1 mL prefilled syringe/autoinjector	2/28 (2ml/28 days)
		300 mg/2 mL prefilled syringe/autoinjector	4/28 (8ml/28 days)
	IgE-mediated Food Allergy	150 mg vial*	8 vials/28 days (9.6ml/28 days)
		75 mg/0.5 mL prefilled syringe/autoinjector	2/28 (1ml/28 days)
		150 mg/1 mL prefilled syringe/autoinjector	2/28 (2ml/28 days)
		300 mg/2 mL prefilled syringe/autoinjector	4/28 (8ml/28 days)

	Systemic mastocytosis	150 mg/1.2mL vial*	2 vials/28 days (1.2 ml/28 days)
		150 mg/1 mL prefilled syringe/autoinjector	1/28 (1ml/28 days)
		300 mg/2 mL prefilled syringe/autoinjector	1/28 (2ml/28 days)

Initial Evaluation

I. **Omalizumab (Xolair)** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); **AND**
   B. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, dupilumab, mepolizumab, reslizumab, etc.); **AND**
   C. A diagnosis of one of the following:
      1. **Moderate to severe persistent allergic asthma; AND**
         i. Member is six years of age or older; **AND**
         ii. Member has a positive skin test or in vitro reactivity to a perennial aeroallergen; **AND**
         iii. Member must weigh between 20 kg (44 lbs.) and 150 kg (330 lbs.); **AND**
         iv. Member has a serum total IgE level, measured before the start of treatment, of either:
            a. ≥ 30 IU/mL and ≤ 700 IU/mL in members age ≥ 12 years; **OR**
            b. ≥ 30 IU/mL and ≤ 1300 IU/mL in members age 6 to <12 years; **AND**
         v. Member has **MODERATE** asthma as defined by one of the following:
            a. Daily symptoms
            b. Nighttime awakenings > 1x/week but not nightly
            c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs daily
            d. Some limitation to normal activities
            e. Lung function (percent predicted FEV1) >60%, but <80%
            f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to mild asthma; **OR**
         vi. Member has **SEVERE** asthma as defined by one of the following:
            a. Symptoms throughout the day
            b. Nighttime awakenings, often 7x/week
            c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs several times per day
            d. Extremely limited normal activities
            e. Lung function (percent predicted FEV1) <60%
            f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**
         vii. Member is currently being treated with:

a. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
    i. One additional asthma controller medication (e.g., long-acting beta-2 agonist [LABA] {e.g., Serevent Diskus}, long-acting muscarinic antagonist [LAMA] {e.g., Spiriva Respimat}, leukotriene receptor antagonist [e.g., Singular], or theophylline); **OR**
b. A maximally tolerated ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **OR**

2. **Chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU)**; **AND**
    i. Member is 12 years of age or older; **AND**
    ii. Underlying cause of the member's condition is NOT considered to be any other allergic condition(s) or other form(s) of urticaria; **AND**
    iii. Member is avoiding triggers (e.g., NSAIDs, etc.); **AND**
    iv. A baseline score from an objective clinical evaluation tool has been provided, such as: urticaria activity score (UAS7), angioedema activity score (AAS), Dermatology Life Quality Index (DLQI), Angioedema Quality of Life (AE-QoL), or Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL); **AND**
    v. Member had an inadequate response to a minimum (1) month trial on previous therapy of a second-generation H1-antihistamine product*****; **AND**
    vi. Member had an inadequate response to a minimum (1) month trial on previous therapy of at least **one** of the following:
        1. Updosing/dose advancement (up to 4-fold) of a second generation H1-antihistamine*****
        2. Add-on therapy with a leukotriene antagonist (e.g., montelukast, zafirlukast, etc.)
        3. Add-on therapy with another H1-antihistamine*****
        4. Add-on therapy with a H2-antagonist (e.g. ranitidine, etc.)
        5. Add-on therapy with cyclosporine; **OR**

3. **Systemic mastocytosis; AND**
    i. Member is 18 years of age or older; **AND**
    ii. Used for the prevention of **one** of the following:
        a. Chronic mast-cell-mediator-related cardiovascular (e.g., pre-syncope, tachycardia, etc.) or pulmonary (e.g., wheezing, throat-swelling, etc.) symptoms insufficiently controlled by conventional therapy (e.g., H1 or H2 blockers or corticosteroids); **OR**
        b. Unprovoked anaphylaxis; **OR**
        c. Hymenoptera or food-induced anaphylaxis in members with a negative test for specific IgE antibodies or a negative skin test; **OR**
    iii. Used to improve tolerance while on immunotherapy (i.e., venom immunotherapy [VIT]); **OR**

4. **Chronic rhinosinusitis with nasal polyposis (CRSwNP); AND**
    i. Member is 18 years of age or older; **AND**

ii. Member must weigh between 30 kg (66 lbs.) and 150 kg (330 lbs.); **AND**
iii. Member has a serum total IgE level ≥ 30 IU/mL and ≤ 1500 IU/mL measured before the start of treatment; **AND**
iv. Provider attests that the member has ALL of the following:
    a. Diagnosis of bilateral sinonasal polyposis as evidenced by an endoscopy or computed tomography (CT); **AND**
    b. Member has impaired Health-Related Quality of Life due to ongoing nasal congestion, blockage, or obstruction with moderate to severe symptom severity; **AND**
    c. Member has at least **one** of the following symptoms:
        i. Nasal discharge
        ii. Facial pain or pressure
        iii. Reduction or loss of smell; **AND**
v. Provider attestation or clinical documentation that member has current persistent symptomatic nasal polyps despite maximal treatment with ALL of the following, unless ineffective, not tolerated, or contraindicated:
    a. Intranasal corticosteroid; **AND**
    b. Oral systemic corticosteroid therapy within the last 12 months; **AND**
vi. Background intranasal corticosteroid will be continued with the use of omalizumab (Xolair), unless contraindicated; **OR**

5. **Food Allergies; AND**
i. Member is one year of age or older; **AND**
ii. Omalizumab (Xolair) not be used in combination with oral immunotherapy (e.g., peanut allergen powder-dnfp (Palforzia) or other peanut desensitization therapy); **AND**
iii. Member has a diagnosis of **IgE-mediated food allergy**, as demonstrated by:
    a. Confirmation of positive skin test and/or serologic evidence of IgE-mediated antibody to a potent extract of the allergen; **AND**
        i. Total IgE level and body weight are provided; **AND**
    b. History of allergy to peanuts; **AND**
    c. Member has food allergies to at least two of the following:
        i. Milk
        ii. Egg
        iii. Wheat
        iv. Cashew
        v. Hazelnut
        vi. Walnut; **AND**
iv. Provider attestation of all of the following:
    a. Medical history of severe peanut allergy, with reactions that cannot be managed despite food avoidance to control allergic symptoms and conventional therapies such as antihistamines (e.g., reaction causes anaphylaxis, requires epinephrine use, allergy that can be triggered by smell); **AND**

b. Member is at high risk of accidental cross contamination exposure (e.g., school, travel, restaurants); **AND**
c. Member will continue to practice food avoidance to reduce risk of anaphylaxis while on omalizumab (Xolair); **AND**
d. Member has an active prescription for epinephrine.

II. Omalizumab (Xolair) is considered investigational when used for all other conditions, including but not limited to:
A. Management of Immune Checkpoint Inhibitor related toxicity
B. Eosinophilic esophagitis
C. Interstitial cystitis
D. Painful bladder syndrome
E. Eosinophilic bronchitis
F. Multi-food oral immunotherapy
G. Bullous pemphigoid
H. Solar urticaria
I. Cholinergic urticaria
J. Seasonal allergic rhinitis
K. Emergency treatment of any allergic reaction, including anaphylaxis
L. Non-IgE-mediated food allergy, other food reactions (e.g., celiac disease)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, dupilumab, mepolizumab, reslizumab, etc.); **AND**
IV. A diagnosis of one of the following:
i. **Moderate to severe persistent allergic asthma; AND**
1. Member must weigh between 20 kg (44 lbs.) and 150 kg (330 lbs.); **AND**
2. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **OR**
ii. **Chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU)**; **AND**
1. Member has exhibited improvement or stability of disease symptoms from baseline using objective clinical evaluation tools (e.g., urticaria activity score [UAS7], angioedema activity score [AAS], Dermatology Life Quality Index [DLQI], Angioedema Quality of Life [AE-QoL], or Chronic Urticaria Quality of Life Questionnaire [CU-Q2oL]); **AND**
2. Submitted current UAS7, AAS, DLQI, AE-QoL, or Cu-Q2oL was recorded within the past **30** days; **OR**
iii. **Systemic mastocytosis**; **AND**

1. Member has exhibited improvement or stability of disease symptoms compared to baseline (e.g., decreased frequency of exacerbations); **OR**

iv. **Chronic rhinosinusitis with nasal polyposis (CRSwNP); AND**

1. Member must weigh between 30 kg (66 lbs.) and 150 kg (330 lbs.); **AND**
2. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in nasal congestion/obstruction severity, reduction in nasal polyps); **AND**
3. Background intranasal corticosteroid (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of omalizumab (Xolair), unless contraindicated.

4. **IgE-mediated Food Allergies**; **AND**

i. Member continues to be at high risk of accidental cross contamination exposure (e.g., school, travel, restaurants); **AND**

ii. Provider attestation that omalizumab (Xolair) continues to reduce allergic reactions to more than one type of food after accidental exposure and treatment provides clinical benefit to the member; **AND**

iii. Treatment will not be used in combination with oral immunotherapy (e.g., peanut allergen powder-dnfp (Palforzia) or other peanut desensitization therapy); **AND**

iv. Member continues to practice food avoidance to reduce risk of anaphylaxis; **AND**

v. Member has an active prescription for epinephrine

Supporting Evidence

I. There is a lack of evidence supporting treatment with dual use of biologic therapies and a potential for increased risk of side effects.

II. Omalizumab (Xolair) is FDA approved for moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (ICS), as add-on maintenance treatment for patients 18 years of age with chronic rhinosinusitis with nasal polyps (CRSwNP), as chronic spontaneous urticaria in patients 12 years of age and older who remain symptomatic despite H1 antihistamine treatment, and for immunoglobin E (IgE)-mediated food allergy in adult and pediatric patients 1 year of age and older for the reduction of allergic reactions (Type I) that may occur with accidental exposure to one or more foods.

- Omalizumab (Xolair) is not FDA approved for use in the setting of systemic mastocytosis; however, it is compendia recommended.

III. Omalizumab (Xolair) prefilled syringes and autoinjectors have been FDA approved for self-administration for the treatment of asthma in patients 6 years and older, chronic spontaneous urticaria (CSU) in patients 12 years and older, nasal polyps in patients aged 18 years and older, and IgE-mediated food allergies in patients aged 1 year and older. According to the package insert, therapy should be initiated in a healthcare setting. Once therapy has been safely established, the healthcare provider may determine whether self-administration of omalizumab (Xolair) is appropriate, based on careful assessment of risk for anaphylaxis and risk reduction

strategies. Patient-specific factors considered when selecting patients for self-administration include the following criteria:

- Patient should have no prior history of anaphylaxis, including to XOLAIR or other agents, such as latex, foods, drugs, biologics, etc.
- Patient should receive at least 3 doses of XOLAIR under the guidance of a healthcare provider with no hypersensitivity reactions
- Patient or caregiver is able to recognize symptoms of anaphylaxis
- Patient or caregiver is able to treat anaphylaxis appropriately
- Patient or caregiver is able to perform subcutaneous injections with XOLAIR prefilled syringe or autoinjector with proper technique according to the prescribed dosing regimen and Instructions for Use

IV. Omalizumab (Xolair) autoinjectors at all doses are not intended for use in pediatric patients under 12 years of age.

V. **Moderate to severe persistent allergic asthma**

- For patients 12 years of age and older, omalizumab (Xolair) was studied in 3 randomized, double-blind, placebo-controlled, multicenter trials. The patients enrolled in these trials were 12 to 76 years of age, with moderate to severe persistent asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE level between 30 and 700 IU/mL and body weight ≤150 kg. Patients with IgE levels less than 30 IU/mL, greater than 700 IU/mL, or a weight greater than 150 kg have not been studied and efficacy has not been demonstrated in a randomized controlled clinical trial.
    i. Trials 1 and 2: All patients were symptomatic and were treated with ICS/SABA. The primary endpoint was mean number asthma exacerbations per patient during steroid stable phase versus steroid reduction phase in comparison to placebo. In the stable steroid phase, the mean number of exacerbations per patient was 0.2 in the active arm compared to 0.3 in the placebo arm, p-value=0.005 (Trial 1) and 0.1 in the active arm compared to 0.4 in the placebo arm, p-value<0.001 (Trial 2). In the steroid reduction phase, the mean number of exacerbations per patient was 0.2 in the active arm compared to 0.4 in the placebo arm, p-value=0.004 (Trial 1) and 0.2 in the active arm compared to 0.3 in the placebo arm, p-value<0.001 (Trial 2).
    ii. Trial 3: Long-acting beta2-agonists were allowed. Patients received at least 1000 mcg/day fluticasone propionate and a subset also received oral corticosteroids (OCS). The primary endpoint was percentage of patients with at least 1 exacerbation during steroid stable phase versus steroid reduction phase in comparison to placebo. In the stable steroid phase, the treatment difference in percentage of patients with at least one exacerbation was 0.9 (95% CI -9.7, 13.7) in the ICS only arm compared to 9.8 (95% CI -10.5, 31.4) in the OCS/ICS arm. In the steroid reduction phase, the treatment difference in percentage of patients with at least one exacerbation was -4.4 (95% CI -17.6, 7.4) in the ICS only arm compared to -0.2 (95% CI -22.4, 20.1) in the OCS/ICS arm.

- For patients 6 to <12 years of age, omalizumab (Xolair) was studied in one double-blind, placebo controlled, multi-center trial. All patients were required to have a baseline IgE level between 30 and 1300 IU/mL and body weight between 20 to 150 kg. The primary endpoint was the rate of asthma exacerbations during the 24-week, fixed steroid treatment phase, which was 0.45 in the active arm compared to 0.64 in the placebo arm (RR 0.69, 95% CI 0.53, 0.9).
- The Global Initiative for Asthma (GINA) 2020 update recommends the addition of respiratory biologics, with respect to their allergic biomarkers, after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 (medium dose ICS-LABA) or Step 5 (high dose ICS-LABA) therapy. Other controller options for Step 4 include high dose ICS-LABA or add-on tiotropium, or add-on LTRA. Other controller options for Step 5 include add-on anti-IL5, or add-on low dose OCS, though guidelines note to consider side effects.
- Dose adjustments should be considered for drastic changes in body weight. Dosing should not be adjust based off IgE levels unless therapy has been interrupted for greater than one year. A minimum of three to six months of treatment is suggested to reach maximum efficacy.

VI. **Chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU)**

- Omalizumab (Xolair) was studied in two placebo-controlled, multiple-dose clinical trials. Patients received omalizumab (Xolair) 75 mg, 150 mg, or 300 mg or placebo by subcutaneous injection every 4 weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. Per the prescribing label, the 75-mg dose did not demonstrate consistent evidence of efficacy and is not approved for use in CIU. Clinical trials required a UAS7 score of greater than or equal to 16 with weekly reassessments to objectively measure treatment benefit. The primary endpoints were mean weekly itch severity score and weekly hive count.

	XOLAIR 75mg	XOLAIR 150mg	XOLAIR 300mg	Placebo
n	77	80	81	80
Weekly Itch Severity Score				
Mean Baseline Score (SD)	14.5 (3.6)	14.1 (3.8)	14.2 (3.3)	14.4 (3.5)
Mean Change Week 12 (SD)	−6.46 (6.14)	−6.66 (6.28)	−9.40 (5.73)	−3.63 (5.22)
Difference in LS means vs. placebo	−2.96	−2.95	−5.80	
95% CI for difference	−4.71, −1.21	−4.72, −1.18	−7.49, −4.10	-
Weekly Hive Count Score†				
Mean Baseline Score (SD)	17.2 (4.2)	16.2 (4.6)	17.1 (3.8)	16.7 (4.4)
Mean Change Week 12 (SD)	−7.36 (7.52)	−7.78 (7.08)	−11.35 (7.25)	−4.37 (6.60)
Difference in LS means vs. placebo	−2.75	−3.44	−6.93	
95% CI for difference	−4.95, −0.54	−5.57, −1.32	−9.10, −4.76	-

- Per the EAACI/GA²LEN/EDF/WAO guidelines for the definition, classification, diagnosis, and management of urticaria the recommended starting dose of Omalizumab (Xolair) for CIU is 300 mg every 4 weeks.
- Per clinical trials of patients with CIU taking Omalizumab (Xolair), 36% of patients treated with 300 mg reported no itch or hives at week 12 compared to 15% treated with 150 mg, 12% with 75mg, and 9% with placebo.

- There is limited data regarding the continuation of Omalizumab (Xolair) and the need for dose reductions. Preliminary studies discuss the potential for dose reductions or increased dosing intervals, although there is currently no consensus on the best method.

VII. **Systemic mastocytosis**

- Omalizumab (Xolair) is recommended per NCCN guidelines for Systemic Mastocytosis for the treatment of mast-cell-mediator-related cardiovascular or pulmonary symptoms after prior trial of an H1 blocker, H2 blocker, and corticosteroids. Use of omalizumab (Xolair) for the management of Systemic Mastocytosis is supported by case studies and prospective reviews, though no clinical trials have been completed. Omalizumab (Xolair) has been found to prevent mast-cell-mediator-related cardiovascular or pulmonary symptoms despite use of conventional therapies and has been shown to improve tolerance while on immunotherapy.

VIII. **Chronic rhinosinusitis with nasal polyposis (CRSwNP)**

- Omalizumab (Xolair) was studied as an add-on therapy with background intranasal corticosteroid in adult patients with CRSwNP with inadequate response to intranasal corticosteroids. Omalizumab (Xolair) was evaluated in two identical phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter trials. Trials enrolled patients aged 18 through 75 years with persistent bilateral nasal polyps, nasal congestion, impaired HRQoL, and weight 30-150 kg and serum IgE level 30- 1500 IU/mL. The primary endpoints were change from baseline to week 24 in endoscopic nasal polyp score (NPS) and mean daily nasal congestion score (NCS). Key secondary endpoints were change from baseline at week 24 in Sino-Nasal Outcome Test-22 (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, and Asthma Quality of Life Questionnaire (AQLQ).

	POLYP 1			POLYP 2		
	PBO N=66	**OMA N=72**	**Treatment Difference (95% CI), p-value**	**PBO N=65**	**OMA N=62**	**Treatment Difference (95% CI), p-value**
Primary Endpoint						
NPS (range, 0-8)	0.06 (0.16)	-1.08 (0.16)	-1.14 (-1.59 to -0.69) p<0.0001	-0.31 (0.16)	-0.9 (0.19)	-0.59 (-1.05 to 0.12) p<0.14
NCS (range, 0-3)	-0.35 (0.11)	-0.89 (0.1)	-0.55 (-0.84 to -0.25) p<0.0004	-0.20 (0.11)	-0.70 (0.11)	-0.50 (-0.80 to -0.19) p<0.0017
Secondary Endpoint						
SNOT-22 score (range, 0-110)	-8.58 (2.08)	-24.70 (2.01)	-16.12 (-21.86 to -10.38) p<0.0001	-6.55 (2.19)	-21.59 (2.25)	-15.04 (-21.26 to -8.82) p<0.0001
UPSIT score (range, 0-40)	0.63 (0.90)	4.44 (0.84)	3.81 (1.38-6.24) p<0.0024	0.44 (0.81)	4.31 (0.83)	3.86 (1.57-6.15) p<0.0011
AQLQ score, OR of MCID (≥0.5-point improvement)	OR 3.71 (95% CI 1-13.71, p=0.0492)			OR 4.04 (95% CI 1.07-15.25, p=0.0396)		

MCID: minimal clinically important difference

- The American Academy of Allergy, Asthma, and Immunology (AAAAI), American College of Allergy, Asthma, and Immunology (ACAAI), and Joint Council of Allergy, Asthma, and Immunology (JCAAI) 2014 guidelines recommend short-term treatment with oral steroids in patients with CRSwNP "because it decreases nasal polyp size

and symptoms". Additionally, guidelines recommend both intranasal corticosteroids and omalizumab for treatment of CRSwNP.

IX. **IgE-mediated Food Allergies**

- Omalizumab (Xolair) is the first FDA-approved medication to reduce the health impact of allergic reactions to more than one type of food after accidental exposure. Goals of treatment include increasing tolerance to small amounts of food allergens and reducing the chances of having a severe anaphylactic reaction upon accidental ingestion. There is currently no cure for food allergy; management requires the patient strictly avoid any exposure to known allergens, along with prompt administration of epinephrine to treat anaphylaxis if accidental exposures occur. Therefore, the use of omalizumab (Xolair) is reserved for members at high risk of accidental cross contamination exposure (e.g., school, travel, restaurants), with medical history of severe peanut allergy reactions that cannot be managed despite food avoidance to control allergic symptoms and conventional therapies such as antihistamines (e.g., reaction causes anaphylaxis, requires epinephrine use, allergy that can be triggered by smell).
- Coverage requires a confirmed food allergy diagnosis consisting of a clinical history of allergy along with confirmatory values with a positive skin prick test and elevated serum IgE levels, as per guideline recommendations.
- The efficacy and safety of omalizumab (Xolair) was evaluated in 168 pediatric patients in a phase 3, randomized, placebo-controlled trial (OUtMATCH). The study enrolled patients 1 - 55 years of age who were allergic to peanut and at least two other foods, including milk, egg, wheat, cashew, hazelnut, or walnut. Patients were randomized 2:1 to receive Xolair or placebo SC based on serum total IgE level and body weight, for 16 to 20 weeks. The study excluded patints with severe anaphylaxis and high baseline IgE levels (>1500mg). The primary endpoint evaluated the percentage of patients who were able to consume a single dose of ≥600 mg of peanut protein (~2.5 peanuts or ½ teaspoon of regular peanut butter) without moderate to severe allergic symptoms. Omalizumab (Xolair) treatment led to a statistically higher response rate compared to placebo (68% omalizumab vs. 5% placebo; treatment difference, 63% [95% CI, 50% to 73%]). However, 17% of subjects receiving omalizumab (Xolair) had no significant change in the amount of peanut protein tolerated (could not tolerate 100 mg or more of peanut protein). The incidence of adverse events was similar between groups and no new safety signals were identified.
- Omalizumab (Xolair) does not modulate any food response and patients must still practice food avoidance. There is unknown clinical significance and meaningfulness of improving tolerance of a single dose of 600 mg peanut protein. Furthermore, tolerance of 600 mg of peanut protein did not result in improvements in quality of life and reductions in reactions to accidental exposure to peanuts in the clinical trial.
- Restricted to treating peanut allergy, peanut allergen powder-dnfp (Palforzia) is an oral immunotherapy product approved in patients 4–17 years of age for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Safety and efficacy of combination treatment has

not been evaluated and is therefore considered experimental and investigational. Furthermore, patients taking Palforzia were excluded from participating in the clinical trial evaluating omalizumab (Xolair).

Investigational or Not Medically Necessary Uses

I. Omalizumab (Xolair) has not been adequately studied for the following conditions and does not have established safety and efficacy in these populations:
   A. Management of Immune Checkpoint Inhibitor related toxicity
      i. Though use is supported by NCCN guidelines for Management of Immunotherapy-related toxicities, there are no clinical trials demonstrating clinical efficacy or safety of the use of omalizumab (Xolair) in the treatment of Immune Checkpoint Inhibitor related toxicity.
   B. Emergency treatment of any allergic reaction, including anaphylaxis
   C. Non-IgE-mediated food allergy, other food reactions (e.g., celiac disease)
      i. Non-IgE mediated food allergies present as more subacute and/or chronic symptoms that are typically isolated to the GI tract and/or skin. Of note, celiac disease is caused by a non–IgE-mediated immune reaction to a food protein (gluten) and having a diagnosis alone is not considered a food allergy.
   D. Ongoing clinical trials for the following conditions without outcomes demonstrating efficacy of treatment:
      i. Eosinophilic esophagitis
      ii. Interstitial cystitis
      iii. Painful bladder syndrome
      iv. Eosinophilic bronchitis
      v. Multi-food oral immunotherapy
      vi. Bullous pemphigoid
      vii. Solar urticaria
      viii. Cholinergic urticaria
      ix. Seasonal allergic rhinitis

Appendix

I. Table 1: Indication and dosing

Indication	Dose
Allergic Asthma	75 to 375 mg administered subcutaneously every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See tables below.
Chronic idiopathic urticaria	150 or 300 mg administered subcutaneously every 4 weeks. Dosing is not dependent on serum IgE (free or total) level or body weight.
Chronic rhinosinusitis with nasal polyposis	75 to 600 mg SC administered subcutaneously every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See tables below.

IgE-mediated Food Allergies	75 to 600 mg SC administered subcutaneously every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See tables below.
All other indications	150 or 300 mg administered subcutaneously by a health care provider every 4 weeks. Dosing is not dependent on serum IgE (free or total) level or body weight.

II. Table 1: Weight based dosing every 2 or 4 weeks in members ≥ 12 years of age and older with Asthma

	Omalizumab administered every 2 or 4 weeks (mg) in members ≥ 12 years with asthma				
Pre-treatment serum IgE (IU/mL)		**Body weight (kg)**			
	Dosing Frequency	**30 to 60**	**> 60 to 70**	**> 70 to 90**	**> 90 to 150**
≥ 30 to 100	Every 4 weeks	150	150	150	300
> 100 to 200		300	300	300	225
> 200 to 300		300	225	225	300
>300 to 400	Every 2 weeks	225	225	300	
>400 to 500		300	300	375	
>500 to 600		300	375	Insufficient Data to recommend a dose	
>600 to 700		375			

III. Table 2: Weight based dosing every 2 or 4 weeks for in members who begin Xolair between the ages of 6 to <12 years for Asthma

Omalizumab Doses Administered Every 2 or 4 Weeks (mg) for Pediatric Members with Asthma Who Begin Xolair Between the Ages of 6 to <12 Years											
Pre-treatment IgE (IU/mL)	Dosing Freq. (weeks)	Body Weight (kg)									
		20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
30-100	Every 4 weeks	75	75	75	150	150	150	150	150	300	300
>100-200		150	150	150	300	300	300	300	300	225	300
>200-300		150	150	225	300	300	225	225	225	300	375
>300-400		225	225	300	225	225	225	300	300		
>400-500		225	300	225	225	300	300	375	375		
>500-600		300	300	225	300	300	375				

>600-700		300	225	225	300	375	Insufficient data to recommend a dose
>700-900	Every 2 weeks	225	225	300	375		
>900-1100		225	300	375			
>1100-1200		300	300				
>1200-1300		300	375				

IV. Table 3. Weight based dosing every 2 or 4 weeks for adults with CRSwNP

Omalizumab Doses Administered Every 2 or 4 Weeks (mg) for adults with CRSwNP									
Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight							
		>30-40kg	>40-50kg	>50-60kg	>60-70kg	>70-80kg	>80-90kg	>90-125kg	> 125-150kg
		Dose (mg)							
30 - 100	Every 4 weeks	75	150	150	150	150	150	300	300
>100 -200		150	300	300	300	300	300	450	600
>200 - 300		225	300	300	450	450	450	600	375
>300 - 400		300	450	450	450	600	600	450	525
>400 - 500		450	450	600	600	375	375	525	600
>500 - 600		450	600	600	375	450	450	600	
>600 - 700		450	600	375	450	450	525		
>700 - 800	Every 2 weeks	300	375	450	450	525	600		
>800 - 900		300	375	450	525	600			
>900 - 1000		375	450	525	600				
>1000 - 1100		375	450	600					
>1100 - 1200		450	525	600					
>1200 - 1300		450	525						
>1300 - 1500		525	600						

Insufficient Data to Recommend a Dose

V. Table 4: Weight based dosing for adult and pediatric members with IgE-mediated Food Allergies

Omalizumab Doses Administered Every 2 or 4 Weeks (mg) for adult and pediatric members with IgE-Mediated Food Allergy														
Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight (kg)												
		≥10-12	>12-15	>15-20	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	> 125-150
		Dose (mg)												
30 - 100	Every 4 weeks	75	75	75	75	75	75	150	150	150	150	150	300	300
>100 -200		75	75	75	150	150	150	300	300	300	300	300	450	600
>200 - 300		75	75	150	150	150	225	300	300	450	450	450	600	375

>300 - 400		150	150	150	225	225	300	450	450	450	600	600	450	525
>400 - 500		150	150	225	225	300	450	450	600	600	375	375	525	600
>500 - 600		150	150	225	300	300	450	600	600	375	450	450	600	
>600 - 700		150	150	225	300	225	450	600	375	450	450	525		
>700 - 800	Every 2 weeks	150	150	150	225	225	300	375	450	450	525	600		
>800 - 900		150	150	150	225	225	300	375	450	525	600			
>900 - 1000		150	150	225	225	300	375	450	525	600				
>1000 - 1100		150	150	225	225	300	375	450	600					
>1100 - 1200		150	150	225	300	300	450	525	600					
>1200 - 1300		150	225	225	300	375	450	525						
>1300 - 1500		150	225	300	300	375	525	600						
>1500 - 1850			225	300	375	450	600							

Insufficient Data to Recommend a Dose

VI. Abbreviated list of H1 antihistamine products:

*H1 Antihistamine Products (not all inclusive)	
• fexofenadine	• chlorpheniramine
• loratadine	• hydroxyzine
• desloratadine	• cyproheptadine
• cetirizine	• brompheniramine
• levocetirizine	• triprolidine
• clemastine	• dexchlorpheniramine
• diphenhydramine	• carbinoxamine

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
dupilumab (Dupixent®) Policy	Asthma (moderate to severe)
	Atopic Dermatitis (moderate to severe)
	Chronic rhinosinusitis with nasal polyposis
	Eosinophilic esophagitis
	Prurigo nodularis
benralizumab (Fasenra Pen™) Policy	Asthma (severe)
mepolizumab (Nucala®)	Asthma (severe)
	Eosinophilic granulomatosis with polyangiitis
	Hypereosinophilic Syndrome
	Chronic Rhinosinusitis with Nasal Polyps
reslizumab (Cinqair®) Policy	Asthma (severe)
Tezepelumab (Tezspire®) Policy	Asthma (severe)
peanut allergen powder-dnfp (Palforzia™)	Peanut allergy

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to include IgE-mediated food allergies indication. Updated quantity limits table. Updated CSU to CIU given name change as adapted by clinical practice guidelines. Updated E/I to remove urticaria given Xolair, and added emergency treatment of any allergic reaction, including anaphylaxis and	03/2024

non-IgE-mediated food allergy, other food reactions (e.g., celiac disease). Updated appendix with dosing tables, supporting evidence, references. Added related policies.	
Updated quantity limit for CIU and supporting evidence (dose recommendation)	06/2022
Update to supporting evidence (self-administration of Xolair)	05/2021
Updated policy to include chronic rhinosinusitis with nasal polyposis (CRSwNP) indication. Updated policy to include route of administration under Description, PBO program under Quantity Limits. For Initial Evaluation: added medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); asthma: removed moderate and severe asthma definition table in supporting evidence and built into criteria set, revised verbiage of previous combination therapy use and added ";OR a maximally tolerated ICS/LABA combination product". For Renewal Evaluation: asthma: revised to updated renewal verbiage and consolidated list of clinical improvement examples; CIU and systemic mastocytosis: revised to updated renewal verbiage. For supporting evidence: removed subjective verbiage and included more detailed information regarding each policy indication.	03/2021
Convert to Policy format. Removed Management of Immune Checkpoint Inhibitor related toxicity criteria to investigational rational given lack of clinical evidence to support. Removed toxicity assessment in renewal portion as this is managed by the provider.	02/2020
Previous reviews	10/2019, 10/2018, 06/2018, 03/2018, 12/2017, 09/2017, 06/2017, 03/2017, 12/2016, 09/2016, 07/2016, 07/2015, 09/2014, 04/2014, 02/2013, 06/2012
Policy created	01/2012

Policy Type: PA Pharmacy Coverage Policy: UMP276

Description

Omaveloxolone (Skyclarys) is a nuclear factor erythroid 2-related factor 2 (Nrf2) activator.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
omaveloxolone (Skyclarys)	Friedreich's ataxia	50 mg capsule	90 capsules / 30 days

Initial Evaluation

I. **Omaveloxolone (Skyclarys)** may be considered medically necessary when the following criteria are met:
   A. Member is 16 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. A diagnosis of **Friedreich's ataxia** when the following are met:
      1. Documentation of FXN gene mutation; **AND**
      2. Documentation of baseline score from an objective evaluation tool, such as the modified Functional Assessment Rating Scale (mFARS) or Scale for the Assessment and Rating of Ataxia (SARA); **AND**
      3. Provider attestation that the member does not have advanced disease [Note: advanced disease may include loss of multiple physical functionalities such as ability to swallow, speak, walk etc.]; **AND**
      4. The provider attests the member can successfully swallow the capsule by mouth (Note: omaveloxolone (Skyclarys) capsule cannot be opened, crushed, or given via feeding tube).

II. Omaveloxolone (Skyclarys) is considered investigational when used for all other conditions, including but not limited to:
   A. Alzheimer's disease
   B. Amyotrophic lateral sclerosis
   C. Huntington's disease
   D. Parkinson's disease
   E. Progressive supranuclear palsy
   F. Frontotemporal dementia

G. Epilepsy
H. Malignant melanoma
I. Non-small cell lung cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has responded to therapy, defined as stability or improvement in net motor function, compared to pretreatment baseline (e.g., stability or improvement in mFARS or SARA scores)

Supporting Evidence

I. FA (Friedreich's ataxia) is a progressive genetic neurodegenerative disorder that affects nearly 5,000 individuals in the United States. FA is caused by mutations in the frataxin (FXN) gene, which encodes the mitochondrial protein, frataxin. Genetic testing for the triplet repeats expansions in the first intron of the frataxin (FXN) gene that cause Friedreich ataxia should be performed in all patients with progressive cerebellar ataxia and autosomal recessive inheritance. Frataxin deficiency leads to dysregulation of antioxidative defense mechanisms and affects the function of the cerebellum, spinal cord, and peripheral nervous system. FA has been diagnosed in patients two to 50 years old and disease progression is inversely correlated with age of onset. Patients with FA may experience impaired muscle coordination, balance, and speech, loss of coordination, difficulty walking, and impaired muscle coordination, and heart disease. A study evaluating the natural progression of FA found that patients with FA will have on average, a two-point increase in modified FA rating scale (mFARS) score per year.
II. Omaveloxolone is a nuclear factor erythroid 2-related factor 2 (Nrf2) activator and the first FDA-approved treatment for Friedreich's ataxia (FA). The 2022 Friedreich's ataxia clinical management guidelines note that treatment is limited to supportive and symptomatic care in an effort to maintain comfort and function. Guidelines have not been updated to include omaveloxolone (Skyclarys®) in treatment recommendations.
III. Omaveloxolone was studied in a phase II, multicenter, double-blind, randomized, placebo-controlled trial (MOXIe, part 2) in 103 participants ages 16 to 40 years old with genetically confirmed Friedreich's ataxia (FA) with baseline mFARS scores between 20 to 80. Participants were included if they were able to swallow capsules and complete maximal exercise testing on a recumbent stationary bicycle. Participants with pes cavus (foot morphology with high arch that does not flatten with weightbearing) were allowed in the study but limited to 20% of total subjects enrolled. Patients were excluded if they had uncontrolled diabetes (A1c >11.0%) or clinically significant cardiac disease. Baseline characteristics consistent with more advanced disease (e.g., longer GAA1 repeat length and history of cardiomyopathy) were more prevalent in the omaveloxolone group. The mean baseline mFARS score was 38 (+/- 11), mean age 23.7 years old, and 92% of all participants were able to ambulate.

- Pes cavus occurs in up to 50-70% of individuals with FA. In MOXIe part 1, omaveloxolone improved mFARS in subjects with pes cavus to a lesser degree than those without pes cavus and investigators concluded that participants designated as having pes cavus represented a more severely affected set of individuals with FA.

IV. The primary endpoint was change in mFARS score from baseline to week 48. A total of 94 participants completed treatment through week 48; however, those with pes cavus were not included in efficacy analysis (omaveloxolone n=40, placebo n=42). Treatment with omaveloxolone resulted in statistically significant lower mFARS scores (less impairment) relative to placebo at Week 48. The placebo-corrected difference between the two groups was -2.40 points (95% CI, -4.31 to -0.50, p= 0.014). Additionally, a sensitivity analysis for all participants, including those with pes cavus (n= 103), reported a treatment difference of −1.93 +/- 0.90 (95% CI, −3.7, −0.15; *p* 0.034). Secondary endpoints of change in Patient Global Impression of Change, Clinical Global Impression of Change, 9-HPT: 9-Hole Peg Test, and T25-FW: Timed 25-Foot Walk did not meet statistical significance.
    - The mFARS score is a series of physical examination assessments to measure disease progression in patients with FA. The mFARS score consists of 4 sections (bulbar function, upper lib coordination, lower limb coordination, upright stability) and ranges from 0-93 points (20-25 at FA diagnosis, ~40 loss of ambulation, 93 indicative of death). Validity of the FARS scales have been assessed in many observational studies, demonstrating its high correlation with age of onset, genetic burden of disease. There is no clinically meaningful threshold in reduction of mFARS scores. The SARA scale is an 8-item performance scale used to assess ataxia (gait, stance, sitting, speech disturbances, finger chase, hand movement, extremity kinetics, etc). It ranges from 0 to 40 (40 indicative of severe ataxia). Both mFARS and SARA scales may be used in practice. SARA is a timelier assessment compared to mFARS and scores from each assessment cannot be directly compared.
    - The FDA accepts mFARS as an appropriate primary endpoint in clinical trials, however, request that additional patient-reported or performance-based outcome endpoints are also assessed.

V. All participants included in analysis experienced mild to moderate adverse events. Safety was similar between the active and placebo groups. The most common adverse events reported for omaveloxolone included contusion (37%), headache (25%), upper respiratory tract infection (29%), excoriation (23%), and nausea (14%).

VI. Participants who completed MOXIe part 2 were eligible to enroll in a non-inferiority open-label extension study (up to 144 weeks of total treatment). A total of 73 individuals enrolled in the extension study, including 39 participants who were initially randomized to placebo (placebo-omaveloxolone group) and 34 initially randomized to omaveloxolone (omaveloxolone-omaveloxolone group). Participants received omaveloxolone 150mg once daily. The difference in mFARS between omaveloxolone and placebo observed at the end of placebo-controlled MOXIe part 2 (least squared (LS) mean difference -2.17 +/- 1.09 points, *p*=0.0471).
    - The quality of evidence is considered moderate given a well-designed randomized clinical trial with supporting OLE data reporting consistent improvement in mFARS scores. Omaveloxolone demonstrated significant reduction in mFARS score; however, there is currently no standard clinically meaningful threshold for

improvement in mFARS score. Although time-specific, the change in mFARS is directly correlated with age of onset, genetic burden of disease, and patient reported outcomes. Similarly, a reduction in mFARS may be indicative of disease stability. Generalizability of current clinical data may be limited due to exclusion of patients with severe disease (mFARS > 80), non-ambulatory patients and those with pre-existing cardiac conditions. However, for majority of patients with mild to moderate FA, omaveloxolone (Skyclarys) may provide a potential clinical benefit. It is unclear if omaveloxolone will deliver similar responses outside of the clinical trial setting.

Investigational or Not Medically Necessary Uses

I. Omaveloxolone (Skyclarys) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Reata Pharmaceuticals noted that the MOXIe trial provided proof of concept for use of omaveloxolone in other neurological diseases where mitochondrial dysfunction and neuroinflammation are common features. Reata has observed activity in preclinical models.
      i. Alzheimer's disease
      ii. Amyotrophic lateral sclerosis
      iii. Huntington's disease
      iv. Parkinson's diseases
      v. Progressive supranuclear palsy
      vi. Frontotemporal dementia
      vii. Epilepsy
   B. Malignant melanoma
      i. Omaveloxolone was previously evaluated in a phase 1b/2 non-randomized, open-label trial as adjunct to ipilimumab or nivolumab in stage 3/4 malignant melanoma. The primary outcome was overall response rate and 23 out of 34 participants had a response.
   C. Non-small cell lung cancer
      i. Omaveloxolone was previously evaluated in a phase 1 study in patients with metastatic or incurable non-small cell lung cancer or melanoma. Omaveloxolone did not prevent disease progression.

References

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Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2023

Policy Type: PA Pharmacy Coverage Policy: UMP173

Description
To combat the opioid use disorder in Washington State.

Length of Authorization
- Initial: up to 12 months
- Renewal: up to 12 months

Fill limitations not requiring attestation

Short-Acting Opioids			
- A quantity limit of 18 dosages per prescription for children (ages 20 and under) - A quantity limit of 42 dosages per prescription for adults (ages 21 and older) Note: Prescriber indicating EXEMPT overrides the quantity			
Active ingredients containing* Combination products containing any of these listed ingredients are included in this policy			
morphine sulfate	codeine sulfate	hydromorphone	oxymorphone
hydrocodone	levorphanol	meperidine	oxycodone
pentazocine	tapentadol	tramadol	butorphanol

Long-Acting Opioids			
All quantity and duration requires a signed attestation			
Active ingredients containing*‡ Combination products containing any of these listed ingredients are included in this policy			
morphine sulfate	codeine sulfate	hydromorphone	oxymorphone
oxycodone	fentanyl patches	tramadol	hydrocodone
tapentadaol			

*Please note – acetaminophen products are limited to 4000 mg per day
‡Includes Extended release (ER) formulations as well as short acting or immediate release (IR) formulation use beyond 6 weeks.

Initial Evaluation

I. Chronic opioid use attestation form MUST be filled out and sent in for approval. This form can be found here: https://www.hca.wa.gov/assets/pebb/ump-opioid-attestation-form.pdf; **AND**

II. When use is beyond the quantity limits and duration listed above, or total Morphine Milligram Equivalent (MME) per day is 120 or greater, the following attestation agreement is required:

Criteria for chronic use of opioids or high-dose opioids for the treatment of pain not relating to active cancer treatment, hospice care, palliative care, end-of-life care, or sickle cell disease:

1. The need for chronic opioid use (more than 42 days per 90-day calendar period or use of long-acting opioids) and/or high dose opioids (≥ 120 MMEs per day) is medically necessary and is documented in the medical record; **AND**
2. The patient is currently using or has tried and failed appropriate non-opioid medications, and/or non-pharmacologic therapies; **AND**
3. The provider has recorded baseline and ongoing assessments of measurable, objective pain

scores and function scores. These should be tracked serially in order to demonstrate clinically meaningful improvements in pain and function; **AND**

4. The patient has been screened for mental health disorders, substance use disorder, and naloxone use; **AND**
5. The provider has or will conduct periodic urine drug screens; **AND**
6. The provider has checked the PMP for any other opioid use and concurrent use of benzodiazepines and other sedatives; **AND**
7. If opioids are being prescribed by any other prescriber, the provider has coordinated care with the other prescriber; **AND**

   INDICATE WHICH APPLIES:

   ☐ **For chronic opioid use:**
   - The patient must be using or had trials of short-acting opioid therapy for at least 42 days; **OR**
   - The reason for inadequate response to short-acting opioid therapy is documented in the medical record; **OR**
   - Justification of beginning an opioid naïve patient on a long-acting opioid is documented in the medical record;

   ☐ **For high-dose opioids (≥ 120 MME per day):**
   - The provider is a pain management specialist as defined in WAC 246-919-945; OR
   - The provider successfully completed a minimum of twelve category 1 continuing education hours on chronic pain management within the previous four years and at least two of these hours were dedicated to substance use disorders; **OR**
   - The provider is a pain management physician working in a multidisciplinary chronic pain treatment center or a multidisciplinary academic research facility; **OR**
   - The provider has a minimum of three years of clinical experience in a chronic pain management setting, and at least thirty percent of the providers current practice is the direct provision of pain management care; **OR**
   - The provider has consulted with a pain management specialist regarding use of high dose opioids (≥ 120 MME per day) for this patient which is documented in the medical record; **OR**
   - The patient is following a tapering schedule with a starting dose ≥ 120 MME per day; **AND**

8. The provider has discussed with the patient the realistic goals of pain management therapy and has discussed discontinuation as an option during treatment; AND
9. The provider confirms that the patient understands and accepts these conditions, and the patient has signed a pain contract or informed consent document.

I attest that all of the above criteria are met, or there is documentation in patient's chart for why one or more are not applicable ☐ Yes ☐ No

The requested treatment is medically necessary, does not exceed the medical needs of the member, and is clinically supported in the member's medical record ☐ Yes ☐ No

When should this treatment plan expire? Please specify date in MM/DD/YYYY format: _____
Note: The attestation form will expire on the date specified above or 12 months after the date of signature, whichever is soonest.

Renewal Evaluation

I. See initial evaluation section.

Supporting Evidence

I. The policy aligns with recommendations of the Centers for Disease Control, the Washington State Agency Medical Directors Group, and the Bree Collaborative around safe and appropriate opioid prescribing.
II. This is a Uniform Medical Plan (UMP) mandated criteria on all opioid policies.
This policy is in full compliance with UMP's regulations and mandates regarding the chronic use of opioids.
III. This policy applies to all groups under UMP, including Public Employees Benefit Board (PEBB) and School Employees Benefits Board (SEBB).

Investigational or Not Medically Necessary Uses

I. Chronic use of any opioid beyond 42-days within a 90-day period without a signed attestation from the prescribing provider on file.

References

1. Washington State Agency Medical Directors Group. Interagency Guideline on Prescribing Opioids for Pain. 3rd Edition, June 2015. Available: www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated attestation to include new MME requirements	08/2023
Updated to include QLs not requiring attestation as well as updating chronic attestation and high dose attestation requirements effective 7/1/2023	07/2023
Added APAP limit wording to QL box	03/2020
Creation of policy	02/2020

Policy Type: PA Pharmacy Coverage Policy: UMP144

Description

Methylnaltrexone bromide (Relistor), naldemedine (Symproic), and naloxegol (Movantik) are orally administered mu-opioid antagonists that act specifically in the peripheral tissues with inhibited central nervous system penetration at recommended dosages.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
methylnaltrexone bromide (Relistor)	150 mg tablets	Treatment of opioid-induced constipation in adults with chronic non-cancer pain	90 tablets/30 days
	12 mg vial/syringe	Treatment of opioid-induced constipation with advanced illness or pain caused by active cancer requiring opioid dosage escalation	30 single use vials or syringes/30 days
	8 mg vial/syringe		30 single use vials or syringes/30 days
naldemedine (Symproic)	0.2 mg tablets	Treatment of opioid-induced constipation in adults with chronic non-cancer pain	30 tablets/30 days
naloxegol (Movantik)	12.5 mg tablets		30 tablets/30 days
	25 mg tablets		30 tablets/30 days

Initial Evaluation

I. **Methylnaltrexone bromide (Relistor), naldemedine (Symproic), and naloxegol (Movantik)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Diagnosis of **Opioid-Induced Constipation (OIC)** when the following are met:
      1. Treatment with at least one agent from the following has been ineffective, contraindicated, or not tolerated:
         i. Stool softener (e.g. docusate sodium); **OR**
         ii. Osmotic agent (e.g. polyethylene glycol); **OR**
         iii. Stimulant laxative (e.g. sennoside); **AND**
      2. If the request is for **methylnaltrexone bromide (Relistor):**
         i. Treatment with all of the following has been ineffective, contraindicated, or not tolerated:
            a. naloxegol (Movantik); **AND**

b. naldemedine (Symproic)

II. Methylnaltrexone (Relistor), naldemedine (Symproic) and naloxegol (Movantik) are considered investigational when used for all other conditions, including but not limited to:
   A. Constipation not induced by opioids
   B. Post-operative ileus

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
III. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
IV. Member is continuing to receive chronic opioids; **AND**
V. Member has shown an improvement in the number of bowel movements they are having

Supporting Evidence

I. The American Gastroenterological Association (AGA) guidelines recommend the use of naloxegol (Movantik) and naldemedine (Symproic) for laxative-resistant patients with OIC. Methylnaltrexone bromide (Relistor) was given a conditional recommendation for laxative-resistant patients with OIC as the evidence was considered low quality. The AGA did not make a recommendation for lubriprostone (Amitiza®) as the evidence was low quality and inconsistent, with one trial not showing any statistical difference from placebo.
II. Methylnaltrexone bromide (Relistor) was studied in four trials compared against placebo. Patients were not on any background therapies in studies one and two. Studies four and five allowed patients to continue on their regular laxative regimen. The evidence is considered low quality with some studies having high rates of dropout and endpoints evaluated in studies four and five having unknown clinical benefit for patients.
    - Study one and two were randomized, double-blind, placebo-controlled trials evaluating 713 patients with OIC and chronic non-cancer pain. Methylnaltrexone bromide (Relistor) tablets and injection demonstrated a statistically significant response for proportion of responders compared to placebo. The percent difference was 13% (CI 3%, 23%) for study one and 20% (CI 10%, 31%) for study two.
    - Study three was a long-term, open-label, uncontrolled trial looking at 1,034 patients with OIC and chronic non-cancer pain. Safety was the primary endpoint with the most common adverse events being abdominal pain, diarrhea, nausea, and psychiatric disorders. The mean change in bowel movements from baseline was 1.5 bowel movements per week ($p<0.001$).
    - Study four and five were double-blind, placebo-controlled trials evaluating 287 patients with OIC and advanced illness (patients receiving palliative opioid therapy). Methylnaltrexone bromide (Relistor) injection demonstrated a statistically

significant improvement in the proportion of patients with a rescue-free laxation within four hours of study medication compared to placebo. Results from study four were 62%, 58%, 14% ($p<0.0001$) for the 0.15 mg/kg dose, 0.3 mg/kg dose, and placebo, respectively, and study five results were 48% and 16% ($p<0.0001$) for methylnaltrexone bromide (Relistor) and placebo, respectively.

III. Naloxegol (Movantik) was studied in two randomized, double-blind, placebo-controlled trials in patients with OIC and chronic non-cancer pain. The primary endpoint for both studies evaluated response to therapy defined as ≥3 spontaneous bowel movements (SBMs) per week and a change from baseline of ≥1 SBM per week for at least nine out of the 12 study weeks and three out of the last four study weeks.
    - Study one and two evaluated 1,352 patients comparing 12.5 mg and 25 mg of naloxegol (Movantik) against placebo. There was a statistically significant difference for both strengths compared to placebo in study one and only the 25 mg strength in study two. A treatment difference of 11.4% (2.4%, 20.4%) and 15% (5.9%, 24%) for 12.5 mg and 25 mg, respectively, was seen in study one and 10.3% (1.7%, 18.9%) in study two.

IV. Naldemedine (Symproic) was studied in four randomized, double-blind, placebo-controlled trials looking at patients with OIC and chronic non-cancer pain. The primary endpoint for both studies evaluated response to therapy defined as ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least nine out of the 12 study weeks and three out of the last four study weeks.
    - Study one and two were 12 week trials evaluating 1,080 patients comparing 0.2 mg of naldemedine (Symproic) against placebo. There was a statistically significant difference for naldemedine (Symproic) compared to placebo with a treatment difference of 13% (CI 5%, 21%) for study one and 19% (CI 11%, 27%) for study two.
    - Study three was a 52 week trial evaluating 1246 patients comparing 0.2 mg of naldemedine (Symproic) against placebo. The primary outcome measured was treatment emergent adverse events which did not have any difference between treatment arms. There was sustained improvement in bowel movement frequency for naldemedine (Symproic) compared to placebo ~3.5 vs ~2.5, respectively ($p<0.0001$).
    - Naldemedine (Symproic) was compared against placebo in a two week, randomized, double-blind, placebo-controlled trial with an open-label 12 week extension evaluating 193 patients with active cancer. Naldemedine (Symproic) had a statistically significant difference over placebo for the primary endpoint of proportion of SBM responders with a treatment difference of 36.8% (CI 23.7%, 49.9%).

Investigational or Not Medically Necessary Uses

I. These therapies have not been studied in the following conditions:
    A. Constipation not induced by opioids
    B. Post-operative Ileus

References

1. Relistor [Prescribing Information]. Bridgewater, NJ: Salix Pharmaceuticals, Inc. November 2018.
2. Movantik [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals. May 2019.
3. Symproic [Prescribing Information]. Raleigh, NC: BioDelivery Sciences International, Inc. April 2019.
4. Uptodate, Inc. Prevention and management of side effects in patients receiving opioids for chronic pain [database online]. Waltham, MA. Updated 11/11/19. Available at: http://www.uptodate.com/home/index.html. [Accessed 11/19/19].
5. Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. *Gastroenterology*. 2019;156(1):218-226.
6. Webster LR, Michna E, Khan A, Israel RJ, Harper JR. Long-Term Safety and Efficacy of Subcutaneous Methylnaltrexone in Patients with Opioid-Induced Constipation and Chronic Noncancer Pain: A Phase 3, Open-Label Trial. *Pain Med*. 2017;18(8):1496-1504.
7. Webster LR, Nalamachu S, Morlion B, et al. Long-term use of naldemedine in the treatment of opioid-induced constipation in patients with chronic noncancer pain: a randomized, double-blind, placebo-controlled phase 3 study. *Pain*. 2018;159(5):987-994.
8. Katakami N, Harada T, Murata T, et al. Randomized Phase III and Extension Studies of Naldemedine in Patients With Opioid-Induced Constipation and Cancer. *J Clin Oncol*. 2017;35(34):3859-3866.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria for Movantik and Symproic from requiring trial and failure of two OTC alternatives to one	01/2022
Transitioned criteria to policy: removed required trial and failure of lubiprostone (Amitiza) for all agents	11/2019
Previous Reviews	01/2018; 02/2018; 03/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP017

Description

Deferasirox (Exjade, Jadenu), and deferiprone (Ferriprox) are orally administered iron chelating agents.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
deferasirox (generic Exjade)	125 mg tablet for suspension	Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome Hemosiderosis (chronic iron overload) – transfusion thalassemia	Non-transfusion thalassemia syndrome: Monthly quantity to allow for a maximum of 20 mg/kg per day Setting of transfusions: Monthly quantity to allow for a maximum of 40 mg/kg per day
	250 mg tablet for suspension		
	500 mg tablet for suspension		
deferasirox (Exjade)	125 mg tablet for suspension		
	250 mg tablet for suspension		
	500 mg tablet for suspension		
deferasirox (generic Jadenu)	90 mg tablet	Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome Hemosiderosis (chronic iron overload) – transfusion thalassemia	Non-transfusion thalassemia syndrome: Monthly quantity to allow for a maximum of 14 mg/kg per day Setting of transfusions: Monthly quantity to allow for a maximum of 28 mg/kg per day
	180 mg tablet		
	360 mg tablet		
	90 mg granule		
	180 mg granule		
	360 mg granule		
deferasirox (Jadenu)	90 mg tablet		
	180 mg tablet		
	360 mg tablet		
	90 mg granule (sprinkle)		
	180 mg granule (sprinkle)		
	360 mg granule (sprinkle)		
	500 mg tablet	Hemosiderosis	

deferiprone (generic Ferriprox)	1000 mg tablet	(chronic iron overload) – transfusion thalassemia and transfusions related to sickle cell disease or other anemias	Monthly quantity to allow for a maximum of 99 mg/kg per day
deferiprone (Ferriprox)	100 mg/1 mL solution		
	80 mg/1mL solution		
	500 mg tablet		
	1000 mg tablet		

Initial Evaluation

I. **Deferasirox (Exjade, Jadenu), and deferiprone (Ferriprox)** may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in consultation with, a specialist (e.g., hematologist); **AND**
   B. Documentation of the members weight that has been measured in the past three months; **AND**
   C. A diagnosis of one of the following:
      1. **Chronic iron overload due to <u>non-transfusion</u> dependent thalassemia (NTDT) syndromes**; **AND**
         i. Member is ten years of age or older; **AND**
         ii. Documentation of a liver iron (Fe) concentration (LIC) of at least 5 mg per gram of dry weight; **AND**
         iii. Documentation serum ferritin levels are greater than 300 mcg/L; **AND**
         iv. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
            a. Brand Exjade or Jadenu is prescribed and **<u>both</u>** generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication) (Please note: deferiprone [Ferriprox] is not FDA-approved for this indication); **OR**
      2. **Chronic iron overload due to <u>blood transfusions</u>**; **AND**
         i. Member is two years of age or older and brand or generic deferasirox (Exjade) or deferasirox (Jadenu) are prescribed; **OR**
            a. Member is eight years of age or older and deferiprone (Ferriprox) tablets are prescribed; **OR**
            b. Member is three years of age or older and deferiprone (Ferriprox) solution is prescribed; **AND**
         ii. Documentation is provided that the member has received transfusions that have resulted in consistent serum ferritin level greater than 1000 mcg/L; **OR**

a. Documentation is provided that the member has received transfusions that have resulted in liver iron concentration (LIC) ≥5mg/g dry weight (dw); **AND**

iii. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**

a. Brand Exjade, Jadenu, or generic deferiprone (Ferriprox) is prescribed and **both** generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication)

b. Brand Ferriprox is prescribed and **both** generic deferasirox (generic for Exjade) **AND** deferasirox (generic for Jadenu) **AND** generic deferiprone have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication)

II. Deferasirox (Exjade), deferasirox (Jadenu) and deferiprone (Ferriprox) are considered not medically necessary when criteria above are not met and/or when used for:
   A. Plasmodium falciparum parasitemia

III. Deferasirox (Exjade), deferasirox (Jadenu) and deferiprone (Ferriprox) are considered investigational when used for all other conditions, including but not limited to:
   A. Hereditary hemochromatosis
   B. Porphyria cutanea tarda

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Documentation of the member's weight, measured in the past three months; **AND**
   A. **Chronic iron overload due to non-transfusion dependent thalassemia syndromes**; **AND**
      1. Documentation of a serum ferritin levels are greater than 300 mcg/L; **AND**
      2. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
         i. Brand Exjade or Jadenu is prescribed and **both** generic deferasirox (generic for Exjade) AND generic deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication) (deferiprone [Ferriprox] is not FDA-approved for this indication); **AND**
      3. A response to treatment, defined by a decline in serum ferritin level OR liver iron concentration (LIC), has been documented; **OR**

B. **Chronic iron overload due to <u>blood transfusions</u>; AND**
   a. Documentation that the member is continuing to receive transfusions resulting in serum ferritin levels consistently greater than 500 mcg/L; **AND**
   b. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
      i. Brand Exjade, Jadenu, or generic deferiprone (Ferriprox) is prescribed and **<u>both</u>** generic deferasirox (generic for Exjade) AND generic deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication); **OR**
      ii. Brand Ferriprox is prescribed and both generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) AND generic deferiprone have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication); **AND**
   c. A response to treatment, defined by a decline in serum ferritin level OR liver iron concentration (LIC), has been documented

Supporting Evidence

I. The agents listed in this policy are iron chelating agents indicated for chronic iron overload but have not been shown to improve survival or disease-related symptoms. Of note, the products are not interchangeable on a dose basis. Deferiprone (Ferriprox) is an iron chelator indicated only for transfusional iron overload in patients with thalassemia, sickle cell disease, or other anemias. Although deferiprone (Ferriprox) was previously reserved for use when other chelation therapy had been inadequate, labeling has been updated to no longer require use of other chelation therapy prior to therapy with deferiprone (Ferriprox). Deferasirox (Exjade, Jadenu) remains the most cost-effective therapy in this class; the requirement of trial and failure of therapy with deferasirox (Exjade, Jadenu) prior to coverage of deferiprone (Ferriprox) has been maintained in this policy.

II. Per the package inserts for the medications listed in this policy, doses are based on weight. Safety and efficacy of the medications have been studied for FDA-approved weight-based doses. Doses escalation beyond these limits has not been evaluated.

III. Clinical trials evaluated deferasirox (Exjade) and deferasirox (Jadenu) in patients 10 years of age or older for chronic iron overload due to non-transfusion dependent thalassemias, and for two years of age an older for iron overload due to blood transfusions. Deferiprone (Ferriprox) has not been adequately evaluated for safety and efficacy in patients younger than eight years of age for the tablet formulation and three years of age for the solution formulation.

IV. **Chronic iron overload due to <u>non-transfusion</u> dependent thalassemia (NTDT) syndromes**
   - For iron overload not due to transfusion, deferasirox (Exjade) and deferasirox (Jadenu) were studied in patients with an LIC of at least 5 mg of iron per dry weight and a serum ferritin greater than 300 mcg/L. Levels of serum ferritin below 300 mcg/L are considered within normal range and would not meet medical necessity for dosing of iron overload treatment products.

V. **Chronic iron overload due to <u>blood transfusions</u>**

- Although deferasirox (Exjade, Jadenu) has not been approved in chronic iron overload in patients with sickle cell disease specifically, there is evidence of clinical benefit in this indication. Deferasirox (Exjade, Jadenu) was studied in one phase 2, randomized, open-label trial in comparison to deferoxamine in 195 patients age two and older with sickle cell disease and transfusional hemosiderosis. At end of study, the mean change in LIC in the per protocol-1 (PP-1) population, which consisted of patients who had at least 1 post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving deferasirox tablets for oral suspension (n = 113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n = 54).
- For iron overload due to transfusion in patients with sickle cell disease and other anemias, deferiprone (Ferriprox) was studied in one randomized, controlled, open-label, non-inferiority trial against deferoxamine in 228 patients age two and older. The primary endpoints were change from baseline in liver iron concentration (LIC) at 12 months; the non-inferiority criteria was met with a mean decrease from baseline in LIC of 4.04 ± 0.48 mg/g dw (deferiprone) vs. 4.45 ± 0.57 mg/g dw (deferoxamine). Adverse drug reactions (ADRs) observed during the clinical trial were consistent with those already seen in the thalassemia population. The rates of agranulocytosis were also comparable to those seen in patients with thalassemia; no new safety signals or concerns were noted.

VI. For transfusion related iron overload, patient with a serum ferritin level greater than or equal to 1000 mcg/L or a liver iron concentration of 3 to 5 mg/g dry weight (dw), or higher, will be considered for iron overload products. Upon renewal, patients with a serum ferritin level below 500 mcg/L will have therapy temporarily discontinued.

VII. As of December 2019, AB-rated generics for Exjade and Jadenu tablets were available on the market.

VIII. As of February 2021, AB-rated generics for Ferriprox 500mg tablets were available on the market. All other strengths and dosage forms remain available in the Brand formulation only.

Investigational or Not Medically Necessary Uses

I. Plasmodium falciparum parasitemia
   A. In a prospective, double-blind, placebo-controlled trial, deferiprone was found to be clinically ineffective against plasmodium falciparum parasitemia.

II. Hereditary hemochromatosis and porphyria cutanea tarda
   A. Clinical trials are investigating iron overload agents in these settings.

References

1. Exjade [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May, 2018.
2. Jadenu [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May, 2018.
3. Ferriprox [Prescribing Information]. Toronto, Ontario, Canada. Apotex Inc. April, 2021.
4. Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in beta-thalassemia major. Blood. 2008;111(2):583-7.

5. Taher AT, Porter JB, Viprakasit V, et al. Deferasirox demonstrates a dose-dependent reduction in liver iron concentration and consistent efficacy across subgroups of non-transfusion-dependent thalassemia patients. Am J Hematol. 2013;88(6):503-6.
6. Vichinsky E, Onyekwere O, Porter J, et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. Br J Haematol. 2007;136(3):501-8.
7. Tricta F, Uetrecht J, Galanello R, et al. Deferiprone-induced agranulocytosis: 20 years of clinical observations. Am J Hematol. 2016;91(10):1026-31.
8. Elalfy M, et al. Deferiprone versus deferoxamine for transfusion-dependent anemias (FIRST study). Chiesi [unpublished].
9. Elafly M, et al. Long-term efficacy and safety of deferiprone for patients with sickle cell disease or other anemias (FIRST-EXT study). Chiesi [unpublished].

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 1000mg strength of deferiprone (generic Ferriprox)	02/2022
Addition of generic deferasirox oral granules and generic deferiprone tablets to policy; requirement to have trial and failure or contraindication to both generic Exjade and Jadenu for prior to payment consideration of generic deferiprone, and generic Exjade and Jadenu AND generic deferiprone prior to payment consideration for brand Ferriprox. Criteria updated regarding the following: age for use of deferiprone tablets (8 years old) and deferiprone solution (3 years old), addition of LIC as baseline and renewal measurement for transfusional iron overload. Update to supporting evidence.	09/2021
Addition of generic Jadenu and new strength of deferiprone to the policy, with requirement to have trial and failure or contraindication, to both generic Exjade and Jadenu prior to payment consideration for brand products of this policy.	12/2019
Iron chelating agent policies combined, criteria added regarding the following: weight documentation, ferritin level documentation, addition of a policy to Jadenu, specialist prescribing, additional of generic deferasirox (Exjade) tablet for oral suspension and step through this product. Transition to policy format.	05/2019
Criteria created	08/2013

Policy Type: PA Pharmacy Coverage Policy: UMP045

Description

Ospemifene (Osphena) is an orally administered estrogen agonist and antagonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
ospemifene (Osphena)	Moderate to severe dyspareunia due to vulvar and vaginal atrophy associated with menopause; Moderate to severe vaginal dryness due to vulvar and vaginal atrophy associated with menopause	60 mg tablets	30 tablets/30 days

Initial Evaluation

I. **Ospemifene (Osphena)** may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of **moderate to severe vaginal dryness; AND**
      1. Member is being treated for vaginal dryness as a symptom of vulvar and vaginal atrophy, due to menopause; **AND**
      2. Treatment with the following has been ineffective, contraindicated, or not tolerated:
         i. One systemic hormone replacement therapy (e.g., estradiol oral tablets, estradiol patch, estradiol injection); **AND**
         ii. One vaginal hormone replacement therapy (e.g., Estring, generic estradiol cream)

II. Ospemifene (Osphena) is an excluded medication when the following criteria below are met:
   A. A diagnosis of **moderate to severe dyspareunia** (difficult or painful sexual intercourse) as a symptom of vulvar and vaginal atrophy, due to menopause

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Request is for a diagnosis of moderate to severe vaginal dryness; **AND**
IV. Member has exhibited improvement or stability of disease symptoms [e.g., decreased genital dryness, burning, irritation, urinary symptoms of urgency, dysuria, and recurrent UTIs]

Supporting Evidence

I. Genitourinary syndrome of menopause (GSM) is defined as a collection of symptoms and signs caused by hypoestrogenic changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder that occur in menopausal patients. The term GSM was introduced by the International Society for the Study of Women's Sexual Health and the North American Menopause Society in 2014 and replaced the term vaginal atrophy (other terms include vulvovaginal atrophy, urogenital atrophy, or atrophic vaginitis).
II. Vaginal atrophy is a direct consequence of the hypoestrogenic state associated with menopause resulting in anatomic and physiologic changes in the genitourinary tract. The North American Menopause Society estimates that 10–40% of menopausal women will experience one or more symptoms of vaginal atrophy. Vaginal atrophy causes bothersome vaginal symptoms commonly associated with menopause including, vaginal or vulvar dryness, discharge, itching, and dyspareunia. A loss of superficial epithelial cells in the genitourinary tract causes thinning of tissue. Loss of vaginal rugae and elasticity occur with a narrowing and shortening of the vagina. Epithelial tissues are more fragile and may tear, leading to bleeding and fissures. There also is a loss of subcutaneous fat in the labia majora. These changes result in narrowing of the introitus, fusion of the labia minora, and shrinking of the clitoral prepuce and urethra. Vaginal pH becomes more alkaline, which may alter the vaginal flora and increase the risk of urogenital infection.
III. American College of Obstetricians and Gynecologist (ACOG) stated in their Clinical Guidelines on Management of Menopausal Symptoms that vaginal symptoms (e.g., dyspareunia, vaginal or vulvar dryness, discharge, itching) are best treated with systemic or topical hormone therapy. These guidelines recommend both systemic and vaginal/local estrogen preparations.
IV. The 2022 hormone therapy position statement of The North American Menopause Society attest hormone therapy remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture. The risks of hormone therapy differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing therapy. For bothersome genitourinary syndrome of menopause symptoms not relieved with over-the-counter therapies in women without indications for use of systemic hormone therapy, low-dose vaginal estrogen therapy or other therapies (eg, vaginal dehydroepiandrosterone or oral ospemifene) are recommended.
V. Dyspareunia is defined as difficult or painful sexual intercourse. Ospemifene (Osphena) for dyspareunia, a form of sexual dysfunction is in a category of medications that are not covered

under the prescription benefit. Drugs used for sexual dysfunction are excluded from coverage. Please reference the member handbook/certificate of coverage for further information regarding this denial.

References

1. Oregon Insurance Division Bulletin INS 2014-1 Mental Health Parity.
2. Diagnostic and Statistical Manual of Mental Disorders (DSM) Versions IV-TR and V.
3. Osphena [prescribing information]. Shionogi Inc.: Florham Park, NJ; January 2019
4. Gracia C. The American College of Obstetricians and Gynecologist Clinical Guidelines on Management of Menopausal Symptoms. Am Fam Physician. 2014; 90(5):338-340.
5. The 2022 Hormone Therapy Position Statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022;29(7):767-794.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated supporting evidence to reflect new guideline updates from the 2022 hormone therapy position statement of the North American Menopause Society. Updated quantity limit table and renewal criteria to standard formatting.	07/2023
Updated policy to remove coverage in the setting of dyspareunia as this is an excluded benefit.	09/2019
Converted criteria to the new policy format. Added newly FDA approved indication of moderate to severe vaginal dryness due to vulvar and vaginal atrophy associated with menopause. The route for approval in the setting of vaginal dryness follows the ACOG Clinical Guidelines.	03/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP261

Description

Oteseconazole (Vivjoa) is an orally administered azole antifungal.

Length of Authorization

- Initial: Three months
- Renewal: Cannot be renewed

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
oteseconazole (Vivjoa)	Recurrent vulvovaginal candidiasis (RVVC) in females of non-reproductive potential	150mg capsules	18 capsules/84 days

Initial Evaluation

I. **Oteseconazole (Vivjoa)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. A diagnosis of **recurrent vulvovaginal candidiasis (RVVC)** when the following are met:
      1. Member has a history of three or more acute vulvovaginal candidiasis (VVC) episodes within the last 12 months; **AND**
      2. Member is currently experiencing signs and symptoms consistent with an acute episode of VVC (e.g., vulvovaginal pain, pruritis or irritation, abnormal vaginal discharge, etc.); **AND**
      3. Diagnosis of acute VVC has been confirmed by positive KOH or culture; **AND**
      4. Member is of non-reproductive potential, defined as one of the following:
         i. Postmenopausal; **OR**
         ii. Member has undergone surgical sterilization (e.g., history of tubal ligation, bilateral salpingo-oophorectomy, or hysterectomy); **OR**
         iii. Other means of permanent infertility (documentation is verified by a clinical pharmacist at the health plan); **AND**
      5. Member has been treated with weekly oral fluconazole for a period of 6 months; **OR**
         i. Treatment with fluconazole is not tolerated or contraindicated; **OR**
         ii. Antifungal susceptibility testing has been conducted and confirms fluconazole resistance; **OR**
         iii. Member has experienced a recurrence during or following maintenance therapy with fluconazole

II. Oteseconazole (Vivjoa) is considered investigational when used for all other conditions, including but not limited to:
   A. Acute vulvovaginal candidiasis
   B. Onychomycosis or other nail fungal infections
   C. Tinea pedis
   D. Systemic fungal infections

Renewal Evaluation

I. See initial evaluation

Supporting Evidence

I. Oteseconazole (Vivjoa) is an oral azole antifungal that has been FDA-approved to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC). Oteseconazole (Vivjoa) was studied in three Phase 3, randomized, double-blind, placebo-controlled pivotal trials: two VIOLET studies and one ultraVIOLET study. The trial population consisted of a total of 875 post-menarchal females aged 12 years and older who had a diagnosis of RVVC, defined as at least three prior episodes of acute VVC in the past 12 months.

II. The VIOLET trials consisted of an induction phase with fluconazole 150mg on days one, four, and seven. On day 14 participants were assessed for infection clearance; only participants who had cleared their initial infection were then randomized to receive oteseconazole (Vivjoa) or placebo for the maintenance period. The dosing of oteseconazole (Vivjoa) during the maintenance period was 150mg once daily for one week, followed by 150mg weekly for 11 weeks. The primary efficacy endpoint for both VIOLET trials was the proportion of patients with one or more culture verified acute VVC episodes during the maintenance phase of the study.

III. In ultraVIOLET, participants were randomized prior to the induction phase to receive oteseconazole (Vivjoa) or fluconazole/placebo. In the oteseconazole (Vivjoa) group, participants received 600mg on day one and 450mg on day two for induction therapy, then oteseconazole (Vivjoa) weekly for 11 weeks starting on day 14 for maintenance therapy. In the fluconazole/placebo group, participants received fluconazole 150mg on days one, four, and seven for induction therapy, then placebo weekly for 11 weeks starting on day 14 for maintenance therapy. Results below:

	Trial 1 (VIOLET)		Trial 2 (VIOLET)		Trial 3 (ultraVIOLET)	
	OTE N = 217	PBO N = 109	OTE N = 218	PBO N = 108	OTE N = 218	FLU/PBO N = 108
Induction regimen	FLU		FLU		OTE	FLU
Maintenance regimen	OTE 150mg QD x7 days, then QW x11 weeks	PBO	OTE 150mg QD x7 days, then QW x11 weeks	PBO	OTE 150mg QW x11 weeks	PBO
Proportion of patients with ≥1 culture-verified acute VVC episode (Day 1 – week 48)*	6.7%	42.8%	3.9%	39.4%	10.3%	42.9%
Proportion of patients with ≥1 culture-verified	27.3%	50.8%	21.3%	49.7%	43.5%	59.0%

acute VVC episode or received VVC medication (Day 1 – week 48)*						
FLU = fluconazole 150mg on days 1, 4, and 7; PBO = matching placebo; OTE = oteseconazole *All results were statistically significant in favor of oteseconazole						

IV. Although the trial was designed to allow providers to treat participants with fluconazole for episodes of recurrence, other VVC medications were used during the trial to treat suspected acute VVC infections. The investigators did not initially consider all instances where participants used other VVC medications as incidence of recurrence. A post-hoc sensitivity analysis conducted by the FDA considered the use of other VVC medications as recurrence shows a slightly different efficacy profile, and results are reported in the second endpoint in the table above. Although the post-hoc analysis cannot formally be considered for statistical significance, this shows a more realistic efficacy profile that remains clinically meaningful.

V. The most commonly reported adverse events consisting of headache (7.4%) and nausea (3.6%). Although the clinical trials included participants who were of reproductive potential, oteseconazole (Vivjoa) is contraindicated in females of reproductive potential and in pregnant and lactating women due to embryo-fetal toxicity risks, including ocular abnormalities based on data from animal trials, that cannot be adequately mitigated given the drug exposure window of approximately 690 days.

VI. The FDA label defines 'non-reproductive potential' as follows: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy). Although contraception is highly effective at preventing pregnancy, there is always a chance of contraceptive failure with any contraceptive method. Additionally, because the effects of contraception are reversible, use of various contraceptive methods, including abstinence, are not considered 'permanent infertility'.

VII. Although the pivotal clinical trials enrolled post-menarchal patients aged 12 years and older, the majority of participants were between age 18 and 34 years and only two total patients under age 18 years participated. Due to the small population size, the true safety and efficacy profile of oteseconazole (Vivjoa) has not been established in patients under the age of 18 years.

VIII. Clinical guidelines, including those published by the Centers for Disease Control and Prevention (CDC) and Infectious Disease Society of America (IDSA), indicate that diagnosis of VVC can typically be made via the presentation of infection signs/symptoms: pruritis, irritation, vaginal soreness, external dysuria, and dyspareunia accompanied by signs of vulvar edema, erythema, excoriation, fissures and white, thick, curd-like vaginal discharge. For complicated VVC and RVVC, diagnosis should be confirmed with a wet-mount preparation with use of saline and 10% potassium hydroxide (KOH). If KOH is negative, a culture for *Candida* should be obtained.

IX. RVVC is usually defined as having at least three episodes of acute VVC within one year and are typically caused by azole-susceptible *C. albicans*. Clinical guidelines recommend beginning treatment with induction therapy with a 10-to-14-day course of a topical azole or oral fluconazole, followed by maintenance therapy with fluconazole 150mg once weekly for six months. If oral fluconazole is not feasible, topical clotrimazole (200mg cream twice weekly or 500mg vaginal suppository once weekly) or other intermittent oral or topical antifungal treatment is recommended. After cessation of maintenance therapy, IDSA approximates a 40-50% recurrence rate. Oteseconazole (Vivjoa) may be considered medically necessary if oral fluconazole has been not tolerated, is contraindicated, fluconazole resistance is confirmed, or if

members experience recurrence of acute VVC symptoms anytime during or after maintenance therapy with fluconazole.

X. According to results of an extension trial reported by the manufacturer, 85% of participants who completed the maintenance regimen with oteseconazole (Vivjoa) did not experience a recurrent episode for up to 96 weeks (approximately two years). However, rates of recurrence beyond two years or safety and efficacy of retreatment with oteseconazole (Vivjoa) has not been established. Due to lack of adequate safety and efficacy data to establish an appropriate timeline for retreatment, renewal requests will be evaluated against initial policy criteria.

Investigational or Not Medically Necessary Uses

I. Oteseconazole (Vivjoa) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Acute vulvovaginal candidiasis
      i. One Phase 2, randomized, double-blind, active-controlled, parallel-group, dose-ranging trial evaluated oteseconazole (Vivjoa) at various doses (300mg once daily, 600mg daily or 600mg twice daily) for three days against a single dose of fluconazole 150mg in the setting of acute VVC. The primary endpoint was the proportion of participants with therapeutic cure at the test-of-care (TOC) day 28 visit. This study was not appropriately powered for statistical analysis and statistical significance could not be evaluated. However, the nominal data indicate that no difference in therapeutic cure was identified between any of the oteseconazole (Vivjoa) groups and the fluconazole group.
   B. Onychomycosis or other nail fungal infections
   C. Tinea pedis
   D. Systemic fungal infections

References

1. Brand SR, Sobel JD, Nyirjesy P, et al. A Randomized Phase 2 Study of VT-1161 for the Treatment of Acute Vulvovaginal Candidiasis. Clinical Infectious Diseases. 2021;73(7):e1518-24.
2. Sobel JD, Nyirjesy P.Oteseconazole: an advance in treatment of recurrent vulvovaginal candidiasis. Future Microbiol. (2021) 16(18), 1453-1461.
3. New Drug Review: oteseconazole (Vivjoa). IPD Analytics. May 2022.
4. Centers for Disease Control and Prevention (CDC). 2015 Sexually Transmitted Diseases Treatment Guideline: Vulvovaginal candidiasis. Accessed July 19, 2021.
5. Pappas PG, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clinical Infectious Diseases. 2016;62(4):e1-50.
6. Vivjoa [Prescribing Information]. Mycovia Pharmaceuticals: Durham, NC. April 2022.
7. Kotch LE. Integrated Review - Application number: 211288Orig1s000. Center for Drug Evaluation and Research. August 26, 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated wording to reflect standard policy language; Added criteria for fluconazole resistance	03/2023
Policy created	08/2022

Policy Type: PA Pharmacy Coverage Policy: UMP206

Description

Oxymetazoline (Upneeq) is an alpha-adrenergic receptor agonist ophthalmic solution.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
oxymetazoline (Upneeq)	0.1% solution dropperette	aponeurotic acquired blepharoptosis	30 dropperettes/30 days

Initial Evaluation

I. Oxymetazoline (Upneeq) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an ophthalmologist; **AND**
   C. A diagnosis of **aponeurotic acquired blepharoptosis** (i.e., not being used in mechanical blepharoptosis, Horner syndrome, myasthenia gravis) when the following are met:
      1. Provider attestation of **ALL** of the following:
         i. Member has functional impairment in activities of daily living due to blepharoptosis; **AND**
         ii. The *superior* visual field is less than 20 degrees when untapped; **AND**
         iii. There is at least a 20-degree improvement when taped; **AND**
         iv. There is a marginal reflex distance (MRD)-1 of 2.0 mm or less

II. Oxymetazoline (Upneeq) is considered investigational when used for all other conditions, including but not limited to:
   A. Non aponeurotic blepharoptosis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Provider attestation indicating member has exhibited improvements in points seen in visual field test

Supporting Evidence

I. Blepharoptosis, also known as ptosis, is a unilateral or bilateral dropping of the upper eyelid due to a congenital or acquired abnormality of the muscles that elevate the eyelid. Acquired blepharoptosis may be due different causes such as aponeurotic (usually age related), mechanical (e.g., eyelid mass), neurologic (e.g., Horner syndrome, myasthenia gravis), and myogenic (e.g., systemic muscular dysfunctions). Aponeurotic is the most common and is associated with aging. Surgery is the standard of care for patients who develop an obscured visual field due to ptosis and can also be considered for cosmetic purposes. However, surgery comes with known risks (e.g., failure of the eye to close completely, infection, edema, under correction/overcorrection, eyelid asymmetry, granuloma formation, and corneal foreign body sensation). Oxymetazoline (Upneeq) is an alternative to surgery in those who are not suitable candidates or those seeking a less costly, non-surgical option.

II. Oxymetazoline (Upneeq) was studied in two phase 3, double masked, randomized, vehicle-controlled trials in patients with acquired blepharoptosis. The primary endpoint was a change in the number of points seen in the top 4 rows of the Leicester Peripheral Field Test (LPFT) on treatment day 1 and 14. Patients included in trial 202 had a mean marginal reflex distance (MRD-1) of 1.04 ± 0.74 mm (Upneeq) and 1.07 ± 0.70 mm (vehicle) at baseline.

<table>
<tr><th rowspan="3">Endpoints</th><th colspan="2">RVL-1201-201 (n=140)</th><th colspan="2">RVL-1201-202 (n=164)</th></tr>
<tr><th>Upneeq</th><th>Vehicle</th><th>Upneeq</th><th>Vehicle</th></tr>
<tr><th>n=94</th><th>n=46</th><th>n=109</th><th>n=55</th></tr>
<tr><td rowspan="2">Mean change in LPFT Day 1 (6 hours post instillation)</td><td>5.2 points</td><td>1.5 points</td><td>6.3 points</td><td>2.1 points</td></tr>
<tr><td colspan="2">Mean difference: 3.7 [1.8, 5.6] P<0.01</td><td colspan="2">Mean difference: 4.2 [2.4, 6.1] P<0.01</td></tr>
<tr><td rowspan="2">Mean change in LPFT Day 14 (2 hours post instillation)</td><td>6.4 points</td><td>2.2 points</td><td>7.7 points</td><td>2.4 points</td></tr>
<tr><td colspan="2">Mean difference: 4.2 [2.0, 6.0] P<0.01</td><td colspan="2">Mean difference: 5.3 [3.7, 7.1] P<0.01</td></tr>
<tr><td rowspan="2">Mean change in MRD-1 from baseline (highest change; day 14, 2 hours post-instillation)</td><td colspan="2" rowspan="2">MRD-1 endpoints not published</td><td>1.3 mm</td><td>0.4 mm</td></tr>
<tr><td colspan="2">P < 0.05</td></tr>
</table>

III. Although oxymetazoline (Upneeq) showed a statistically significant improvement relative to vehicle for improving LPFT, the quality of the evidence is considered low as LPFT is a modified version of Humphrey visual field test that is not typically used in practice, coupled with limited information available on trial data, unknown components used as the vehicle product, and unknown safety with use over 42 days.

IV. Clinical trials noted above excluded certain acquired causes of blepharoptosis (i.e., mechanical, Horner syndrome, myasthenia gravis). Efficacy of oxymetazoline (Upneeq) outside of the aponeurotic acquired blepharoptosis population is unknown.

V. FDA approval of oxymetazoline (Upneeq) is specific to the adult population only. Although one of the clinical trials included patients 9 years and older, the youngest patient that received oxymetazoline (Upneeq) in that trial was 20 years old. Thus, safety and efficacy of oxymetazoline (Upneeq) has not been established in pediatric patients.

Investigational or Not Medically Necessary Uses

I. Oxymetazoline (Upneeq) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Non aponeurotic blepharoptosis

References

1. Upneeq [Prescribing Information]. RVL Pharmaceuticals, Inc.: Bridgewater, NJ. August 2020.
2. Korenfeld M, Kannarr S, Silverstein S, et. al. Effect of oxymetazoline on blepharoptosis: results of a phase 3 randomized, double masked, placebo-controlled study – Poster Presentation Presented at the American Academy of Optometry (AAO) Meeting – October 2019.
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4. UpToDate, Inc. Overview of ptosis. UpToDate [database online]. Waltham, MA. Last updated May 06, 2020. Available at: http://www.uptodate.com/home/index.html.
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8. Kansteiner F. Osmotica bucks pandemic trend with in-person sales calls for eye drug launch [Press Release]. Fierce Pharma. https://www.fiercepharma.com/marketing/osmotica-nets-approval-for-first-class-droopy-eyelid-med. Published July 13, 2020.
9. Prioritized List of Health Services. Oregon Health Authority. August 14, 2020. Available at: https://www.oregon.gov/oha/hpa/dsi-herc/pages/prioritized-list.aspx 2020 Prioritized List of Health Services.pdf.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

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U.S. Department of Health and Human Services
200 Independence Avenue, SW Room 509F, HHH Building
Washington, D.C. 20201

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ATENȚIE: Dacă vorbiți limba română, vă punem la dispoziție serviciul de asistență lingvistică în mod gratuit. Sunați la 1-888-361-1611 (TRS: 711)

THOV CEEB TOOM: Yog hais tias koj hais lus Hmoob, muaj cov kev pab cuam txhais lus, pub dawb rau koj. Hu rau 1-888-361-1611 (TRS: 711)

ត្រូវចងចាំ៖ បើអ្នកនិយាយភាសាខ្មែរ ហើយត្រូវការសេវាកម្មជំនួយផ្នែកភាសាដោយឥតគិតថ្លៃ គឺមានផ្តល់ជូនលោកអ្នកៗសូមទូរស័ព្ទទៅកាន់លេខ 1-888-361-1611 (TRS: 711)

HUBACHIISA: Yoo afaan Kshtik kan dubbattan ta'e tajaajiloonni gargaarsaa isiniif jira 1-888-361-1611 (TRS: 711) tiin bilbilaa.

โปรดทราบ: หากคุณพูดภาษาไทย คุณสามารถใช้บริการช่วยเหลือด้านภาษาได้ฟรี โทร 1-888-361-1611 (TRS: 711)

FA'AUTAGIA: Afai e te tautala i le gagana Samoa, o loo avanoa fesoasoani tau gagana mo oe e le totogia. Vala'au i le 1-888-361-1611 (TRS: 711)

IPANGAG: Nu agsasaoka iti Ilocano, sidadaan ti tulong iti lengguahe para kenka nga awan bayadna. Umawag iti 1-888-361-1611 (TRS: 711)

UWAGA: Dla osób mówiących po polsku dostępna jest bezpłatna pomoc językowa. Zadzwoń: 1-888-361-1611 (obsługa TRS: 711)