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

Updates effective 09/01/2022

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) includes 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/ump-pdl.
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

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

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 (Venclexta) 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 investigative 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


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<th>Date</th>
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<td>Added 100mg tablet formulation to the policy</td>
<td>08/2022</td>
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<tr>
<td>Removed initial criteria and moved MCL indication to investigational or not medically necessary uses section</td>
<td>01/2022</td>
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<tr>
<td>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.</td>
<td>12/2019</td>
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<td>Previous Reviews</td>
<td>02/2018</td>
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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

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<th>Product Name</th>
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<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
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<tr>
<td>crizotinib (Xalkori)</td>
<td>200 mg capsules</td>
<td>ALK+ NSCLC, metastatic;</td>
<td>60 capsules/30 days</td>
</tr>
<tr>
<td></td>
<td>250 mg capsules</td>
<td>ROS1+ NSCLC, metastatic</td>
<td>60 capsules/30 days</td>
</tr>
<tr>
<td></td>
<td>200 mg capsules</td>
<td>ALK+ systemic ALCL</td>
<td>120 capsules/30 days</td>
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<tr>
<td></td>
<td>250 mg capsules</td>
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<td>120 capsules/30 days</td>
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<td>ceritinib (Zykadia)</td>
<td>150 mg capsules</td>
<td>ALK+ NSCLC, metastatic</td>
<td>84 capsules/28 days</td>
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<tr>
<td></td>
<td>150 mg tablets</td>
<td></td>
<td>84 tablets/28 days</td>
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<tr>
<td>alectinib (Alecensa)</td>
<td>150 mg capsules</td>
<td>ALK+ NSCLC, metastatic</td>
<td>240 capsules/30 days</td>
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<td>brigatinib (Alunbrig)</td>
<td>30 mg tablets</td>
<td>ALK+ NSCLC, metastatic</td>
<td>180 tablets/30 days</td>
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<td>90 mg tablets</td>
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<td></td>
<td>90 mg and 180 mg tablet titration pack</td>
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<td>30 tablets/30 days</td>
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<tr>
<td></td>
<td>180 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
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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)

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.

September 01, 2022
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 March 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) and brigatinib (Alunbrig) (both category 1). However, alectinib (Alecensa) remains the preferred agent for first-line treatment per the National Comprehensive Cancer Network (NCCN) NSCLC panel (V4.2021), for the treatment of ALK-positive NSCLC (based on clinical trial data from ALEX and J-ALEX trials). As of April 2021, 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.

III. 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.

Washington State Rx Services is administered by

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.

September 01, 2022
IV. 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).

V. 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).

VI. 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.

VII. 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.

VIII. 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.

IX. 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.

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 clinical outcomes (e.g., overall survival, quality of life) in patients with ALCL. Improvement in this surrogate endpoint has not been correlated with improved outcomes. Crizotinib (Xalkori) remains an investigational treatment in all patients with ALCL.

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

* 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

Policy Implementation/Update:

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<th>Action and Summary of Changes</th>
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<tr>
<td>Updated supporting evidence around alectinib being the preferred first-line therapy</td>
<td>11/2021</td>
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<tr>
<td>Added supporting evidence around stage IV metastatic disease and metastases.</td>
<td>10/2021</td>
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<td>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</td>
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<td>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 Zykdia tablets that are available in addition to the capsules.</td>
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<td>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. Zykdia 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.</td>
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| Past criteria reviews                                                                         | 12/2012, 09/2014, }
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Allergen Immunotherapy

UMP POLICY

Policy Type: PA/SP  Pharmacy Coverage Policy: UMP110

Description
The specific mechanism of action of allergen immunotherapy has not been established. It is believed that immunotherapy works by allowing the body to develop tolerance to specific allergens through manipulation of the humoral and cellular immune responses.

Specific immunotherapy (SIT) may act by inducing a switch from T-helper 2 cell response (Th2) to T-helper 1 cell (Th1) response, resulting in the production of IgG-blocking antibodies that compete with IgE antibodies for allergen binding.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>grass pollen-timothy, standard</td>
<td>2800 BAU sublingual</td>
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<td>30 tablets/30 days</td>
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<td>(Grastek)</td>
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<td>mite,d.farinae-d.pteronyssinus</td>
<td>12 SQ-HDM sublingual</td>
<td>Allergic rhinitis due to dust mite</td>
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<td>300 IR sublingual tablet</td>
<td></td>
<td></td>
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<tr>
<td>weed pollen-short ragweed</td>
<td>12 Amb a 1-U sublingual tablet</td>
<td>Allergic rhinitis due to ragweed</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>(Ragwitek)</td>
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</table>

Initial Evaluation

I. **Grastek, Odactra, Oralair, or Ragwitek** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an allergist or ear, nose, and throat (ENT) specialist; 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. **All** the following treatments have been ineffective, contraindicated, or not tolerated:
   1. Over-the-counter oral or intranasal corticosteroids (e.g. budesonide, fluticasone propionate, mometasone furoate); **AND**
   2. Over-the-counter oral or intranasal anti-histamine (e.g. diphenhydramine, loratadine, cetirizine, azelastine); **AND**
   3. Montelukast (Singulair); **AND**

C. A diagnosis of one of the following:
   1. **Dust mite-induced allergic rhinitis; AND**
      i. Member is 18 years of age or older; **AND**
      ii. Confirmed in-vitro testing for *Dermatophagoides farinae* or *D. pteronyssinus* house dust mites; **OR**
      iii. Skin testing to a licensed house dust mite allergen extract; **AND**
   2. **Grass pollen-induced allergic rhinitis due to one of the following:**
      i. Timothy grass or cross-reactive pollens; **AND**
         a. Member is five years of age or older; **AND**
         b. Confirmed by positive skin or in-vitro testing for pollen specific IgE antibodies for Timothy grass or cross-reactive pollens; **AND**
         c. Request is for Grastek or Oralair; **OR**
      ii. Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass; **AND**
         a. Member is five years of age or older; **AND**
         b. Confirmed by positive skin test or in-vitro testing for pollen specific IgE antibodies for Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass, or cross-reactive pollens; **AND**
         c. Request is for Oralair; **OR**
      iii. Short ragweed pollen; **AND**
         a. Member is 5 years of age or older; **AND**
         b. Confirmed by positive skin test, or in-vitro testing for pollen specific IgE antibodies for short ragweed pollen; **AND**
         c. Request is for Ragwitek

II. Grastek, Odactra, Oralair, or Ragwitek is considered **investigational** when used for all other conditions, including but not limited to:
   A. Allergic asthma
   B. Atopic dermatitis
   C. Food allergy
Renewal Evaluation

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

II. Continuance is not for a regimen initially established 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 experienced a decrease of allergic rhinitis during previous use

Supporting Evidence

I. Allergic rhinitis (AR) is an inflammatory, IgE-mediated disease characterized by nasal congestion, rhinorrhea (nasal drainage), sneezing, and/or nasal itching. AR may be classified by the temporal pattern of exposure to a triggering allergen, such as seasonal (e.g., pollens), perennial/year-round (e.g., dust mites), or episodic (environmental from exposures not normally encountered in the patient’s environment, e.g., visiting a home with pets); frequency of symptoms; and severity of symptoms. It is estimated that an IgE-mediated AR may affect 1 in 6 persons within the United States. The United States population is most commonly sensitized to grass pollen, dust mites, and ragweed pollen.

II. Allergen avoidance and pharmacotherapy should be considered first when treating allergic rhinitis. Symptom management with pharmacotherapy should be considered prior to initiating immunotherapy.

III. Currently there are three classes of drugs recommended as Grade A evidence per the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNSF) 2015 guidelines in treating AR: intranasal steroids, oral or intranasal antihistamines, and oral leukotriene receptor antagonist (i.e. Montelukast). The guidelines mention that short courses of oral corticosteroids are often done in severe AR cases; however, superiority to intranasal steroids has not been shown. All three of these classes are more cost effective and have shown clinical benefit to helping lessen symptoms and symptom severity, while improving patient quality of life overall in regard to lowering the impact of AR.

IV. Allergen-specific immunotherapy (SIT) involves controlled, repetitive dosing of allergen(s) in patients diagnosed with IgE-mediated AR by history and confirmation via specific allergy testing in order to increase immune tolerance to the offending allergen(s). The ultimate goal of SIT is to decrease AR symptoms. SIT is the only proven treatment for AR that has the potential to change the natural history of the disease. Sublingual immunotherapy (SLIT) was first approved in 2014 and usually has a typical duration of 3 to 5 years of efficacy.

V. Allergen immunotherapies may cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. It is recommended to monitor and administer the first dose in the presence of a health care provider and to prescribe an auto-injectable epinephrine device for home administration.

VI. Patient must have a positive skin test or in vitro testing for allergen specific IgE antibodies pertaining to the allergen immunotherapy being requested.

VII. Safety and efficacy of Grasteck, Ragwitek, and Oralair has not been established in patients younger than five years old.
VIII. Safety and efficacy of Odactra has not been established in patients younger than 18 years old.

Investigational or Not Medically Necessary Uses

I. There is limited data to show safety and efficacy for all other indications.
   A. Allergic asthma
   B. Atopic dermatitis
   C. Food allergy

References

### Policy Implementation/Update:

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<td>Updated Ragwitek approval through age 5. Updated supporting evidence section.</td>
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<td>Updated to policy format. Combined existing criteria into one policy, added age requirements to match FDA-indications.</td>
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<td>Edit to Allergen Immunotherapy Criteria; add Odactra information and related mapping; general edits to format and criteria to accommodate Odactra.</td>
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<td>Combine existing criteria to create Allergen Immunotherapy Criteria</td>
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<td>Effective and created date of Grastek, Oralair, and Ragwitek criteria</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP003

Split Fill Management*

Description
Alpelisib (Piqray) is an orally administered kinase inhibitor with predominant activity against PIK3.

Length of Authorization
- Initial: Three months, split fill
- Renewal: 12 months

Quantity limits

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<th>Product Name</th>
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<td>alpelisib (Piqray)</td>
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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. Diagnosis of **advanced or metastatic breast cancer** when the following are met:
      1. The breast cancer is HR-positive, HER2-negative; **AND**
      2. PIK3CA mutation has been tested and confirmed; **AND**
      3. The provider attests the member is endocrine resistant or refractory; **AND**
      4. The member has not previously progressed on a CDK4/6 inhibitor (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.); **AND**
      5. The medication will be used in combination with fulvestrant (Faslodex) only; **AND**
         i. 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 criteria above are not met and/or when used for:
   A. Breast cancer that is not PIK3CA mutated.

III. Alpelisib (Piqray) is considered **investigational** when used for all other conditions, including but not limited to:
   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

**Renewal Evaluation**

I. The medication is prescribed by, or in consultation with, an oncologist; **AND**
II. The member will be using 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**
III. The member has experienced positive response to treatment, defined by the stabilization of disease or a decrease in tumor size or tumor spread.

**Supporting Evidence**

I. **Alpelisib (Piqray)** was evaluated in one double-blind, Phase 3, placebo-controlled randomized trial. Both arms were in combination with fulvestrant. The trial evaluated 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.

II. 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 purpose was to focus 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% vs. 45.3% respectively.

III. Of the 169 patients that received alpelisib (Piqray), 9 (5.3%) had history of use of a CDK4/6 inhibitor (e.g., Ibrance, Kisqali, Verzenio). It is unknown whether these patients had progressed on therapy, or, discontinued due to intolerance; however, at this time the evidence for safety and efficacy in the CDK4/6 inhibitor treatment refractory or relapsed population is unknown. Too few patients were included in the trial with this characterization to extrapolate the entirety of the trial results to the patients that have progressed on CDK4/6 inhibitors and it is currently...
considered experimental and investigational. The population included in the trial is often treated with CDK4/6 inhibitors, so recommendations on optimal sequence of therapy shall be determined upon further clinical evaluation and real-world data. Although it is not uncommon for patients to become resistant to CDK4/6 inhibitors, the available efficacy information on alpelisib (Piqray) as subsequent therapy in this population is lacking. The outcomes described are not correlated with clinically meaningful outcomes such as overall survival or quality of life parameters. This shall be weighed with the very significant safety concerns associated with alpelisib (Piqray).

IV. Alpelisib (Piqray) was evaluated in an open-label, three-cohort, non-comparative phase 2 trial (BYLieve trial), in order to assess efficacy and safety of alpelisib (Piqray) in patients, who previously progressed on CDK 4/6 inhibitors. Cohorts A (N=127) and B (N= not known) included patients, who had prior treatment with CDK 4/6 inhibitor plus aromatase inhibitor, or CDK 4/6 inhibitor plus fulvestrant, respectively. Cohort A received treatment with alpelisib (Piqray) plus fulvestrant, while cohort B received alpelisib (Piqray) plus letrozole. As of 08/2020, efficacy data for cohort A was available. Primary endpoint of proportion of patients alive without disease progression at 6 months was 50.4% (N=61; 95% CI: 41.2,59.6). Secondary outcomes were overall response rate of 17.7% (95% CI: 11.1,25.3), and median progression-free survival of 7.3 months (59.5%, 95% CI: 5.6-8.3). Overall quality of the evidence is considered low given the lack of comparator and open-label trial design. Additionally, this is an ongoing clinical trial, wherein the final results for all cohorts are not available. This may lead to concerns about clinical applicability of the trial outcomes. Based on available results, the efficacy of alpelisib (Piqray) in CDK 4/6 inhibitor refractory population continues to remain uncertain.

V. There is a high risk of serious safety events with alpelisib (Piqray). Serious adverse events occurred in 34.9% vs. 16.7% for the placebo group. Adverse events of serious grade that occurred more often in the alpelisib (Piqray) arm vs. 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 concern. 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 within from this trial arm required a dose-interruption and 64% required a dose-reduction vs. 32% and 9% for the placebo group respectively. Permanent discontinuation of drug due to adverse events occurred in 25% of alpelisib (Piqray) subjects vs. 4.2% for placebo.

Investigational or Not Medically Necessary Uses

I. 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.

II. Aleplisib (Piqray) 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.

References

4. Rugo HS et al. Alpelisib + fulvestrant in patients with PIK3CA mutated hormone-receptor positive (HR+), human epidermal growth factor receptor-2-negative (HER2-) advanced breast cancer (ABC) previously treated with cyclin-dependent kinase 4/6 inhibitor (CDKi) + aromatase inhibitor (AI): BYLieve study results. Oral presentation at: American Society of Clinical Oncology (ASCO); May 29 - May 31, 2020; Chicago, IL. Presentation 1006.

Policy Implementation/Update:

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<tr>
<th>Action and Summary of Changes</th>
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<tr>
<td>Updated supporting evidence section to include data from BYLieve clinical trial</td>
<td>09/2020</td>
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<tr>
<td>Policy created</td>
<td>08/2019</td>
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</table>
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

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<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>amifampridine (Firdapse)</td>
<td>Lambert-Eaton myasthenic syndrome</td>
<td>10 mg tablets</td>
<td>240 tablets/30 days</td>
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<tr>
<td>amifampridine (Ruzurgi)*</td>
<td></td>
<td>10 mg tablets</td>
<td>240 tablets/30 days</td>
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</tbody>
</table>

*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-diaminopyrididine) 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)

References

1. Firdapse [prescribing information]. Coral Gables, FL: Catalyst Pharmaceuticals; February 2021.
4. FDA. Center for Drug Evaluation and Research. Application number: 209321Orig1s000 Summary Review.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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</thead>
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<tr>
<td>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.</td>
<td>04/2022</td>
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<td>Addition of Ruzurgi to policy</td>
<td>07/2019</td>
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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

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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**

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.
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 months 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.
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

1. FDA approves a new antibacterial drug to treat a serious lung disease using a novel pathway to spur innovation [FDA Press Release]. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622048.htm.

Policy Implementation/Update:

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<td>Date Effective</td>
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Action and Summary of Changes:  

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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)**
  1. **Anemias**
     1. Initial: Six months
     2. Renewal: 12 months
  2. **Cachexia associated with AIDS:**
     1. Initial: Three months
     2. Renewal: Three months

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

Quantity Limits

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

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

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.

September 01, 2022
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/m²; OR
      v. For females, BCM < 23% and BMI < 27 kg/m²; OR
      vi. BMI < 18 kg/m²; 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/m²; OR
         v. For females, BCM < 23% and BMI < 27 kg/m²; OR
         vi. BMI < 18 kg/m²; 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 trials, 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.

References

1. Oxandrin prescribing information. Savient Pharma, Inc. June 2005
3. Olson, TS. Management and prognosis of Fanconi anemia. In: UpToDate, Mahoney, DH (Ed), UpToDate, Waltham, MA, 2019
4. Bruera, E. Assessment and management of anorexia and cachexia in palliative care. In: UpToDate, Smith, TJ (Ed), UpToDate, Waltham, MA, 2019
### Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<td>New policy created</td>
<td>12/2019</td>
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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: 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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<td>Apomorphine</td>
<td>10 mg/mL</td>
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<td>(Apokyn)</td>
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<td></td>
<td>10 mg/ml</td>
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<td>20 mg/ml</td>
<td>Parkinson’s Disease</td>
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<td></td>
<td>25 mg/ml</td>
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<td></td>
<td>30 mg/ml</td>
<td>Parkinson’s Disease</td>
<td>150 films/30 days</td>
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<td>film</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10/15/20/25/30mg titration kit</td>
<td>1 kit/30 days</td>
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</tbody>
</table>

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-HT₃ 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-HT₃ 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
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<tr>
<td>• Added apomorphine sublingual films (Kynmobi) to policy</td>
<td>03/2021</td>
</tr>
<tr>
<td>• Added requirement of member is experiencing predictable acute, intermittent hypomobility “off” episodes</td>
<td></td>
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<tr>
<td>• Updated renewal criteria to require prior approval through this OR prior health plan (not established via samples)</td>
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<tr>
<td>• Removed renal criteria requirement confirming lack of toxicity to therapy</td>
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<tr>
<td>• Updated apomorphine subcutaneous injection (Apokyn) QLL to align with FDA label and package size of 3mL/cartridge</td>
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Criteria transitioned to policy 10/2019

Previous reviews
11/2014
12/2008
09/2008

Criteria created 09/2005

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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

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

*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 

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(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/mm³ 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 (ASCENBL) 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 cytogenetic 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 (Synergy), 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, uncontrolled 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


Policy Implementation/Update:

<table>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tbody>
<tr>
<td>Policy created</td>
<td>02/2022</td>
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</table>
Policy Type: PA  
Pharmacy Coverage Policy: UMP006

**Policy Type: PA**

**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**

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

*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. Pseudohypophosphatasia
   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

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

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.
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.

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

<table>
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<tr>
<th>Body Weight (kg)</th>
<th>Dose to Inject</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>3 mg</td>
<td>0.08 mL</td>
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<td>24</td>
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<tr>
<td>4</td>
<td>4 mg</td>
<td>0.1 mL</td>
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<td>5</td>
<td>5 mg</td>
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<td>18 mg/0.45 mL</td>
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<tr>
<td>6</td>
<td>6 mg</td>
<td>0.15 mL</td>
<td>18 mg/0.45 mL</td>
<td>24</td>
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<tr>
<td>7</td>
<td>7 mg</td>
<td>0.18 mL</td>
<td>18 mg/0.45 mL</td>
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<tr>
<td>8</td>
<td>8 mg</td>
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<td>18 mg/0.45 mL</td>
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<tr>
<td>9</td>
<td>9 mg</td>
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<td>15</td>
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<td>20</td>
<td>20 mg</td>
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<td>28 mg/0.7 mL</td>
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<tr>
<td>25</td>
<td>25 mg</td>
<td>1.63 mL</td>
<td>28 mg/0.7 mL</td>
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<td>30</td>
<td>30 mg</td>
<td>0.75 mL</td>
<td>40 mg/mL</td>
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<td>35</td>
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<td>0.88 mL</td>
<td>40 mg/mL</td>
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<td>40</td>
<td>40 mg</td>
<td>1 mL</td>
<td>40 mg/mL</td>
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<tr>
<td>50</td>
<td>50 mg</td>
<td>0.5 mL</td>
<td>80 mg/0.8 mL</td>
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<tr>
<td>60</td>
<td>60 mg</td>
<td>1.6 mL</td>
<td>80 mg/0.8 mL</td>
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<tr>
<td>70</td>
<td>70 mg</td>
<td>0.7 mL</td>
<td>80 mg/0.8 mL</td>
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<tr>
<td>80</td>
<td>80 mg</td>
<td>0.8 mL</td>
<td>80 mg/0.8 mL</td>
<td>24</td>
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### References


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September 01, 2022
### Policy Implementation/Update:

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<th>Action and Summary of Changes</th>
<th>Date</th>
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<td>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.</td>
<td>12/2020</td>
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<td>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.</td>
<td>09/2019</td>
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<td>Previous reviews</td>
<td>8/2017</td>
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<td>Policy created</td>
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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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>avacopan (Tavneos)</td>
<td>10 mg capsules</td>
<td>Antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis</td>
<td>180 capsules/30 days</td>
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</table>

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

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.
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 (60 mg, 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.

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
<th>Avacopan (n=166)</th>
<th>Prednisone (n=164)</th>
<th>Difference (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission at wk 26, no %</td>
<td>120 (72.3)</td>
<td>115 (70.1)</td>
<td>3.4 (-6.0-12.8)</td>
<td>Noninferiority: p&lt;0.001 Superiority: p=0.24</td>
</tr>
<tr>
<td>Sustained remission at wk 52, no %</td>
<td>109 (65.7)</td>
<td>90 (54.9)</td>
<td>12.5 (2.6-22.3)</td>
<td>Noninferiority: p&lt;0.001 Superiority: p=0.007</td>
</tr>
</tbody>
</table>

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

References


Policy Implementation/Update:

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<th>Date</th>
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<td>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.</td>
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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 (PDGFRα) and v-kit Hardy Zukerman 4 feline sarcoma viral oncogene homolog (KIT) mutants.

Length of Authorization
•  N/A

Quantity Limits

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<td></td>
<td>100 mg tablets</td>
<td>Advanced Systemic Mastocytosis, including aggressive systemic mastocytosis, systemic mastocytosis with an associated hematological neoplasm and mast cell leukemia</td>
<td></td>
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<tr>
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Initial Evaluation
I.  **Avapritinib (Ayvakit)** is considered investigational when used for all conditions, including but not limited to gastrointestinal stromal tumor (GIST) and advanced systemic mastocytosis (AdvSM) [e.g., aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematological neoplasm (SM-AHN), mast cell leukemia (MCL)].

Renewal Evaluation
I.  N/A

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.

September 01, 2022
Supporting Evidence

I. Gastrointestinal Stromal Tumors (GIST)

- 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)]. NCCN recommendations as of January 2021 were to treat patients with a PDGFRA mutation with avapritinib (Ayvakit) which is considered category 2A.

- 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.

- 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.

- 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.

- 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.

- 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.
• 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.

• Avapritinib (Ayvakit) has not been compared against other treatments [e.g., imatinib (Gleevec), sunitinib (Sutent)] FDA-approved for unresectable or metastatic GIST. 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.

• Avapritinib (Ayvakit) showed a 49% dose reduction rate, a 57% dose interruption rate, and a 22% permanent discontinuation rate due to intolerable adverse events.

• There is one ongoing randomized, open-label, phase 3 clinical trial studying avapritinib (Ayvakit) against regorafenib (Stivarga) in patients with locally advanced unresectable or metastatic GIST (VOYAGER). The primary endpoint is progression-free survival (PFS), notable secondary endpoints of objective response rate (ORR), and overall survival (OS). Preliminary results indicate the primary endpoint of statistically significant improvement in PFS was not met, and therefore patients are not being followed for OS. As of October 2021, the mature clinical trial data is not available.

II. Advanced Systemic Mastocytosis (AdvSM)

• Systemic mastocytosis (SM) is a rare, clonal neoplastic proliferation of mast cells driven by the KIT/WD816V 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 aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated hematologic neoplasm (SM-AHN), and mast cell leukemia (MCL).

• According to NCCN guidelines, as of March 2021, treatment options for all forms of AdvSM include midostaurin, cladribine, and enrollment in clinical trial. Peginterferon alfa-2a ± prednisone may also be considered as another treatment option for patients diagnosed with ASM or SM-AHN. All therapies carry a category 2A recommendation.

• Avapritinib (Ayvakit) was FDA-approved based on the data from one phase 1 (EXPLORER) and one ongoing 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.

- 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.

- 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.

- 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). No new safety signals were observed during the clinical trials for AdvSM.

- 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.

**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
   B. Advanced Systemic mastocytosis (e.g., AdvSM, ASM, SM-ANH, MCL)
   C. Non-advanced systemic mastocytosis (e.g., ISM, SSM)
   D. Soft Tissue Sarcoma
* 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


Policy Implementation/Update:

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<th>Date</th>
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</thead>
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<tr>
<td>Addition of new indication advanced systemic mastocytosis (AdvSM) and updated trial information for gastrointestinal stromal tumors (GIST)</td>
<td>10/2021</td>
</tr>
<tr>
<td>Policy created</td>
<td>05/2020</td>
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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: UMP169

Description

Avatrombopag (Doptelet®), eltrombopag (Promacta®), lusutrombopag (Mulpleta®), fostamatinib (Tavalisse™) 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 (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
  - 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 (Promacta) and fostamatinib (Tavalisse)
    - Chronic Immune Thrombocytopenia (ITP), refractory severe aplastic anemia, chronic thrombocytopenia due to chronic hepatitis C: six months
### Quantity Limits

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<th>Product Name</th>
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<tr>
<td>avatrombopag (Doptelet)</td>
<td>20 mg tablet</td>
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<td>Chronic Immune Thrombocytopenia (ITP)</td>
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<td>eltrombopag (Promacta)</td>
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<td>Severe aplastic anemia</td>
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<td>[2 to 5 Years of age] 2.5mg/kg/day [6 to 11 Years of age] 2.5mg/kg/day [12 years and older] 2.5mg/kg/day 90 packets/30 days (3 kits/30 days)</td>
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<td>12.5 mg tablet</td>
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lusutrombopag (Mulpleta) | 3 mg tablet | Thrombocytopenia associated with chronic liver disease, prior to planned procedure | 7 tablets/365 days
---|---|---|---
fasmatatinib (Tavalisse) | 100 mg tablets | Chronic Immune Thrombocytopenia | 60 tablets/30 days
| 150 mg tablets |

**Initial Evaluation**

I. Avatrombopag (Doptelet), eltrombopag (Promacta), 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 10⁹/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 [e.g. pegylated interferon (Pegasys®) and ribavirin]; AND
      
      b. Request is for *eltrombopag (Promacta)* tablet formulation; OR
      
      c. Request is for *eltrombopag (Promacta)* packets; AND
         
         1. Member is unable to swallow tablets; 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 10⁹/L with symptoms of bleeding; AND

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

      a. Request is for *eltrombopag (Promacta)* tablet formulation; OR
      
      b. Request is for *eltrombopag (Promacta)* packets; AND
         
         1. Member is unable to swallow tablets; OR

   iv. Member is 18 years of age or older; AND

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

3. **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); AND
   a. Member is two years of age or older; AND
   b. Eltrombopag (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 antithymocyte globulin (ATG) and cyclosporine A (CSA) has been ineffective, contraindicated or not tolerated; AND
iv. Request is for eltrombopag (Promacta) tablet formulation; OR
v. Request is for eltrombopag (Promacta) packets; AND
   a. Member is unable to swallow tablets

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

V. 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; 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 (Promacta), 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 (Promacta), 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 (Promacta), 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 $150 \times 10^9$/L to $450 \times 10^9$/L).

V. Avatrombopag (Doptelet) and lusutrombopag (Mupleta) 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 $150 \times 10^9$/L to $450 \times 10^9$/L).

VI. Eltrombopag (Promacta) 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 outside of this indication (normal platelet count in adults ranges from $150 \times 10^9$/L to $450 \times 10^9$/L).

VII. There is no safety and efficacy data to show superiority of one formulation over the other.

VIII. Avatrombopag (Doptelet), eltrombopag (Promacta), 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. Patients with platelet counts less than $30 \times 10^9$/L were included in clinical trials for avatrombopag (Doptelet), eltrombopag (Promacta), and fostamatinib (Tavalisse).

X. The efficacy and safety of eltrombopag (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, $50 \times 10^9$/L for at least six out of eight weeks, generally seen between weeks five and 12. Pediatric patients (75%) treated with eltrombopag (Promacta), compared with placebo (21%), saw an increased value with at least one platelet count greater than, or equal to, $50 \times 10^9$/L during the first 12 weeks of randomized treatment in absence of rescue therapy. Platelet response to eltrombopag (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]).

XI. 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.

XII. Eltrombopag (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.

XIII. 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.

XIV. 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.

XV. Ninety-two patients were enrolled in a prospective phase 1-2 study of immunosuppressive therapy plus eltrombopag. The three consecutively enrolled cohorts differed regarding the timing of initiation and the duration of the eltrombopag regimen (cohort 1 received eltrombopag 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 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.

XVI. Eltrombopag (Promacta) 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.

XVII. Eltrombopag (Promacta) 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 × 10^9/L to 450 × 10^9/L).

XVIII. Treatment with avatrombopag (Doptelet), eltrombopag (Promacta), 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).

XIX. 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 × 10^9/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 × 10^9/μL as at least a 100% increase in ANC, or an ANC increase >0.5 × 10^9/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 (Promacta)
   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) 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
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.

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- Serous 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.

  - Part 3 is an extension ongoing study.

  - 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 (Promacta) 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.
      o 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.
      o 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).

References

15. Dan Xu, Nanfang Hospital of Southern Medical University. Eltrombopag Used in Thrombocytopenia after Consolidation Therapy in AML. ClinicalTrials.gov Identifier: NCT03701217
19. Zhang Lei, Institute of Hematology & Blood Diseases Hospital. Evaluate the Efficacy and Safety of Eltrombopag for Thrombocytopenia With Chronic HBV Infection. ClinicalTrials.gov Identifier: NCT03664518
24. AstraZeneca. Study to Learn if 200mg Test Drug (Fostamatinib) Helps People With Large B-Cell Lymphoma, a Type of Blood Cancer. ClinicalTrials.gov Identifier: NCT01499303
25. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Clinical Trial of Combined Fostamatinib and Paclitaxel in Ovarian Cancer. ClinicalTrials.gov Identifier: NCT03246074
27. AstraZeneca. A Long Term Study to Assess the Safety of Fostamatinib in Patients in Asia With Rheumatoid Arthritis (OSKIRA-Asia-1X). ClinicalTrials.gov Identifier: NCT01640054
29. Imperial College London. Fostamatinib in the Treatment of Chronic Active Antibody Mediated Rejection (FOSTAMR). ClinicalTrials.gov Identifier: NCT03991780
30. Stefanie Sarantopoulos, MD, PhD. Evaluation of Fostamatinib in Patients With cGVHD After Allogeneic Stem Cell Transplant. ClinicalTrials.gov Identifier: NCT02611063

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Added new strength of 25mg eltrombopag (Promacta) packet for oral suspension</td>
<td>05/2020</td>
</tr>
<tr>
<td>• Added investigational indications for avatrombopag (Doptelet), eltrombopag (Promacta),</td>
<td></td>
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<tr>
<td>lusutrombopag (Mupleta)</td>
<td></td>
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<tr>
<td>• 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.</td>
<td>02/2020</td>
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<tr>
<td>• 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]</td>
<td>02/2020</td>
</tr>
<tr>
<td>• Added member is 18 years of age or older if request is for avatrombopag (Doptelet), fostamatinib (Tavalisse) [and fostamatinib (Tavalisse) [for chronic ITP]</td>
<td></td>
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<tr>
<td>• Added criteria if request is for eltrombopag (Promacta) packets, member has demonstrated inability to swallow tablets</td>
<td></td>
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<tr>
<td>• Changed QL for eltrombopag (Promacta) packets</td>
<td></td>
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<tr>
<td>• Changed QL for avatrombopag (Doptelet) for chronic immune thrombocytopenia (ITP)</td>
<td></td>
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<tr>
<td>• Changed initial and renewal length of authorization for all agents</td>
<td></td>
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</table>
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.

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tbody>
<tr>
<td>Previous reviews fostamatinib (Tavalisse)</td>
<td>06/2018, 11/2019</td>
</tr>
<tr>
<td>Conversion to policy format fostamatinib (Tavalisse)</td>
<td>11/2019</td>
</tr>
<tr>
<td>Avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) combined as policy: TPO-Receptor Agonists</td>
<td>10/2019</td>
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<td>Previous reviews avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)</td>
<td>10/2019</td>
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<tr>
<td>Policy created avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)</td>
<td>10/2019</td>
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<tr>
<td>Policy created fostamatinib (Tavalisse)</td>
<td>06/2018</td>
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</table>

• Combined as one policy: avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) with fostamatinib (Tavalisse)
axitinib (Inlyta®)
UMP POLICY

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

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>axitinib (Inlyta)</td>
<td>1 mg tablets</td>
<td>Advance renal cell carcinoma</td>
<td>180 tablets/30 days</td>
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<tr>
<td></td>
<td>5 mg tablets</td>
<td></td>
<td>60 tablets/30 days</td>
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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:

Washington State Rx Services is administered by moda health

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.
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.

References


Policy Implementation/Update:

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<th>Date Created</th>
<th>July 2012</th>
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<tr>
<td>Date Effective</td>
<td>April 2016</td>
</tr>
<tr>
<td>Last Updated</td>
<td>June 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>03/2016, 06/2019</td>
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Action and Summary of Changes

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.

<table>
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<th>Date</th>
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<tr>
<td>06/2019</td>
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</table>
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP2018

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

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>azacitidine (Onureg)</td>
<td>200 mg tablet</td>
<td>Acute Myeloid Leukemia (AML), maintenance treatment after first complete remission</td>
<td>14 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>300 mg tablet</td>
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</table>

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 complete intensive consolidation therapy; **AND**
      4. Provider attests that the member is ineligible for allogenic hematopoietic stem cell transplant (HSCT); **AND**
   E. Treatment with IV 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 on 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, chromosomal (i.e. 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
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.

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 (Category 2B recommendation). 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 AE’s, and 16% dose reduction rates.

IX. Azacitidine (Onureg) 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 use of hypomethylating agents in the maintenance treatment of AML are rooted in the trials for the IV 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 azacitidine (Onureg) over IV azacitidine (Vidaza) and/or IV decitabine (Dacogen). Weighing the safety, efficacy, cost, and clinical experience, IV 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


Policy Implementation/Update:

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<th>Date</th>
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<tr>
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<td>02/2021</td>
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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.
aztreonam (CAYSTON™)
UMP POLICY

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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>aztreonam (Cayston)</td>
<td>75 mg/vial inhalation powder</td>
<td>Cystic Fibrosis (CF)</td>
<td>6,300 mg (84 vials)/28 days*</td>
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* 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 FEV₁ 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 FEV₁, 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 FEV₁ 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 cepacia.

References


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<td>06/2020</td>
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<td>Criteria update: The FEV₁ requirements were added to initial criteria as that was part of the inclusion criteria. Additionally, renewal criteria and supporting evidence sections were added.</td>
<td>10/2019</td>
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<td>Criteria update: quantity limit has been updated to reflect the clinical use of Cayston.</td>
<td>2/2019</td>
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<td>07/2011</td>
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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

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<tr>
<td>belimumab (Benlysta)</td>
<td>200 mg/mL syringe</td>
<td>Systemic Lupus Erythematosus (SLE); Lupus Nephritis (LN)</td>
<td>4 syringes/28 days</td>
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Initial Evaluation
I. Belimumab (Benlysta) 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 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; 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 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 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. 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.

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

V. 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-creatinine 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.

VI. 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.

VII. 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.

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September 01, 2022
• 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


Policy Implementation/Update:

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<th>Date</th>
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<td>Added voclosporin (Lupkynis) in examples of biologics that cannot be used in combination with Benlysta</td>
<td>08/2021</td>
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<td>Addition of new indication of lupus nephritis and further specified specialist to include nephrologist. Removal of criteria excluding concomitant use of cyclophosphamide</td>
<td>02/2021</td>
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<td>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.</td>
<td>11/2019</td>
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<td>11/2017</td>
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<tr>
<td>Criteria created</td>
<td>09/2017</td>
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belumosudil (Rezurock™)
COMMERCIAL POLICY

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

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<th>Dosage Form</th>
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<tbody>
<tr>
<td>belumosudil (Rezurock)</td>
<td>200 mg tablets</td>
<td>Chronic graft-versus-host disease after failure of at least two prior lines of therapy</td>
<td>30 tablets/30 days*</td>
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*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 an 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], ibrutinib [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 not medically necessary when criteria above are not met and/or when used:
   A. In combination with proton pump inhibitors
   B. At doses greater than 200 mg daily

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September 01, 2022
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

Policy Implementation/Update:

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<td>11/2021</td>
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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

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

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, 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


Policy Implementation/Update:

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<td>11/2021</td>
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**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**

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<th>Quantity Limit</th>
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<tbody>
<tr>
<td>bempedoic</td>
<td>180 mg tablets</td>
<td>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</td>
<td>30 tablets/30 days</td>
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<tr>
<td>acid (Nexletol)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bempedoic</td>
<td>180 mg/10 mg tablets</td>
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<td></td>
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<tr>
<td>acid/ezetimibe (Nexlizet)</td>
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</table>

**Initial Evaluation**

1. 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 failure 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; **OR**

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).

<table>
<thead>
<tr>
<th>Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria</td>
</tr>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
</tbody>
</table>

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 | 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

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>• First-degree relative with known premature (men: &lt;55 years; women: &lt;60 years) coronary or vascular disease, or</td>
<td>1</td>
</tr>
<tr>
<td>• First-degree relative with known LDL-C above the 95th percentile</td>
<td></td>
</tr>
<tr>
<td>• First-degree relative with tendinous xanthomata and/or arcus cornealis, or</td>
<td>2</td>
</tr>
<tr>
<td>• Children &lt;18 years of age with LDL-C above the 95th percentile</td>
<td></td>
</tr>
<tr>
<td>Clinical History</td>
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<tr>
<td>• Patient with premature (men: &lt;55 years; women: &lt;60 years) coronary artery disease</td>
<td>2</td>
</tr>
<tr>
<td>• Patient with premature (men: &lt;55 years; women: &lt;60 years) cerebral or peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Physical examination</td>
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<tr>
<td>• Tendinous xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>• Arcus cornealis before age 45 years</td>
<td>4</td>
</tr>
<tr>
<td>LDL-C levels</td>
<td></td>
</tr>
<tr>
<td>• LDL-C ≥8.5 mmol/L (325 mg/dL)</td>
<td>8</td>
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<tr>
<td>• LDL-C 6.5-8.4 mmol/L (251-325 mg/dL)</td>
<td>5</td>
</tr>
<tr>
<td>• LDL-C 5.0-6.4 mmol/L (191-250 mg/dL)</td>
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<tr>
<td>• LDL-C 4.0-4.9 mmol/L (155-190 mg/dL)</td>
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<tr>
<td>DNA analysis</td>
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<tr>
<td>• Functional mutation in the LDLR, apoB, or PCSK9 gene</td>
<td>8</td>
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</table>

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


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Washington State Rx Services is administered by moda HEALTH

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: 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

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<td>benralizumab (Fasenra)</td>
<td>30 mg/mL autoinjector</td>
<td>Asthma (severe)</td>
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<td>1 autoinjector/56 days</td>
</tr>
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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**

Washington State Rx Services is administered by **moda HEALTH**

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.

September 01, 2022
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 FEV₁ 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>03/2021</td>
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<tr>
<td>Policy created</td>
<td>02/2020</td>
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</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>betaine anhydrous (generic Cystadane)</td>
<td>Homocystinuria</td>
<td>1 g/1.7 mL powder</td>
<td>540 grams/30 days</td>
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<tr>
<td>betaine anhydrous (Cystadane)</td>
<td></td>
<td>1 g/1.7 mL powder</td>
<td>540 grams/30 days</td>
</tr>
</tbody>
</table>

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-methylene-tetrahydrofolate 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

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.
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


Related Policies

Currently there are no related policies.

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added requirement to have tried and failed generic betaine anhydrous prior to use of branded Cystadane</td>
<td>04/2022</td>
</tr>
<tr>
<td>Policy created</td>
<td>11/2019</td>
</tr>
</tbody>
</table>
betrixaban (Bevyxxa®)

UMP POLICY

Policy Type: PA

Pharmacy Coverage Policy: UMP114

Description
Betrixaban (Bevyxxa) is an oral factor XA (FXa) inhibitor that inhibits free FXa and prothrombinase activity thereby decreasing thrombin generation without any effect on platelet aggregation.

Length of Authorization
- Initial: Duration of request or up to 42 days (whichever is less)
- Renewal: not eligible

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>betrixaban</td>
<td>40 mg capsules</td>
<td>Prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE</td>
<td>44 capsules/365 days</td>
</tr>
<tr>
<td></td>
<td>80 mg capsules</td>
<td></td>
<td>44 capsules/365 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Betrixaban (Bevyxxa) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; AND
   B. Member has not already taken a 42-day course of betrixaban (Bevyxxa) due to hospitalization for an acute medical illness; AND
   C. Member has been recently hospitalized for an acute medical illness; AND
   D. Member requires venous thromboembolism (VTE) prophylaxis due to moderate or severe restricted mobility, and other risk factors for VTE [e.g. heart failure, stroke, infection, pulmonary disease, age ≥ 75 years, history of VTE, or active cancer]; AND
   E. Member does not have active bleeding or is at risk for bleeding; AND
   F. Dosage does not exceed 80 mg per day; AND
   G. Betrixaban (Bevyxxa) has been initiated during member’s hospitalization and will be continuing therapy upon discharge; 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.
H. Provider states in documentation that member has medical necessity for using betrixaban (Bevyxxa) over enoxaparin or fondaparinux

Renewal Evaluation

I. Duration of treatment beyond 42 days is not eligible for renewal; AND
II. If continuing therapy of current treatment course or requesting a new course, please see initial criteria

Supporting Evidence

I. Betrixaban (Bevyxxa) is FDA-approved only for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.

II. There is currently no evidence to demonstrate the use of betrixaban (Bevyxxa) beyond 42 days. Total duration of use listed by the provider should be evaluated to ensure this limit is not exceeded. However, if a member is re-hospitalized, clinician should review as a new course of therapy.

III. The recommended duration of treatment is 35 to 42 days.

IV. Though extended duration (42 days) of betrixaban (Bevyxxa) is associated with significantly less VTEs compared to standard duration (14 days) enoxaparin, it has higher non-major bleeding risk in comparison to enoxaparin for VTE prophylaxis. Therefore, if betrixaban (Bevyxxa) was not initiated in the hospital, it may be more beneficial to utilize enoxaparin over betrixaban (Bevyxxa) unless patient has a very low bleeding potential.

V. Patients who are actively bleeding or are at risk for bleeding should not start betrixaban (Bevyxxa); there is currently no reversal (antidote) for betrixaban (Bevyxxa).

Investigational or Not Medically Necessary Uses

I. All condition(s) listed as investigational use
   A. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)
   B. Prevent the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

References

### Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>September 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>November 2017</td>
</tr>
<tr>
<td>Last Updated</td>
<td>November 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>11/2019</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Action and Summary of Changes</strong></th>
<th><strong>Date</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria updated to new policy format. Specific changes include: member is 18 years of age or older was added.</td>
<td>11/2019</td>
</tr>
<tr>
<td>Criteria created</td>
<td>09/2017</td>
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</table>
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: 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

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

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 fungoides, 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 seen 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. Responses 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**


**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Updated to include generic bexarotene gel (generic Targretin); added trial and failure of</td>
<td>06/2022</td>
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<td>generic bexarotene gel (generic Targretin) prior to use of the branded product</td>
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<td>Prior authorization criteria transitioned to policy format, age edit added, updated</td>
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<td>specialist prescriber requirement to new format, removal of liver function test monitoring</td>
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<tr>
<td>requirements. Addition of topical bexarotene (Targretin) to the policy. Initial approval</td>
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<tr>
<td>criteria increased from six to 12 months.</td>
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Previous Reviews:

08/2008; 10/2008; 07/2012; 09/2012; 12/2012; 11/2019

Washington State Rx Services is administered by Moda Health

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.

September 01, 2022
**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**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>bosutinib (Bosulif)</td>
<td>100 mg tablets</td>
<td>CML, newly diagnosed chronic phase</td>
<td>90 tablets/30 days</td>
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<tr>
<td></td>
<td>400 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>500 mg tablets</td>
<td>CML, resistant or intolerant to prior therapy</td>
<td>30 tablets/30 days</td>
</tr>
</tbody>
</table>

**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

*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.*

September 01, 2022
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

<table>
<thead>
<tr>
<th>THERAPY</th>
<th>CONTRAINDIcusTED MUTATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosutinib</td>
<td>T315I, V299L, G250E, or F317L</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>T315I/A, F317L/V/I/C or V299L</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>T315I, Y253H, E255K/V, or F359V/C/I or G250E</td>
</tr>
</tbody>
</table>

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


Policy Implementation/Update:

<table>
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<tr>
<th>Date Created</th>
<th>February 2013</th>
</tr>
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<tr>
<td>Date Effective</td>
<td>February 2013</td>
</tr>
<tr>
<td>Last Updated</td>
<td>December 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>01/2018, 12/2018</td>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
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<tr>
<td>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.</td>
<td>12/2019</td>
</tr>
</tbody>
</table>

Washington State Rx Services is administered by

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: UMP258

Description
Budesonide (Tarpeyo™) is an orally administered corticosteroid indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression.

Length of Authorization
- N/A

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>budesonide (Tarpeyo)</td>
<td>Primary Immunoglobulin A Nephropathy (IgAN)</td>
<td>4 mg capsules</td>
<td>120 capsules/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation
I. **Budesonide (Tarpeyo)** is considered not medically necessary when used for all conditions, including but not limited to primary immunoglobulin A nephropathy (IgAN).

II. Budesonide (Tarpeyo) is considered investigative 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

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 at risk of rapid disease progression (UPCR ≥ 1.5 g/g). 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. FDA approval of budesonide (Tarpeyo) was granted under accelerated approval. Confirmation studies to assess whether budesonide (Tarpeyo)
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. Clinical studies NEFIGAN and NefigArdd 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. 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.

IV. Reduced glomerular filtration rates can be a marker of kidney disease; specifically, those under 35mL/min/1.73 m² 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.

V. 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.

VI. 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.

VII. 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.

VIII. 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. No corticosteroid, including budesonide (Tarpeyo), has been found to slow kidney function decline (reduce eGFR decline or progression to ESRD) in IgAN patients. 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.

IX. Endpoints from 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. 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. Primary immunoglobulin A nephropathy (IgAN)
   A. Budesonide (Tarpeyo) for the treatment of primary IgAN adjunct to supportive therapy with ACE inhibitors and ARBs has been evaluated in clinical trials. Results showed reduction in proteinuria; however, available data do not support clinically meaningful long term renal outcomes (reduction of eGFR decline or progression to ESRD). Other glucocorticoid therapies (prednisone, methylprednisolone, and IV methylprednisolone) have demonstrated similar reductions in proteinuria and have comparable safety profiles to budesonide (Tarpeyo). At this time it is unproven if budesonide (Tarpeyo) is more likely to produce similar therapeutic results or is superior to other glucocorticoid therapies that could be utilized. Additionally, budesonide (Tarpeyo) is significantly more costly than other glucocorticoid therapies that could be utilized. Given these factors, budesonide (Tarpeyo) is not medically necessary.

II. 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.

References


Related Policies

Currently there are no related policies.

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created.</td>
<td>04/2022</td>
</tr>
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</table>
**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**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
</table>
| 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)   | **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 |
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 mg/vial (5000 mcg/vial)</td>
<td>Control and prevention of bleeding episodes – Factor VII deficiency: Up to 30 mcg/kg every four to six hours until hemostasis is achieved</td>
<td>Control and prevention of bleeding episodes – Factor VII deficiency: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td></td>
<td>8 mg/vial (8000 mcg/vial)</td>
<td>Control and prevention of bleeding episodes – Glanzmann’s Thrombasthenia: Up to 90 mcg/kg every two to six hours until hemostasis is achieved</td>
<td>Control and prevention of bleeding episodes – Glanzmann’s Thrombasthenia: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Routine prophylaxis – hemophilia A or B with inhibitors: 90 mcg/kg once daily</td>
<td>Routine prophylaxis – Hemophilia A or B with inhibitors: 2,520 mcg/kg per 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td>Perioperative management – hemophilia A or B with inhibitors: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td>Perioperative management – acquired hemophilia: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td>Perioperative management – factor VII deficiency: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perioperative management – Glanzmann’s Thrombasthenia: Up to 90 mcg/kg immediately before surgery and repeat every two hours for the duration of the procedure,</td>
<td>Perioperative management – Glanzmann’s Thrombasthenia: Up to the number of doses requested for 28 days</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sevenfact</strong>, coagulation factor VIIa (recombinant) [eptacog beta]</td>
<td>1 mg/vial (1000 mcg/vial)</td>
<td>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</td>
<td>Treatment and control of bleeding – Hemophilia A or B with inhibitors: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td></td>
<td>5 mg/vial (5000 mcg/vial)</td>
<td></td>
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</tbody>
</table>

**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 IX [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 IX [i.e. high anti-IX titer (≥ 5 Bethesda units)]; **AND**
   
   D. Use is planned for on-demand treatment and control of bleeding episodes only

**Acquired Hemophilia**

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

**Congenital Factor VII Deficiency**

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

**Glanzmann’s Thrombasthenia**
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. 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.

XI. 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.

XII. 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.

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.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Addition of Sevenfact</td>
<td>08/2020</td>
</tr>
<tr>
<td>New policy created for bypassing agents</td>
<td>08/2019</td>
</tr>
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</table>

September 01, 2022
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

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit*</th>
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<tbody>
<tr>
<td>cabozantinib (Cabometyx®)</td>
<td>20 mg tablet</td>
<td>Advanced and metastatic renal cell carcinoma (aRCC)</td>
<td>30 tablets/30 days</td>
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<td></td>
<td>40 mg tablet</td>
<td>Progressive or metastatic Hepatocellular (Liver) carcinoma (HCC), in patients previously treated with sorafenib</td>
<td>30 tablets/30 days</td>
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<td></td>
<td>60 mg tablet</td>
<td>Advanced or metastatic differentiated thyroid carcinoma (DTC) in patients previously treated with vascular endothelial growth factor (VEGF) targeted therapy</td>
<td>30 tablets/30 days</td>
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<tr>
<td>cabozantinib (Cometriq®)</td>
<td>60 mg per day blister cards</td>
<td>Progressive or metastatic medullary thyroid carcinoma</td>
<td>84 capsules/28 days</td>
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<td>140 mg per day blister cards</td>
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*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 one 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 **investigational** when used for all other conditions, including but **not limited to:**
   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.
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.

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 m² and 40 mg once daily in pediatric patients 12 years of age and older, with BSA less than 1.2m².

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 0.64; 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 0.74; 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 naive 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 0.38-0.94; 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

Washington State Rx Services is administered by Moda Health

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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


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.

<table>
<thead>
<tr>
<th>Policy</th>
<th>Disease State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)</td>
<td>Thyroid Carcinoma</td>
</tr>
<tr>
<td></td>
<td>Hepatocellular Carcinoma (HCC)</td>
</tr>
<tr>
<td></td>
<td>Renal Cell Carcinoma (RCC)</td>
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<tr>
<td></td>
<td>Soft Tissue Sarcoma (STS)</td>
</tr>
<tr>
<td></td>
<td>Endometrial Carcinoma (EC)</td>
</tr>
<tr>
<td></td>
<td>RET Fusion-Positive Non-Small Cell Lung Cancer</td>
</tr>
<tr>
<td></td>
<td>RET-Mutant Medullary Thyroid Cancer</td>
</tr>
</tbody>
</table>

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

**Policy Implementation/Update**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>03/2022</td>
</tr>
<tr>
<td>Transitioned criteria to policy format, added hepatocellular carcinoma indication, added age criteria and monotherapy criteria to all indications.</td>
<td>02/2019</td>
</tr>
<tr>
<td>Removed step therapy in RCC; Updated renewal language to assess response to therapy</td>
<td>01/2018</td>
</tr>
<tr>
<td>Previous Reviews</td>
<td>12/2012</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
</thead>
<tbody>
<tr>
<td>calcifediol (Rayaldee)</td>
<td>30 mcg ER Capsule</td>
<td>Secondary hyperparathyroidism in Stage 3 or 4 CKD</td>
<td>60 capsules/30 days</td>
<td>195578</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (mL/min/1.73 m²)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>≥ 90</td>
<td>Normal kidney or high</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>Mildly reduced kidney function</td>
</tr>
<tr>
<td>3 A</td>
<td>45-59</td>
<td>Mild to moderately reduced kidney function</td>
</tr>
<tr>
<td>3 B</td>
<td>30-44</td>
<td>Moderate to severely reduced kidney function</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>Severely reduced kidney function</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15 or on dialysis</td>
<td>End stage kidney failure (sometimes called established renal failure)</td>
</tr>
</tbody>
</table>

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 hyperparathyroidism without CKD stage 3 or 4.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria was transitioned into policy format with the addition of renewal criteria, investigational section, and supporting evidence.</td>
<td>10/2019</td>
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</tbody>
</table>

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

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: 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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>erenumab (Aimovig)</td>
<td>Migraine prophylaxis</td>
<td>70 mg/1 mL autoinjector</td>
<td>1 mL/30 days</td>
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<td></td>
<td></td>
<td>140 mg/1 mL autoinjector</td>
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<tr>
<td>galcanezumab (Emgality)</td>
<td>Migraine prophylaxis</td>
<td>120 mg/1 mL autoinjector</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>120 mg/1 mL prefilled syringe</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Episodic cluster headache</td>
<td>100 mg/1 mL prefilled syringe</td>
<td>3 mL/30 days</td>
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<tr>
<td>fremanezumab (Ajovy)</td>
<td>Migraine prophylaxis</td>
<td>225 mg/1.5 mL prefilled syringe</td>
<td>1.5 mL/30 days OR 4.5 mL per 90-day supply</td>
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<tr>
<td></td>
<td></td>
<td>225 mg/1.5 mL autoinjector</td>
<td></td>
</tr>
<tr>
<td>rimegepant (Nurtec ODT)</td>
<td>Acute migraine treatment</td>
<td>75 mg orally disintegrating tablet</td>
<td>8 tablets/30 days</td>
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<td></td>
<td>Migraine prophylaxis</td>
<td>10 mg tablet</td>
<td>16 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg tablet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 mg tablet</td>
<td></td>
</tr>
<tr>
<td>atogepant (Qulipta)</td>
<td>Migraine prophylaxis</td>
<td>10 mg tablet</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mg tablet</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>60 mg tablet</td>
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</tr>
</tbody>
</table>
Initial Evaluation

Migraine

I. **Erenumab (Aimovig), galcanezumab (Engility), 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 provider has attested that the member has not received onabotulinum toxin (e.g., Botox, etc.) within the past three months; **AND**
   F. The member will not receive onabotulinum toxin (e.g., Botox, etc.) concurrently with any agent in this policy (with the exception of rimegepant (Nurtec ODT) at a dose of less than, or equal to, 8 tablets per 30 days); **AND**
   G. The member has a history of four or more monthly migraine days; **AND**
   H. The member has experienced migraine for one year or longer; **AND**
   I. 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**
   J. 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**
   K. 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(K) 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. Use in combination with onabotulinum toxin (e.g., Botox, etc.), with the exception of rimegepant (Nurtec ODT) at a dose of 8 tablets per 30 days
   B. Chronic cluster headache
   C. Episodic cluster headache, with the exception of galcanezumab (Emgality)
   D. Post-traumatic headache
   E. Pediatric headache or migraine
   F. Vasomotor symptoms or hot flashes
   G. 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 provider has attested that the member has not received onabotulinum toxin (e.g., Botox, etc.) within the past three months; **AND**
         iii. The member will not receive onabotulinum toxin (e.g., Botox, etc.) concurrently; **AND**
         iv. 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**
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.

a. Upon subsequent renewals the member has maintained the initial response or gained further response to therapy; AND

v. 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.

III. Prophylactic dosing of oral and/or injectable CGRPs should not be used in combination with onabotulinum toxin (e.g., Botox, etc.), due to the rationale listed in II. Onabotulinum toxin products have been shown, in part, to play a role in CGRP. The safety profile of combination therapy is unknown at this time with potential significant safety concerns. Additionally, efficacy of combination has not been established in any clinical trials to date or real-world data. Overuse of migraine therapies, acute or prophylactic, may result in medication overuse headache and often results in a prescribing cascade. If adequate reduction in migraine is not achieved from one therapy, it should be discontinued. Another therapy should be initiated after a washout period to ensure the member and provider are realizing baseline migraine frequency and severity.

   Acute Migraine Treatment:

IV. 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:**

V. 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.

VI. 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.

VII. 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, and washed out, 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, cyproheptadine, nortriptyline, 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.

VIII. 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.

IX. 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.

X. 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:**

XI. 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,
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.

XII. 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.

XIII. 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.

- 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.

XIV. 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 episodic 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 attack 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.

XV. 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**

Washington State Rx Services is administered by Moda Health.

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.

September 01, 2022
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. Any indication in combination with onabotulinum toxin (e.g., Botox, etc.), with the exception of rimegepant (Nurtec ODT) at a dose of 8 tablets per 30 days
B. Chronic cluster headache
C. Episodic cluster headache, with the exception of galcanezumab (Emgality)
D. Post-traumatic headache
E. Pediatric headache or migraine
F. Vasomotor symptoms or hot flashes
G. Fibromyalgia

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated initial approval duration to 6 months for all products and to one year for acute treatment setting.</td>
<td>04/2022</td>
</tr>
<tr>
<td>Removed trial of triptan agents upon renewal of Nurtec. Restructured Nurtec requirements to improve clarity.</td>
<td>02/2022</td>
</tr>
<tr>
<td>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.</td>
<td>10/2021</td>
</tr>
<tr>
<td>Addition of new product atogepant (Qulipta) into policy, aligning non-preferred CGRP agents</td>
<td>09/2021</td>
</tr>
<tr>
<td>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.</td>
<td>04/2021</td>
</tr>
<tr>
<td>Update to require treatment of Ajovy prior to Aimovig or Emgality in the setting of migraines; effective 02/01/2021</td>
<td>01/2021</td>
</tr>
<tr>
<td>Added Ajovy autoinjector to policy</td>
<td>04/2020</td>
</tr>
<tr>
<td>Removed PFS and 2-pack of Aimovig from policy as it is no longer available one the market</td>
<td>02/2020</td>
</tr>
<tr>
<td>Criteria update: update to reflect preferred galcanezumab (Emgality)</td>
<td>11/2019</td>
</tr>
<tr>
<td>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 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.</td>
<td>07/2019</td>
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<tr>
<td>No changes made</td>
<td>01/2019</td>
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<tr>
<td>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.</td>
<td>10/2018</td>
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<td>Criteria created</td>
<td>10/2018</td>
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</table>
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

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

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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added in Epidiolex 60mg/mL product</td>
<td>10/2020</td>
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<tr>
<td>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</td>
<td>10/2020</td>
</tr>
<tr>
<td>Policy created</td>
<td>01/2019</td>
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</table>
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

<table>
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<tr>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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<td>30 vials/30 days</td>
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<td>11mg vial</td>
<td>aTTP</td>
<td>28 vials/28 days</td>
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</tr>
</tbody>
</table>

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 ADAMTS13 deficiency and other potential causes of microangiopathic hemolysis.
   - Scoring
     i. Low risk category
        1. Score of 0-4
        2. Indicating 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. Indicating a 56.8% likelihood of severe ADAMTS13 deficiency involvement.
     iii. High risk category
        1. Score of 7
        2. Indicating 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 thrombotic 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

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](https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630851.htm)


**Policy Implementation/Update:**

<table>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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</thead>
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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: UMP189

Split Fill Management*

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

Length of Authorization
- N/A

Quantity Limits

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

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 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. The FDA-approval 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 was treatment-naive patients. Patients had MET-dysregulated advanced NSCLC, with absence of EGFR or ALK mutations.

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. The medication efficacy continues to remain uncertain. Capmatinib (Tabrecta) was FDA-approved under the accelerated approval pathway based on ORR and DoR. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. There are several trials underway for NSCLC and other cancer types.

IV. The safety of capmatinib (Tabrecta) is based on patients from all cohorts (n=334). Median treatment time was 15 weeks, and 31% of patients were exposed to therapy for at least six months. The most common adverse events include peripheral edema, nausea, fatigue, vomiting, dyspnea, and anorexia.

V. Serious adverse events occurred in 51% 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 June 2020, 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. 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Added supporting evidence around stage IV metastatic disease and metastases.</td>
<td>10/2021</td>
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<tr>
<td>Policy created</td>
<td>08/2020</td>
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</table>

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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.

September 01, 2022
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 to 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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>carglumic</td>
<td>Adjunctive therapy for acute hyperammonemia due</td>
<td>200 mg tablet</td>
<td>250 mg/kg/day</td>
</tr>
<tr>
<td>acid (generic Carbaglu)</td>
<td>to NAGS deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintenance therapy for chronic hyperammonemia</td>
<td></td>
<td>100 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>due to NAGS deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjunctive therapy for acute hyperammonemia due</td>
<td></td>
<td>≤15 kg: 150 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>to PA or MMA</td>
<td></td>
<td>&gt;15 kg: 3.3 g/m²/day</td>
</tr>
</tbody>
</table>

Initial Evaluation

1. 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**

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. 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...
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.

(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 outlined in the table below:

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

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 deficient 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 patients (16 of 22 patients). In five patients, it took anywhere from one month to 10 months for the dose
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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 retreatment 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/m²/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

1. Carglumic acid (Carbaglu) [Prescribing Information]. Lebanon, NJ: Recordati Rare Diseases Inc. August 2021.

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added new indication of acute treatment of hyperammonemia due to PA or MMA to initial criteria;</td>
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<tr>
<td>changed initial authorization for acute hyperammonemia due to NAGS deficiency from 3 to 12 months;</td>
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</tr>
<tr>
<td>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.</td>
<td>05/2022</td>
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</table>

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<table>
<thead>
<tr>
<th>Change Description</th>
<th>Date</th>
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<tr>
<td>Added criteria of a trial and failure of generic Carbaglu prior to using branded product</td>
<td>12/2021</td>
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<tr>
<td>Transitioned criteria to policy format; Added requirement for weight documentation and supporting evidence section.</td>
<td>12/2020</td>
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<tr>
<td>Criteria created</td>
<td>12/2015</td>
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</table>
Policy Type: PA          Pharmacy Coverage Policy: UMP013

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

Length of Authorization
- Initial: Eight weeks
- Renewal: Not approvable

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>cenegermin-bkbi (Oxervate)</td>
<td>0.002% (20 mcg/mL) vial</td>
<td>Neurotrophic keratitis</td>
<td>56mL per lifetime</td>
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</table>

Initial Evaluation

I. Cenegermin-bkbi (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 not tolerated; **AND**
      E. Member has **NOT** received prior therapy with cenegermin-bkbi (Oxervate) in the requested eye in their lifetime.

II. Cenegermin-bkbi (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. Treatment beyond the initial eight week duration is considered experimental and investigational.
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.

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


**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>04/2021</td>
</tr>
<tr>
<td>Policy created</td>
<td>01/2019</td>
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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.
chenodiol (Chenodal®)
UMP POLICY

Policy Type: PA/SP  Pharmacy Coverage Policy: UMP200

Description
Chenodiol (Chenodal®) suppresses hepatic 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

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>chenodiol (Chenodal)</td>
<td>250mg tablet</td>
<td>radiolucent gallstones</td>
<td>16 mg/kg/day</td>
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</table>

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 affect 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

7. Retrophin, Inc. Study to Evaluate Patients With Cerebrotendinous Xanthomatosis. ClinicalTrials.gov Identifier: NCT04270682

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>11/2020</td>
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<tr>
<td>Criteria created</td>
<td>02/2014</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
</thead>
<tbody>
<tr>
<td>cholic acid (Cholbam)</td>
<td>50 mg capsules</td>
<td>Single Enzyme Defects (SEDs)</td>
<td>240 capsules/30 days</td>
<td>187995</td>
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<tr>
<td></td>
<td>250 mg capsules</td>
<td>Peroxisomal disorders</td>
<td>240 capsules/30 days</td>
<td>187996</td>
</tr>
</tbody>
</table>

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 gastroenterologist; **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 aldotkoreductase (AKR1D1) deficiency
            c. Cerebrotendinous xanthomatosis (CTX)
            d. Alpha-methylacyl-CoA racemase (AMACR) deficiency

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.

September 01, 2022
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 Adrenoleukodystrophy
      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
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.

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 has not yet been evaluated.

References


Policy Implementation/Update:

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<th>Date Created</th>
<th>April 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>April 2015</td>
</tr>
<tr>
<td>Last Updated</td>
<td></td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>10/2019</td>
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Action and Summary of Changes

<table>
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<th>Date</th>
</tr>
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<tbody>
<tr>
<td>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.</td>
<td>10/2019</td>
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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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indications</th>
</tr>
</thead>
</table>
| 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) |
| apremilast (Otezla®)   | • Plaque Psoriasis  
                          | • Psoriatic Arthritis  
                          | • Behcet Syndrome – ulcer of the mouth |
| brodalumab (Siliq®)    | • Plaque Psoriasis |
| certolizumab (Cimzia®) | • Ankylosing Spondylitis  
                          | • Crohn’s Disease  
                          | • Non-radiographic Axial Spondyloarthritis  
<pre><code>                      | • Plaque Psoriasis |
</code></pre>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept (Enbrel®)</td>
<td>• Psoriatic Arthritis</td>
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<tr>
<td></td>
<td>• Rheumatoid Arthritis</td>
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<tr>
<td></td>
<td>• Ankylosing Spondylitis</td>
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<tr>
<td></td>
<td>• Plaque Psoriasis</td>
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<tr>
<td></td>
<td>• Polyarticular Juvenile Idiopathic Arthritis</td>
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<td></td>
<td>• Psoriatic Arthritis</td>
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<td></td>
<td>• Rheumatoid Arthritis</td>
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<tr>
<td>golimumab (Simponi®/Simponi Aria®)</td>
<td>• Ankylosing Spondylitis</td>
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<td>• Psoriatic Arthritis</td>
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<td>• Rheumatoid Arthritis</td>
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<td></td>
<td>• Ulcerative Colitis</td>
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<tr>
<td>guselkumab (Tremfya®)</td>
<td>• Plaque Psoriasis</td>
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<tr>
<td></td>
<td>• Psoriatic Arthritis</td>
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<tr>
<td>ixekizumab (Taltz®)</td>
<td>• Ankylosing Spondylitis</td>
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<td></td>
<td>• Non-radiographic Axial Spondyloarthritis</td>
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<td></td>
<td>• Adolescent Plaque Psoriasis</td>
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<td></td>
<td>• Plaque Psoriasis</td>
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<tr>
<td></td>
<td>• Psoriatic Arthritis</td>
</tr>
<tr>
<td>rilonacept (Arcalyst®)</td>
<td>• Cryopyrin-Associated Periodic Syndromes (CAPS) (including Familial Cold</td>
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<tr>
<td></td>
<td>Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS))</td>
</tr>
<tr>
<td>risandizumab (Skyrizi®)</td>
<td>• Plaque Psoriasis</td>
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<td></td>
<td>• Psoriatic Arthritis</td>
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<td></td>
<td>• Crohn’s Disease</td>
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<tr>
<td>sarilumab (Kevzara®)</td>
<td>• Rheumatoid Arthritis</td>
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<tr>
<td>secukinumab (Cosentyx®)</td>
<td>• Ankylosing Spondylitis</td>
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<td></td>
<td>• Non-radiographic Axial Spondyloarthritis</td>
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<td></td>
<td>• Plaque Psoriasis</td>
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<td></td>
<td>• Psoriatic Arthritis</td>
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<td>• Enthesitis-related arthritis</td>
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<td>ustekinumab (Stelara®)</td>
<td>• Crohn’s Disease</td>
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<td>• Adolescent Plaque Psoriasis</td>
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<td>• Plaque Psoriasis</td>
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<td></td>
<td>• Psoriatic Arthritis</td>
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<td></td>
<td>• Ulcerative Colitis</td>
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<tr>
<td>tocilizumab (Actemra®)</td>
<td>• Giant Cell Arteritis</td>
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<tr>
<td></td>
<td>• Polyarticular Juvenile Idiopathic Arthritis</td>
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<td></td>
<td>• Rheumatoid Arthritis</td>
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<tr>
<td></td>
<td>• Systemic Juvenile Idiopathic Arthritis</td>
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<tr>
<td></td>
<td>• Systemic Sclerosis-Associated Interstitial Lung Disease</td>
</tr>
<tr>
<td>ozanimod (Zeposia®)</td>
<td>• Ulcerative Colitis</td>
</tr>
</tbody>
</table>

*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.*
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.

**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 (Humira) 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 (Kezvara), or 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 adalimumab (Humira), etanercept (Enbrel), upadacitinib (Rinvoq), AND tofacitinib (Xeljanz/Xeljanz XR) have 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. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to rheumatoid arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.).

**Supporting Evidence**

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

II. 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-naive 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-naive 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-naive patients based on established safety and efficacy. Additionally, JAK inhibitors are not FDA approved for use in csDMARD-naive patients.

- For patients who are DMARD-naive 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).

III. 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:


**Polyarticular Juvenile Idiopathic Arthritis (PJIA)**

**Initial Evaluation**

I. **Adalimumab (Humira) 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) or 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 adalimumab (Humira), etanercept (Enbrel), AND tofacitinib (Xeljanz) have 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 polyarticular juvenile idiopathic arthritis or another auto-immune condition (e.g., Humira, Xeljanz, Infliximab, etc.)

Supporting Evidence

I. 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.

II. 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.

III. 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.
IV. 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.

References

5. Safety and Tolerability of Tofacitinib for Treatment of Polyarticular Course Juvenile Idiopathic Arthritis. 2020 [PROPEL Study] (NCT02592434)

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


**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**

*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. 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 an ACR30 response, which was similar to response rates seen in patients included with other JIA subtypes.
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.

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).

References


Psoriatic Arthritis

Initial Evaluation

1. **Adalimumab (Humira), etanercept (Enbrel), apremilast (Otezla), secukinumab (Cosentyx), 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 two years of age or older and the request is for secukinumab (Cosentyx); **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 guselkumab (Tremfya) 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 (Humira), etanercept (Enbrel), apremilast (Otezla), secukinumab (Cosentyx), ustekinumab (Stelara), risankizumab (Skyrizi), tofacitinib (Xeljanz/Xeljanz XR), AND upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated

*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.)

Supporting Evidence

I. 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.
II. 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-naive 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.

III. 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.

IV. 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).

V. 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.

References:


**Ankylosing Spondylitis**

**Initial Evaluation**

I. **Adalimumab (Humira), 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), or ixekizumab (Taltz)** 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 (Humira), etanercept (Enbrel), secukinumab (Cosentyx), tofacitinib (Xeljanz), AND upadacitinib (Rinvoq) 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 psoriatic arthritis or another auto-immune condition (e.g., Otezla, Olumiant, etc.)

**Supporting Evidence**

I. The above agents are approved for adult patients in the treatment of ankylosing spondylitis based on safety and efficacy data from randomized-controlled trials.

II. The 2015 ACR and Spondylitis Association of America (SAA) 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 ACR strongly recommends use of TNF inhibitors. For those patients with continued active disease, the ACR 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. The 2016 ASAS/EULAR guideline update mirrors that of the ACR/SAA. NSAIDs are also noted as first-line treatment due to robust response of greater than 70% of patients achieving ASAS20, and greater than 50% of patients achieving ASAS40 response. Recommendations against the use of non-biologic DMARDs are made for patients with purely axial disease, however, sulfasalazine may be considered in patients with peripheral disease. In order to qualify for treatment with biologics, ASAS/EULAR recommends patients try and fail at least 2 NSAIDs over 4 weeks, have a trial of glucocorticoid injection or sulfasalazine if peripheral symptoms, and have a high disease activity as defined by a BASDAI of at least 4 or an ASDAS of at least 2.1. The update to the guidelines in 2016 notes that if a patient fails TNF inhibitor therapy, switching to another TNF inhibitor of IL-17 inhibitor can be considered.

III. The ACR conditionally recommends against the use of DMARDs in patients with ankylosing spondylitis that remains active despite NSAID treatment. This is based on 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 ankyllosing spondylitis with predominantly peripheral arthritis symptoms.

References:


**Non-radiographic Axial Spondyloarthritis**

**Initial Evaluation**

1. **Adalimumab (Humira), 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**

*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.*

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3. Disease manifested as axial disease; OR
4. Disease manifested as peripheral arthritis.

II. **Certolizumab (Cimzia) or ixekizumab (Taltz)** 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 (Humira), etanercept (Enbrel), AND secukinumab (Cosentyx) 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 psoriatic arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, etc.)

**Supporting Evidence**

I. Currently, certolizumab pegol, ixekizumab, and secukinumab 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 2016 ASAS/EULAR guidelines note that efficacy in regard to musculoskeletal signs and symptoms appears comparable based off indirect comparison.

II. 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.

III. 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% CI 1.23-4.51, p=0.0094, and week 52: 30% vs 13%, OR 2.82, 95% CI 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.

IV. 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-naive patients on secukinumab 150 mg with loading dose compared to placebo and ASAS40 response at week 52 in TNFi-naive 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.

V. Per 2019 ACR 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. The 2016 guideline update by ASAS/EULAR notes that there is still some debate as to whether the two diseases (radiographic and non-radiographic) should be considered as two different entities, given that some patients with non-radiographic disease may develop radiographic changes over time (and some may not).

References:

**Plaque Psoriasis**

**Initial Evaluation**

I. **Adalimumab (Humira), etanercept (Enbrel), secukinumab (Cosentyx), apremilast (Otezla), 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 if prescribed adalimumab (Humira), apremilast (Otezla), or risankizumab (Skyrizi); 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 one 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), guselkumab (Tremfya), or ixekizumab (Taltz)** 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 (Humira), etanercept (Enbrel), secukinumab (Cosentyx), apremilast (Otezla), ustekinumab (Stelara), AND risankizumab (Skyrizi) have been ineffective, contraindicated, or not tolerated; **AND**

C. The member is 18 years of age or older if prescribed brodalumab (Siliq), certolizumab (Cimzia), or guselkumab (Tremfya); **OR**

D. 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)

### 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 psoriatic arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Rinvoq, etc.)

### Supporting Evidence

I. 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 May 2021, 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.

II. 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.

III. 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:**
  - The following agents statistically and significantly improve PASI by at least 90% compared to ustekinumab (Stelara): brodalumab (Siliq) with low certainty evidence; bimekizumab (investigational), risankizumab (Skyrizi), and secukinumab (Cosentyx) with moderate certainty.

- **Induction:**
The following agents statistically significantly improve PASI by at least 90% compared to adalimumab (Humira) with moderate certainty: guselkumab (Tremfya) and risankizumab (Skyrizi).

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).

Izekizumab (Taltz) statistically significantly improves PASI by at least 90% compared to ustekinumab (Stelara) with moderate certainty.

There is insufficient evidence to suggest that etanercept (Enbrel) is statistically inferior to apremilast (Otezla).

Maintenance:

- Guselkumab (Tremfya) statistically significantly improves PASI by at least 90% compared to adalimumab (Humira) and secukinumab (Cosentyx) with moderate certainty.
- Secukinumab (Cosentyx) statistically significantly improves PASI by at least 90% compared to etanercept (Enbrel) with low certainty.

IV. 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 medications 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 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 trials were available and included during guideline development.
- Guidelines have not provided recommendations for certolizumab (Cimzia).
- 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.
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.

V. 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-to-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.

References:


6. Ixekizumab (Taltz) [Prescribing Information]. Indianapolis, IN; Eli Lilly. Updated May 2020.


10. Ustekinumab (Stelara) [Prescribing Information]. Horsham, PA; Janssen. Updated July 2020.


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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.
Crohn’s Disease

Initial Evaluation

I. Adalimumab (Humira), 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
   B. Member is 6 to 17 years of age and the request is for adalimumab (Humira); AND
      1. Documentation of member’s current weight is provided; AND
   C. Member is being managed by, or in consultation with, a gastroenterologist; AND
   D. Documentation member has severe Crohn’s disease; OR
   E. Documentation member has moderate to severe Crohn’s disease when the following are met:
      1. Treatment with oral corticosteroids (e.g., prednisone, methylprednisolone) used short-term to induce remission or alleviate signs/symptoms of disease flare has been ineffective, contraindicated, or not tolerated; AND
      2. Treatment with at least one immunomodulatory agent (e.g., methotrexate, azathioprine, 6-mercaptopurine) over an eight-week period to maintain remission has been ineffective, contraindicated, or not tolerated; OR

II. Certolizumab pegol (Cimzia) may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(E) above are met; AND
   B. Member is 18 years of age or older; AND
   C. Treatment with adalimumab (Humira), ustekinumab (Stelara), AND risankizumab (Skyrizi) have 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 Crohn’s disease or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant, Infliximab, etc.)

Supporting Evidence

I. 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) and risankizumab (Skyrizi) are FDA-approved in adults only, while adalimumab (Humira) is approved in patients six years of age and older.

II. 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.

III. 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**

IV. 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.

V. 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.

VI. 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.

VII. 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).

VIII. 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).

IX. 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 naive 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.

X. Adalimumab (Humira), ustekinumab (Stelara), certolizumab (Cimzia), infliximab (e.g., Remicade, Inflectra), vedolizumab (Entyvio), natalizumab (Tysabri), and risankizumab (Skyrizi) 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.

XI. 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.

Severe CD

XII. 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.

XIII. 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

XIV. 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.

XV. 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.

XVI. 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.

References
4. Risankizumab (Skyrizi) [Prescribing Information]. North Chicago, IL; AbbVie. Updated January 2021.

Ulcerative Colitis

Initial Evaluation

I. Adalimumab (Humira) 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 (Humira); AND

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1. Documentation of member’s current weight is provided; OR
2. Member is 18 years of age or older; AND
   1. Documentation of the member’s current weight if request is for ustekinumab (Stelara); AND
3. Member is being managed by, or in consultation with, a gastroenterologist; AND
4. A diagnosis of moderate to severe ulcerative colitis when the following are met:
   1. Previous treatment with at least one systemic corticosteroid (e.g., budesonide, prednisone, hydrocortisone, methylprednisolone, etc.) has been ineffective to induce remission, is contraindicated, or is not tolerated; AND
   2. If systemic corticosteroids were used to induce remission, previous treatment with at least one thiopurine (azathioprine or 6-mercaptopurine) over an eight-week period to maintain remission has been ineffective, contraindicated, or not tolerated.

II. Golimumab (Simponi) or ozanimod (Zeposia) may be considered medically necessary when the following criteria below are met:
   A. Criteria I(B)-I(D) above are met; AND
   B. Treatment with adalimumab (Humira), ustekinumab (Stelara), tofacitinib (Xeljanz/Xeljanz XR), AND upadacitinib (Rinvoq) have 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 ulcerative colitis or another auto-immune condition (e.g., Remicade, Entyvio, Cimzia, etc.)

Supporting Evidence

I. 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.
II. Adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), and upadacitinib (Rinvoq) 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), and golimumab (Simponi) is incremental or better when evaluated against placebo. There is moderate certainty that ozanimod (Zeposia) provides promising but inconclusive net health benefit compared to placebo in patients with moderate to severe UC due to evidence being available from only one phase 3 trial and less established safety data compared to other UC treatment options.

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III. 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.

IV. 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.

V. 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.

VI. 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.

VII. 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.

References:

2. Ustekinumab (Stelara) [Prescribing Information]. Horsham, PA; Janssen. Updated December 2020.
Behcet’s Disease (i.e., Behcet Syndrome)

Initial Evaluation

I. **Adalimumab** (Humira), **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 treating 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.).

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 psoriatic arthritis or another autoimmune condition (e.g., Otezla, Xeljanz, Olumiant, Rinvoq, etc.)

Supporting Evidence

I. **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 etanercept
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.

II. 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.

III. Corticosteroids and oral DMARDS (typically azathioprine) have been mainstays of Behcet’s Disease, with oral DMARDS having a particular role in ophthalmic manifestations.

IV. 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.

V. 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.

VI. 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.

VII. 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.
**References:**


**Hidradenitis Suppurativa**

**Initial Evaluation**

I. **Adalimumab (Humira)** 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 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

**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. **Adalimumab (Humira)** is FDA-approved for HS in patients in 12 years or older with moderate to severe disease based off results of the PIONEER I and II RCTs.

II. 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. This mirrors the recent evidence-based guidelines published by the British Association of Dermatologists which recommends adalimumab use be reserved for patients with moderate to severe disease that is unresponsive to more conventional systemic therapies (i.e., antibiotics).

III. 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. While 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. The European Dermatology Forum evidence review notes this and suggests that adalimumab be considered for first-line treatment in patients with more severe disease. 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.

References:


Uveitis and Panuveitis

**Initial Evaluation**

I. **Adalimumab (Humira)** 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 noncorticosteroid systemic immunomodulatory therapy (i.e., mycophenolate mofetil, tacrolimus, cyclosporine, azathioprine, or methotrexate) 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 psoriatic arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant)

**Supporting Evidence**

I. 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.

II. 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.

III. 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:**


**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; **AND**
      2. 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; **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. A large proportion of patients, however, will not have 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.

References:

**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 psoriatic arthritis or another auto-immune condition (e.g., Otezla, Xeljanz, Olumiant)

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:

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)

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 NSAI Ds/aspirin with colchicine for both acute pericarditis and recurrent pericarditis. According to ACC, anti-inflammatory therapy is the cornerstone of acute pericarditis. NSAI Ds 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 NSAI Ds. 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 NSAI Ds/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, NSAI Ds 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.

References:

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 focuSSced 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) ≤ 55%, DLCO ≤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.

<table>
<thead>
<tr>
<th></th>
<th>Overall population</th>
<th>Subgroup without SSc-ILD*</th>
<th>SSc-ILD subgroup*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Tocilizumab</td>
<td>Placebo</td>
</tr>
<tr>
<td>Number of patients</td>
<td>106</td>
<td>104</td>
<td>36</td>
</tr>
</tbody>
</table>

|                          |                          |                          |                  |
| Change from baseline in mRSS score |                          |                          |                  |
| LSM                       | -4.41                  | -6.14                    | -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                    | -0.32            | -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                      | -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.

|                          |                          |                          |
| 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 |                          |                          |

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.
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.

References:
1. Actemra® [prescribing information]. South San Francisco, CA: Genentech; March 2021

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. Familial Mediterranean Fever

A. Current studies for Familial Mediterranean Fever, a subgroup of periodic fever syndrome, are limited to case reports. In evaluating current evidence available, quantitative evaluation of response to biologic treatments (e.g. tocilizumab, infliximab, etanercept, adalimumab, anakinra and canakinumab) is difficult to obtain, and therefore, difficult to assess true efficacy and safety. In the absence of controlled studies to evaluate the safety and efficacy of biologics in the treatment of patients with Familial Mediterranean Fever, the use of biologics in this setting would be considered experimental and investigational.

IV. 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.

V. 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.

VI. 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.

VII. 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.

VIII. 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.

IX. 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.

X. 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 pustulosis 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 pustulosis. 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.

XI. Polymyalgia Rheumatica

A. A phase III placebo-controlled study (n = 40) of etanercept demonstrated mild reduction in disease severity scores, though the response was only analyzed at two weeks. The TNF inhibitor infliximab was also examined in a RCT (n = 51). No statistical difference was observed in relapse between the infliximab and standard of care groups. A phase III study is currently recruiting looking at the IL-6 inhibitors tocilizumab and sarilumab use in this population.

XII. 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.

XIII. 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.

XIV. 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.

XV. 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
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.

XVI. 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).

XVII. 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.

XVIII. 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.

XIX. 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.

References:
55. Abatacept combined with a calcineurin inhibitor and methotrexate for graft versus host disease prophylaxis: a randomized controlled trial. Results posted. Available at: https://clinicaltrials.gov/ct2/show/NCT01743131

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.

<table>
<thead>
<tr>
<th>Policy</th>
<th>Disease State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic Janus Associated Kinase (JAK) Inhibitors in Chronic Inflammatory Disease Policy</td>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td></td>
<td>Polyarticular Juvenile Idiopathic Arthritis (PJIA)</td>
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<tr>
<td></td>
<td>Psoriatic Arthritis</td>
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<td></td>
<td>Ankylosing Spondylitis</td>
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<td></td>
<td>Ulcerative Colitis</td>
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<td></td>
<td>Atopic Dermatitis</td>
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<tr>
<td>Multiple Sclerosis Policy</td>
<td>Multiple Sclerosis</td>
</tr>
<tr>
<td>nintedanib (Ofev®); prifenidone (Esbriet®) Policy</td>
<td>Systemic sclerosis-associated interstitial lung disease (SSc-ILD)</td>
</tr>
</tbody>
</table>

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added Skyrizi to Crohn’s disease criteria, updated supporting evidence section, updated formatting. Updated AS formulary agents to include new indication for Rinvoq.</td>
<td>06/2022</td>
</tr>
<tr>
<td>Added Rinvoq to ulcerative colitis criteria given newly approved indication</td>
<td>05/2022</td>
</tr>
<tr>
<td>Updated criteria in setting of mild-moderate plaque psoriasis to require phototherapy OR treatment with only one of the list groups</td>
<td>04/2022</td>
</tr>
<tr>
<td>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.</td>
<td>03/2022</td>
</tr>
<tr>
<td>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</td>
<td>2/2022</td>
</tr>
</tbody>
</table>

Washington State Rx Services is administered by moda HEALTH

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.
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.

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>12/2021</td>
</tr>
<tr>
<td>Removed criteria defining moderate to severe Crohn’s disease, severe/fulminant Crohn’s disease, and surgical Crohn’s disease. Updated supporting evidence section accordingly.</td>
<td>09/2021</td>
</tr>
<tr>
<td>Added criteria for the treatment of systemic sclerosis-associated interstitial lung disease prompted by new FDA approval of Actemra for this indication.</td>
<td>08/2021</td>
</tr>
<tr>
<td>Updated Plaque Psoriasis, Cosentyx criteria to allow coverage in patients 6 six years of age or older</td>
<td>07/2021</td>
</tr>
<tr>
<td>Updated criteria for treatment of recurrent pericarditis with Arcalyst</td>
<td>06/2021</td>
</tr>
<tr>
<td>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.</td>
<td>06/2021</td>
</tr>
<tr>
<td>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.</td>
<td>05/2021</td>
</tr>
<tr>
<td>Added DIRA indication as E/I for anakinra (Kineret); Updated the supporting evidence and references for plaque psoriasis.</td>
<td>04/2021</td>
</tr>
<tr>
<td>Updated PA policy to include FDA approvals for Xeljanz for PJIA. Updated supporting evidence section with clinical trial data</td>
<td>11/2020</td>
</tr>
<tr>
<td>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</td>
<td>09/2020</td>
</tr>
<tr>
<td>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.</td>
<td>08/2020</td>
</tr>
<tr>
<td>Removed Behçet syndrome from the E/I section</td>
<td>02/2020</td>
</tr>
<tr>
<td>Updated preferred products to also include Cosentyx, Stelara, and Otezla within their FDA label designation.</td>
<td>01/2020</td>
</tr>
<tr>
<td>Updated policy to add new indications for Stelara and Taltz. Included Familial Mediterranean Fever to experimental/investigational section.</td>
<td>11/2019</td>
</tr>
</tbody>
</table>

**Criteria updated to new policy format. Specific changes include:**

**Rheumatoid Arthritis**

- 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  | 08/2019 |

**Polyarticular Juvenile Idiopathic Arthritis (PJIA)**

- 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  | 08/2019 |

**Systemic Juvenile Idiopathic Arthritis (SJIA)**

- Added route to approval of Actemra as Actemra was previously in a separate policy

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September 01, 2022
**Psoriatic Arthritis**
- 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.”

**Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis**
- 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

**Plaque Psoriasis**
- Clarified that moderate to severe disease is needed for payment consideration
- Clarified use of oral DMARD requirement may be bypassed if all are contraindicated

**Crohn’s Disease**
- 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

**Ulcerative Colitis**
- Added age of 18 years or older
- Addition of trial of thiopurine for at least 8 weeks

**Behcet’s Disease**
- New indication added following approval of Otezla in this setting
- Literature supports TNF therapy in oral and ophthalmic manifestations for Bechet’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

**Hidradenitis Suppurativa**
- Updated prescriber language to be consistent with other sections
- Added requirement of a trial of antibiotics for moderate disease

**Uveitis/Panuveitis**
- 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

**Giant Cell Arteritis (GCA)**
- 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

**Cryopyrin-Associated Periodic Syndromes (CAPS)**
Added requirement, of documented laboratory evidence of a genetic mutation

<table>
<thead>
<tr>
<th>Criteria update</th>
<th>07/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria update</th>
<th>06/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added new Kevzara auto injector formulation, Xeljanz new indication in ulcerative colitis, added Cimzia new indication in plaque psoriasis, minor formatting edits.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria update</th>
<th>02/2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Align dosage and administration with quantity limit. Removal of the question pertaining to active infection.</td>
<td></td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>01/2018</th>
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<tr>
<td>07/2018</td>
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</tbody>
</table>
Chronic Opioid Use Attestation Policy

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

Quantity Limits

<table>
<thead>
<tr>
<th>Short Acting: Active ingredients containing*</th>
<th>Combination products containing any of these listed ingredients are included in this policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine sulfate</td>
<td>codeine sulfate</td>
</tr>
<tr>
<td>hydrocodone</td>
<td>levorphanol</td>
</tr>
<tr>
<td>pentazocine</td>
<td>tapentadol</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long Acting: Active ingredients containing†</th>
<th>Combination products containing any of these listed ingredients are included in this policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>morphine sulfate</td>
<td>codeine sulfate</td>
</tr>
<tr>
<td>oxycodone</td>
<td>fentanyl patches</td>
</tr>
<tr>
<td>tapentadaol</td>
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</tr>
</tbody>
</table>

*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 may be considered medically necessary when the following criteria below are met:
   A. All existing prior authorization requirements on the medication beyond the request for attestation have been met; AND
   B. All existing step therapy requirements on the medication beyond the request for attestation have been met; AND
   C. There is a signed prescribing provider attestation on file; AND
   D. The patient has an on-going clinical need for chronic opioid use at the prescribed dose (more than 42 days per 90 day calendar period) that is documented in the medical record; AND
   E. The patient is using appropriate non-opioid medications, and/or non-pharmacologic therapies; OR
   F. The patient has tried and failed non-opioid medications and non-pharmacologic therapies for the treatment of this pain condition; AND
   G. For long-acting opioids, the patient must be using or had trials of short-acting opioid therapy for at least 42 days; OR
H. The reason for inadequate response to short-acting opioid therapy is documented in the medical record; OR
I. Justification of beginning an opiate naïve patient on a long-acting opioid is documented in the medical record; AND
J. 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
K. The patient has been screened for mental health disorders, substance use disorder, naloxone use; AND
L. The provider will conduct periodic urine drug screens; AND
M. The provider has checked the Prescription Drug Monitoring Program (PDMP) for any other opioid use and concurrent use of benzodiazepines and other sedatives; AND
N. The provider has discussed with the patient the realistic goals of pain management therapy and has discussed discontinuation as an option during treatment; AND
O. The provider confirms that the patient understands and accepts these conditions and the patient has signed a pain contract or informed consent document.

P. 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-chronic-opioid-attestation-form.pdf

II. Chronic opioid use attestation is considered not medically necessary when criteria above are not met and/or when used for:
   A. Non-chronic use

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.
III. This policy is in full compliance with UMP’s regulations and mandates regarding the chronic use of opioids.
IV. 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added APAP limit wording to QL box</td>
<td>03/2020</td>
</tr>
<tr>
<td>Creation of policy</td>
<td>02/2020</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation Factor X, human (Coagadex)</td>
<td>250 IU/vial,</td>
<td>Factor X deficiency: On-demand treatment</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>500 IU/vial</td>
<td>&lt;12 years: 30 IU/kg/dose</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>&gt;12 years: 25 IU/kg/dose</td>
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<td></td>
<td></td>
<td>Repeat every 24 hours until bleeding stops.</td>
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<td></td>
<td>Max of 60 IU/kg/day</td>
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<td></td>
<td></td>
<td>Routine prophylaxis</td>
<td>Routine Prophylaxis: 480 IU/kg every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;12 years: 40 IU/kg IV twice weekly initially</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;12 years: 25 IU/kg IV twice weekly initially</td>
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<tr>
<td></td>
<td></td>
<td>Max of 60 IU/kg/day</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Perioperative management</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Max of 60 IU/kg/day</td>
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</tr>
</tbody>
</table>

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
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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>January 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>January 2016</td>
</tr>
<tr>
<td>Last Updated</td>
<td>November 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>11/2019</td>
</tr>
<tr>
<td>Action and Summary of Changes</td>
<td>Date</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>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.</td>
<td>11/2019</td>
</tr>
</tbody>
</table>
cobimetinib (Cotellic®), vemurafenib (Zelboraf®)
UMP POLICY

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>cobimetinib (Cotellic)</td>
<td>Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation</td>
<td>20 mg tablets</td>
<td>63 tablets/28 days</td>
</tr>
<tr>
<td>vemurafenib (Zelboraf)</td>
<td>Unresectable or metastatic melanoma with a BRAF V600E mutation</td>
<td>240 mg tablets</td>
<td>224 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>Erdheim-Chester disease with a BRAF V600 mutation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 IIIIC) 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. Erdheim-Chester disease; AND
   i. The request is for vemurafenib (Zelboraf) monotherapy; AND
   ii. 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 monotherapy or in combination with Zelboraf for Erdheim-Chester disease
   F. Rosai-Dorfman Disease or Langerhans Cell Histiocytosis

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 treatment of Erdheim-Chester disease: the request is for vemurafenib (Zelboraf) monotherapy

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. Erdheim-Chester disease

A. Erdheim-Chester disease (ECD) is a rare histiocytic neoplasm caused by acquired mutations in BRAF or other components of the MAPK signaling pathway that manifests as sclerotic lesions in bones and other major organ systems. Current treatment option for ECD 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 cladribine/interferon alpha (irrespective of mutation); other recommended regimens target identified mutations. Only vemurafenib (Zelboraf) is FDA-approved for ECD with BRAF V600E mutation, though due to limited treatment options, other targeted therapies are used off-label based on limited retrospective data.

B. 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.
Investigational or Not Medically Necessary Uses

I. Cobimetinib (Cotellic) has not been sufficiently evaluated outside of unresectable or metastatic melanoma. 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 monotherapy or in combination with Zelboraf for Erdheim-Chester disease
      i. Cobimetinib (Cotellic) has been granted breakthrough therapy designation for ECD. Current data to support use of cobimetinib (Cotellic) include retrospective studies, though a phase II study is ongoing to evaluate efficacy of cobimetinib in various histiocytic disorders, including ECD. At this time, due to limited evidence of safety and efficacy, use of cobimetinib (Cotellic) monotherapy or in combination with vemurafenib (Zelboraf) is considered investigational.
   F. Rosai-Dorfman Disease or Langerhans Cell Histiocytosis

References

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.

<table>
<thead>
<tr>
<th>Policy Name</th>
<th>Disease state</th>
</tr>
</thead>
<tbody>
<tr>
<td>trametinib (Mekinist®), dabrafenib (Tafinlar®)</td>
<td>Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy&lt;br&gt;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&lt;br&gt;Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy</td>
</tr>
<tr>
<td>encorafenib (Braftovi®), binimetinib (Mektovi®)</td>
<td>Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy&lt;br&gt;Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy</td>
</tr>
</tbody>
</table>

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>06/2022</td>
</tr>
<tr>
<td>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 plan; 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.</td>
<td>01/2021</td>
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<td>Policy created</td>
<td>02/2016</td>
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Washington State Rx Services is administered by moda HEALTH

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.

September 01, 2022
Continuous Glucose Monitoring Systems
UMP POLICY

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexcom G6</td>
<td>System meter</td>
<td>Diabetes Mellitus</td>
<td>1 meter per 365 days</td>
</tr>
<tr>
<td></td>
<td>Transmitter</td>
<td></td>
<td>1 transmitter per 90 days</td>
</tr>
<tr>
<td></td>
<td>Sensors</td>
<td></td>
<td>3 sensors (1 kit) per 30 days</td>
</tr>
<tr>
<td>Freestyle Libre or Freestyle Libre 2</td>
<td>Reader</td>
<td></td>
<td>1 reader per 365 days</td>
</tr>
<tr>
<td></td>
<td>Sensor (14 day)</td>
<td></td>
<td>2 sensors per 28 days</td>
</tr>
<tr>
<td>Medtronic Guardian Connect</td>
<td>Transmitter</td>
<td></td>
<td>1 transmitter per 365 days</td>
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<tr>
<td></td>
<td>Sensor 3</td>
<td></td>
<td>5 sensors per 35 days</td>
</tr>
<tr>
<td>Eversense CGM system</td>
<td>Transmitter</td>
<td></td>
<td>1 transmitter per 365 days</td>
</tr>
<tr>
<td></td>
<td>Sensor</td>
<td></td>
<td>1 sensor per 90 days</td>
</tr>
</tbody>
</table>

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 HbA1c despite adherence to an appropriate glycemic management plan (e.g. intensive insulin therapy; testing glucose more than 4 times per day); OR
         ii. Suffering from 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 or 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. **Medtronic and Eversense CGM products** 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®.

VI. 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.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added Eversense CGM system to policy under non-preferred status</td>
<td>07/2021</td>
</tr>
<tr>
<td>Policy created</td>
<td>12/2020</td>
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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: 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 (CDK4/6) inhibitors, which suppress the activity of CDK 4/6 enzymes in tumor cells leading to 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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>abemaciclib (Verzenio)</td>
<td>50 mg tablets</td>
<td>Breast cancer, HER2-negative, HR-positive, advanced or metastatic; early-stage breast cancer</td>
<td>56 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>100 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>palbociclib (Ibrance)</td>
<td>75 mg capsules/tablets</td>
<td>Breast cancer, HER2-negative, HR-positive, advanced or metastatic</td>
<td>21 capsules or tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>100 mg capsules/tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>125 mg capsules/tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ribociclib (Kisqali)</td>
<td>200 mg tablet dose pack</td>
<td>Breast cancer, HER2-negative, HR-positive, advanced or metastatic</td>
<td>21 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>400 mg tablet dose pack</td>
<td></td>
<td>42 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>600 mg tablet dose pack</td>
<td></td>
<td>63 tablets/28 days</td>
</tr>
<tr>
<td>ribociclib/letrozole (Kisqali/Femara)</td>
<td>200 mg and 2.5 mg tablet dose pack</td>
<td>Breast cancer, HER2-negative, HR-positive, advanced or metastatic</td>
<td>49 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>400 and 2.5 mg tablet dose pack</td>
<td></td>
<td>70 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>600 and 2.5 mg tablet dose pack</td>
<td></td>
<td>91 tablets/28 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

1. **Abemaciclib (Verzenio), palbociclib (Ibrance), and ribociclib (Kisqali)** 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 not 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 of the following:
      i. Histopathological tests showing four or more (≥ 4) axillary lymph nodes are affected (pALN); OR
      ii. Histopathological tests showing one to three axillary lymph nodes are affected, and one of the following:
         a. Tumor size is ≥ 5 cm; OR
         b. Histopathological grade 3 disease; AND
   2. The member has a Ki-67 score ≥ 20% as determined by an FDA-approved test; AND
   3. The member has undergone definitive surgical resection of the primary tumor; AND
   4. 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
   5. The request is for abemaciclib (Verzenio); AND
      i. abemaciclib (Verzenio) will be used in combination with 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 in combination with an aromatase inhibitor (e.g., letrozole, anastrozole, exemestane) or fulvestrant as a first-line systemic therapy; AND
      i. Will not be used in combination with any additional oncology therapy; AND
      ii. The member is hormone suppressed male or postmenopausal female (natural or pharmacotherapy induced [e.g., GnRH therapy [e.g., leuprolide] used concomitantly for male and pre/perimenopausal female]; AND
         a. The request is for abemaciclib (Verzenio) or palbociclib (Ibrance); OR
         b. The request is for ribociclib (Kisqali) or ribociclib/letrozole (Kisqali/Femara Co-Pack); AND
            i. The member is postmenopausal female (natural or pharmacotherapy induced [e.g., GnRH therapy [e.g., leuprolide] used concomitantly]); AND
            ii. Documentation that treatment with palbociclib (Ibrance) and abemaciclib (Verzenio) is contraindicated or not tolerated; OR
   3. The medication is being prescribed in combination with fulvestrant (Faslodex) as a Second-line systemic therapy; AND
      i. Will not be used in combination with any additional oncology therapy; AND
ii. The member had disease progression on, or after primary endocrine therapy (as adjuvant or first-line systemic therapy); AND

iii. The member is hormone suppressed male or postmenopausal female (natural or pharmacotherapy induced) [e.g., GnRH therapy [e.g., leuprolide] used concomitantly for male and pre/perimenopausal female]; AND
   a. The request is for abemaciclib (Verzenio) OR palbociclib (Ibrance); OR
   b. The request is for ribociclib (Kisqali) or ribociclib/letrozole (Kisqali/Femara co-pack); AND
      i. The member is postmenopausal female (natural or pharmacotherapy induced [e.g., GnRH therapy [e.g., leuprolide] used concomitantly]); AND
      ii. Documentation that treatment with palbociclib (Ibrance) and abemaciclib (Verzenio) is contraindicated or not tolerated; OR

4. The medication is being prescribed for Subsequent-line (3\textsuperscript{rd} 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. For the treatment of breast cancer in males (ribociclib [Kisqali], abemaciclib [Verzenio] only)
   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 recently 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 Verzenio arm and 986 in comparator ET arm) was reported, which exhibited significant improvement in IDFS for 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). At the time of IDFS analysis, the overall survival (OS) data was immature.

- Abemaciclib (Verzenio) was evaluated as a 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:
  i. MONARCH 3: Verzenio in Combination with an Aromatase Inhibitor. The trial evaluated postmenopausal women 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.

ii. MONARCH 2: 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.

1. 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 plus fulvestrant and 37.3 months for placebo plus fulvestrant (hazard ratio [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.

iii. MONARCH 1: Verzenio Administered as a Monotherapy in Metastatic Breast Cancer. The trial, a single-arm, open-label 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).

IV. Palbociclib (Ibrance): Ribociclib (Kisqali):

- Ribociclib (Kisqali) was evaluated in adult, female subjects with HR-positive, HER2-negative, advanced, or metastatic breast cancer. Please note, ribociclib (Kisqali) has NOT been evaluated in males.
- MONALEESA-2: Randomized, double-blind, placebo-controlled trial comparing ribociclib (Kisqali) in combination with letrozole versus placebo with letrozole. Subjects were treatment naïve for their disease. The outcomes were progression-free survival (PFS) and overall response rate (ORR), which were found to be statistically significant in favor of ribociclib (Kisqali) plus letrozole.
- MONALEESA-7: Kisqali in Combination with an Aromatase Inhibitor. 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).
  i. Overall survival data was reported in June 2019 and showed a hazard ratio (HR) of 0.712 (0.535-0.948; p=0.00973).
- MONALEESA-3: Randomized, double-blind, placebo-controlled study of ribociclib (Kisqali) in combination with fulvestrant for 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).
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.

V. **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.

- Abemaciclib (Verzenio) and palbociclib (Ibrance) 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. FDA-approved indication for ribociclib (Kisqali) is limited to use in the postmenopausal female population.
- 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.
- In the preoperative/adjuvant therapy setting, chemotherapy with or without HER2-targeted 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.
- 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).

VI. 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, CDK4/6 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 National Comprehensive Cancer Network (NCCN) notes a lack of data to support use of an additional CDK4/6 inhibitor after progression on a CDK4/6 regimen. As of September 2021, NCCN guidelines stated “If there is disease progression while on a CDK4/6 inhibitor, there is no data to support an additional line of therapy with another CDK4/6 inhibitor-containing regimen. Of note, those that are unable to tolerate other CDK4/6 inhibitors and are switching to palbociclib (Ibrance) prior to progression would be acceptable candidates for therapy.”

VII. 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

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*Washington State Rx Services is administered by moda HEALTH*
following: doxorubicin, paclitaxel, capecitabine, gemcitabine, cyclophosphamide, carboplatin, docetaxel, cisplatin, and combinations of these therapies.

VIII. 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.

IX. 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.

X. 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) notes a lack of data to support use of an additional CKD4/6 inhibitor after progression on a CDK4/6 regimen. As of September 2020, NCCN guidelines stated “If there is disease progression while on a CDK4/6 inhibitor, there is no data to support an additional line of therapy with another CDK4/6 inhibitor-containing regimen. Of note, those that are unable to tolerate other CDK4/6 inhibitors and are switching to palbociclib (Ibrance) prior to progression would be acceptable candidates for therapy.

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.
References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added add step through abemaciclib (Verzenio) and palbociclib (Ibrance) for Kisqali, effective 1/1/2022.</td>
<td>01/2022</td>
</tr>
<tr>
<td>Added expanded indication for Abemaciclib (Verzenio) for adjuvant therapy of high-risk early 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</td>
<td>11/2021</td>
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<td>Criteria created</td>
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<td>Verzenio</td>
<td>10/2019</td>
</tr>
<tr>
<td>Kisqali</td>
<td>04/2017</td>
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<tr>
<td>Ibrance</td>
<td>02/2015</td>
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<table>
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<tr>
<th>Previews reviews</th>
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<tr>
<td>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)</td>
<td>03/2020</td>
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<td>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 therapy, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2018)</td>
<td>10/2019</td>
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<tr>
<td>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)</td>
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| Transitioned criteria to policy format and merged into one policy | 12/2020 |

Addition of wording related to GnRH therapy to induce menopause in order to clarify the FDA approval for Kisqali in pre/perimenopausal setting | 08/2018 |

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<tr>
<td>Kisqali</td>
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<td>Ibrance</td>
<td>09/2017</td>
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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.

September 01, 2022
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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<td>cyproheptadine</td>
<td>4 mg tablets</td>
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<td>120 tablets/30 days</td>
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<td>cyproheptadine</td>
<td>2 mg/5mL</td>
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<td>1,200 mL/30 days</td>
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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, clonipramine, telmisartan, and benzodiazepeines. 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


Policy Implementation/Update:

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<td>Date Effective</td>
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<tr>
<td>Last Updated</td>
<td>May 2018</td>
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<td>Last Reviewed</td>
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<tr>
<td>Converted to policy</td>
<td>06/06/2019</td>
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<tr>
<td>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.</td>
<td>05/30/2018</td>
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<tr>
<td>Criteria update: Excluded samples and updated renewal language to general improvement.</td>
<td>1/11/2016</td>
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</table>
Cysteamine bitartrate (Cystagon®; Procysbi®)

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

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<tr>
<th>Product Name</th>
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<tbody>
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<td>cysteamine (Cystagon)</td>
<td>50 mg capsule</td>
<td>Nephropathic cystinosis</td>
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<tr>
<td></td>
<td>150 mg capsule</td>
<td></td>
<td>1.95 g/m²/day</td>
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<tr>
<td>cysteamine (Procysbi)</td>
<td>25 mg DR capsule</td>
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<td>60 capsules/30 days</td>
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<td></td>
<td>75 mg DR capsule</td>
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<td>1.95 g/m²/day</td>
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<tr>
<td></td>
<td>75 mg DR granule packet</td>
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<td>1.95 g/m²/day</td>
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<tr>
<td></td>
<td>300 mg DR granule packet</td>
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Initial Evaluation
I. Cysteamine bitartrate (Cystagon; Procysbi) may be considered medically necessary when the following criteria 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. If Procysbi is requested, documentation member has an intolerance, or contraindication to, 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 does not exceed 1.95 g per m² 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; **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 is responding positively to therapy as evidenced by improvement in the leukocyte cystine concentration within the past 3 months; **AND**

V. If request is for a dose increase, new dose does not exceed 1.95 g per m² 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 nephropathic cystinosis, intermediate cystinosis and non-nephropathic (or ocular) cystinosis. Corneal cystine crystal accumulation may present in all three types of cystinosis. Therapy 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). Topical 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 CNTS gene mutation, or demonstration of cystine corneal crystals by the slit lamp examination.

III. The immediate-release preparation of cysteamine bitartrate is the most commonly 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.

IV. 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.

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


Policy Implementation/Update:

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<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of Procysbi granule packets</td>
<td>04/2020</td>
</tr>
<tr>
<td>Policy created</td>
<td>11/2019</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>cysteamine (Cystaran)</td>
<td>0.44% ophthalmic solution</td>
<td>Corneal cystine crystals</td>
<td>60 mL (4 bottles)/28 days</td>
</tr>
<tr>
<td>cysteamine (Cystadrops)</td>
<td>0.37% ophthalmic solution</td>
<td></td>
<td>20 mL (4 bottles)/28 days</td>
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</tbody>
</table>

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

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. 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

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of new formulation, Cystadrops</td>
<td>01/2021</td>
</tr>
<tr>
<td>Policy created</td>
<td>11/2019</td>
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</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivacaftor (Kalydeco)</td>
<td>150 mg tablet</td>
<td>Cystic fibrosis, one mutation in the CFTR gene that is responsive to ivacaftor</td>
<td>56 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>25 mg/packet oral granules</td>
<td></td>
<td>56 packets/28 days</td>
</tr>
<tr>
<td></td>
<td>50 mg/packet oral granules</td>
<td></td>
<td>56 packets/28 days</td>
</tr>
<tr>
<td></td>
<td>75 mg/packet oral granules</td>
<td></td>
<td>56 packets/28 days</td>
</tr>
<tr>
<td>Ivacaftor/lumacaftor (Orkambi)</td>
<td>125/200 mg tablet</td>
<td>Cystic fibrosis, homozygous for F508del mutation</td>
<td>112 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>125/100 mg tablet</td>
<td></td>
<td>112 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>125/100 mg oral granule packet</td>
<td></td>
<td>56 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>188/150 mg oral granule packet</td>
<td></td>
<td>56 tablets/28 days</td>
</tr>
<tr>
<td>Ivacaftor/tezacaftor (Symdeko)</td>
<td>Kit: (ivacaftor; ivacaftor/tezacaftor) 150mg; 150/100mg</td>
<td>Cystic fibrosis, homozygous F508del mutation or at least one mutation in the CFTR gene that is responsive to ivacaftor/tezacaftor</td>
<td>56 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>Kit: (ivacaftor; ivacaftor/tezacaftor) 75mg; 75/50 mg</td>
<td></td>
<td>56 tablets/28 days</td>
</tr>
<tr>
<td>Elexacaftor/tezacaftor/ivacaftor (Trikafta)</td>
<td>Kit (elexacaftor/tezacaftor/ivacaftor) 100/50/75mg; 150 mg</td>
<td>Cystic fibrosis, one F508del mutation or at least mutation if the CFTR gene that is responsive</td>
<td>84 tablets/28 days</td>
</tr>
</tbody>
</table>

*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 four months 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)
      2. For ivacaftor/lumacaftor (Orkambi):
         i. The member is two years 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)
      4. For elexacaftor/tezacaftor/ivacaftor (Trikafta):
         i. The member is six 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. Ivacaftor (Kalydeco) has been evaluated in several clinical trials. 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.

IV. Efficacy and safety of ivacaftor (Kalydeco) was also evaluated in 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.

V. Efficacy and safety of ivacaftor (Kalydeco) was evaluated in patients with R117H mutation which showed a statistically significant change from baseline in FEV1 and CFQ-R score.

VII. 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.

VIII. The efficacy and safety of ivacaftor/lumacaftor (Orkambi) was evaluated in patients homozygous for the F508del mutation in the CFTR gene. Two trials evaluated patients 12 years of age or older. Primary efficacy endpoint was change from baseline in FEV1 and the results were statistically significant in both trials. Secondary endpoints included body weight, CFQ-R Respiratory Domain score, and the number of pulmonary exacerbations through week 24; however, with hierarchical testing, none of these were statistically significant.

IX. 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 (CI 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 age 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.

X. Elexacaftor/tezacaftor/ivacaftor (Trikafta) was evaluated in two trials in subjects 12 years of age and older with a primary outcome of percent predicted forced expiratory volume in one second (ppFEV1):
- Trial 1: 24-week, randomized, double-blind, placebo-controlled trial (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 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 compared to Symdeko was seen in this trial.

XI. Elexacaftor/tezacaftor/ivacaftor (Trikafta) was also evaluated in a 24-week phase 3 open label, multicenter study, which 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.

XII. Statistical and clinical improvement in sweat chloride, body mass index, and reduction in pulmonary exacerbations occurred in the first trial. As of November 2019, the medication was being evaluated for safety and efficacy in patients down to six years of age. Additionally, the manufacturer has stated a plan to evaluate in patients younger than six years of age; however, clinical trials have not yet been started.

XIII. 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

10. A study to evaluate the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in subjects with cystic fibrosis who are less than 24 months of age and have a CFTR gating mutation. 2017. ClinicalTrials.gov (Identifier NCT02725567).
13. Vertex Press Release, April 30, 2019. Investor Relations News and Events. FDA approved Kalydeco (ivacaftor) as first and only CFTR modulator to treat eligible infants with CF as early as six months of age. Available at: Washington State Rx Services is administered by moda HEALTH

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September 01, 2022
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 Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated age for Trikafta with new FDA approval. Updated links to the PI to reflect a link to each manufacturer page</td>
<td>08/2021</td>
</tr>
<tr>
<td>Updated CFTR gene mutation indications with new <em>in vitro</em> data, adding additional attestation and PI for verification to that mutation.</td>
<td>02/2021</td>
</tr>
<tr>
<td>Kalydeco age requirement updated to four months of age (previous six) based on updated FDA-approval.</td>
<td>10/2020</td>
</tr>
<tr>
<td>New FDA-approved therapy, Trikafta, added to the policy. Grammatical changes and formatting edits.</td>
<td>02/2020</td>
</tr>
<tr>
<td>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.</td>
<td>06/2019</td>
</tr>
<tr>
<td>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.</td>
<td>09/2018</td>
</tr>
<tr>
<td>Updated criteria to new format, removed question assessing liver enzymes levels, added references, added question regarding combination therapy with other CFTR modulating medications.</td>
<td>05/2018</td>
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<tr>
<td>Symdeko criteria created.</td>
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<tr>
<td>Criteria update: Excluded samples and updated renewal language to general improvement.</td>
<td>01/2016</td>
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<tr>
<td>Policy created</td>
<td>02/2012</td>
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</tbody>
</table>
Policy Type: PA/SP

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: Three months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>dalfampridine ER (Ampyra)</td>
<td>10 mg tablets</td>
<td>Improve walking in patients with multiple sclerosis</td>
<td>60 tablets/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Dalfampridine ER (Ampyra) may be considered medically necessary when the following criteria below are met:
   A. Member must be 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 CrCl >50 mL/min; AND
      3. Member must be able to ambulate; AND
      4. Member must currently be receiving a disease modifying therapy for multiple sclerosis (i.e. glatiramer acetate, dimethyl fumarate, interferon beta-1a, etc.); 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 demonstrated disease stability or lack of disease progression (e.g. improvement in walking distance); **AND**

II. If request is for brand Ampyra, documentation of treatment with generic dalfampridine ER has been ineffective, contraindicated, or not tolerated

Supporting Evidence

I. 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.

II. Use of dalfampridine ER (Ampyra) is contraindicated in a patient with a prior history of seizure. Seizures have been reported in patients with no history of seizure. Permanent discontinuation is advised if seizures occur.

III. Use of dalfampridine ER (Ampyra) is contraindicated in patients with a CrCl less than 50 mL/min. Minor renal impairment (CrCl 51 to 80 mL/min) may increase risk of seizures.

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

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added requirement to trial generic dalfampridine ER prior to branded Ampyra on continuation</td>
<td>05/2022</td>
</tr>
<tr>
<td>Transitioned criteria to policy</td>
<td>10/2019</td>
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<tr>
<td>Previous reviews</td>
<td></td>
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<td></td>
<td>10/2011;</td>
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<td></td>
<td>05/2013;</td>
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<tr>
<td></td>
<td>01/2016;</td>
</tr>
<tr>
<td></td>
<td>11/2018;</td>
</tr>
</tbody>
</table>

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.
darolutamide (Nubeqa™), apalutamide (Erleada™),
enzalutamide (Xtandi®), abiraterone (Zytiga®, Yonsa®)

UMP POLICY

Policy Type: PA/SP
Pharmacy Coverage Policy: UMP081

Split Fill Management (Only Applies to enzalutamide [Xtandi], and
abiraterone [Zytiga, Yonsa])*

Description
Darolutamide (Nubeqa), apalutamide (Erleada), and enzalutamide (Xtandi) are orally administered
androgen receptor inhibitors. Abiraterone (Zytiga, Yonsa) is an androgen biosynthesis inhibitor of CYP17.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>darolutamide (Nubeqa)</td>
<td>Prostate cancer, non-metastatic,</td>
<td>300 mg tablets</td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>castration resistant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>apalutamide (Erleada)</td>
<td>Prostate cancer, non-metastatic,</td>
<td>60 mg tablets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>castration resistant</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prostate cancer, metastatic,</td>
<td>40 mg capsules</td>
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<td>castration-sensitive</td>
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<tr>
<td>enzalutamide (Xtandi)</td>
<td>Prostate cancer, castration resistant</td>
<td>40 mg tablets</td>
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<td></td>
<td>Prostate cancer, metastatic,</td>
<td>80 mg tablets</td>
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<td></td>
<td>castration-sensitive</td>
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<tr>
<td>abiraterone (Yonsa)</td>
<td>Prostate cancer, metastatic,</td>
<td>125 mg tablets</td>
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</tr>
<tr>
<td></td>
<td>castration-resistant, in combination</td>
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</tr>
<tr>
<td></td>
<td>with methylprednisolone</td>
<td></td>
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<tr>
<td>abiraterone (generic Zytiga)</td>
<td>Prostate cancer, metastatic,</td>
<td>250 mg tablets</td>
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<td></td>
<td>castration-resistant, in combination</td>
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<tr>
<td></td>
<td>with prednisone</td>
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<tr>
<td>abiraterone (Zytiga)</td>
<td>Prostate cancer, metastatic,</td>
<td>250 mg tablets</td>
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<tr>
<td></td>
<td>castration-sensitive, in combination</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>with prednisone</td>
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<td></td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga,
Yonsa) may be considered medically necessary when the following criteria below are met:

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.

September 01, 2022
A. The 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. The member has not previously progressed on darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), OR abiraterone (Zytiga, Yonsa); AND
D. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa) will not be used in combination with any other oncolytic medication with the exception of hormone suppressive therapy outlined below; AND
E. The member has either had a bilateral orchiectomy OR ongoing hormone suppression (e.g., GnRH therapy) will be used concurrently; AND
F. A diagnosis of one of the following:
   1. **Non-metastatic castration resistant prostate cancer**, defined by evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; AND
      i. The member has a PSA-doubling time of 10 months or less during continuous androgen-deprivation therapy or after bilateral orchiectomy; AND
      ii. One of the following is prescribed: darolutamide (Nubeqa), apalutamide (Erleada), OR enzalutamide (Xtandi); OR
   2. **Metastatic castration resistant prostate cancer**, defined by evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; AND
      i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; OR
      ii. The request is for generic abiraterone 500 mg tablets; AND
         a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); OR
         b. If the request is for abiraterone (Zytiga) or abiraterone (Yonsa), will be used in combination with prednisone; OR
   3. **Metastatic castration sensitive or castration naïve prostate cancer**; AND
      i. For generic abiraterone:
         a. The member has at least TWO of the following risk factors:
            i. Gleason Score ≥ 7 (Grade Group > 2)
            ii. Bone lesions
            iii. Presence of measurable visceral metastases; AND
         b. Will be used in combination with prednisone; AND
         c. The request is for generic abiraterone 250 mg tablets; OR
i. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); OR

ii. For BRAND abiraterone (Zytiga), apalutamide (Erleada), or enzalutamide (Xtandi):
   a. The member has at least TWO of the following risk factors:
      i. Gleason Score ≥ 7 (Grade Group ≥ 2)
      ii. Bone lesions
      iii. Presence of measurable visceral metastases; AND
   b. The member must have had inadequate response, intolerance, or contraindication to generic abiraterone (Note: if criteria is met for generic abiraterone, use of the 250 mg tablets will be required); AND
   c. If the request is for abiraterone (Zytiga), will be used in combination with prednisone

II. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), and abiraterone (Zytiga, Yonsa) are considered investigational when used for all other conditions, including but not limited to:
   A. Cushing’s Syndrome
   B. Breast cancer
   C. Hepatocellular carcinoma
   D. Fallopian tube, ovarian, or uterine 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 or urologist; AND

IV. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa) will not be used in combination with any other oncolytic medication with the exception of hormone suppressive therapy outlined below; AND

V. The member has either had a bilateral orchiectomy OR ongoing hormone suppression (e.g., GnRH therapy) will be used concurrently; AND

VI. The member has experienced a response to therapy (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); AND
   1. Non-metastatic castration resistant prostate cancer;
      i. The request is for one of the following: darolutamide (Nubeqa), apalutamide (Erleada), OR enzalutamide (Xtandi); OR
   2. Metastatic castration resistant prostate cancer;
3. **Metastatic castration sensitive prostate cancer;**
   i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
   a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
   b. Will be used in combination with prednisone

   ii. The request is for brand abiraterone (Zytiga) plus prednisone **OR** brand abiraterone (Yonsa) plus methylprednisolone; **AND**
      a. The member has an intolerance or contraindication to generic abiraterone (use of 250 mg tablets required); **OR**
      b. The member has had inadequate response, intolerance, or contraindication to generic abiraterone (use of 250 mg tablets required); **AND**

   iii. The request is for enzalutamide (Xtandi) or apalutamide (Erleada); **OR**

   iv. The request is for enzalutamide (Xtandi); **OR**

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**Supporting Evidence**

I. Prostate cancer therapies have been evaluated for safety and efficacy in adults. There are multiple treatment modalities with the direction of therapy depending 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.

II. Many treatment options exist and initial and further line therapy are contingent upon patient specific characteristics. These options include, but are not limited to, radiation therapy, prostatectomy, androgen deprivation pharmacotherapy, bilateral orchiectomy, chemotherapy, abiraterone (Zytiga, Yonsa), or androgen receptor inhibitors (e.g., enzalutamide (Xtandi), darolutamide (Nubeqa), apalutamide (Erleada)). Multi-modal therapy, such as abiraterone or enzalutamide with ADT, is commonly utilized; however, abiraterone and/or androgen receptor inhibitor combinations have not been evaluated for safety and efficacy to date. Continuation of ADT is commonly employed and is recommended as concomitant therapy as discontinuation of GnRH agonists are likely to result in an increase in serum testosterone and disease progression.

III. Use of androgen receptor inhibitor (e.g., darolutamide [Nubeqa], apalutamide [Erleada], enzalutamide [Xtandi]) therapy after disease progression on abiraterone, or vice versa (i.e., abiraterone/androgen receptor inhibitor crossover therapy), has not yet been evaluated for safety and efficacy in quality clinical trials. One retrospective trial evaluating enzalutamide after...
treatment with abiraterone showed that very few patients (10% or less) had a significant decrease in PSA with enzalutamide therapy. A retrospective case series showed a similar lack of efficacy in regards to abiraterone after enzalutamide (Xtandi). Additionally, there are studies to suggest cross resistance between the two therapies.

IV. Non-metastatic castration resistant prostate cancer: darolutamide (Nubeqa), apalutamide (Erleada), and enzalutamide (Xtandi) are the androgen receptor inhibitors that have been evaluated in this stage of disease. Concurrent treatment with steroids is not required. Patients in the trials for each of these medications had a prostate-specific antigen doubling time of 10 months or less and received GnRH therapy concurrently. Each therapy was evaluated in a double-blind, placebo-controlled trial.

- Darolutamide (Nubeqa) was evaluated in the ARAMIS TRIAL. The primary outcome, metastasis free survival (MFS), showed a statistical significance over placebo (40 vs 18 months, p<0.001). Apalutamide (Erleada) was evaluated in the SPARTAN trial, MFS was statistically significant compared to placebo (40 vs 16 months), and enzalutamide (Xtandi) was evaluated in the PROSPER trial. The MFS was significant compared to placebo (37 months vs 15 months).
- Darolutamide (Nubeqa) does not cross the blood brain barrier; thus, may offer an improved safety profile compared to enzalutamide and even apalutamide (Erleada). There were low rates of fatigue, falls, fractures, and seizures; however, head-to-head trials have not yet been conducted and caution should be used when comparing across trials to make treatment decisions.

V. Metastatic, castration resistant prostate cancer: enzalutamide (Xtandi) and abiraterone (Zytiga, Yonsa) have been evaluated for safety and efficacy. Enzalutamide (Xtandi) versus placebo was evaluated in those that had previously been treated with chemotherapy and those that were chemotherapy naïve. Overall survival was prolonged in both settings. Abiraterone (Zytiga, Yonsa) plus prednisone has also shown prolonged survival in this setting in those that have been previously treated with chemotherapy and those chemotherapy naïve. Head-to-head trials have not been completed to provide insight to superior therapy between abiraterone (Zytiga, Yonsa) and enzalutamide (Xtandi). Abiraterone (Zytiga, Yonsa) is indicated in combination with prednisone; however, enzalutamide has safety concerns including CNS toxicities and seizures. Additionally, abiraterone (Zytiga, Yonsa) has generic availability.

VI. Metastatic high-risk castration sensitive prostate cancer: abiraterone (Zytiga, Yonsa) plus prednisone has been evaluated for safety and efficacy. High risk disease was defined as having at least two of the following three risk factors: Gleason score eight or greater, presence of three or more bone lesions, evidence of measurable visceral metastases. Overall survival over placebo was shown to be statistically significant for abiraterone (Zytiga, Yonsa). Although both strengths (250 mg and 500 mg) of abiraterone (Zytiga) are available in generic formulations, the 500 mg tablet remains at a significantly higher cost (40x greater) than the 250 mg tablet. Thus, use of generic abiraterone 250 mg is required over abiraterone 500 mg tablet. Apalutamide (Erleada) was evaluated in the metastatic, castration sensitive prostate cancer setting in combination with ADT versus ADT alone. This was not specifically in high risk disease; however, 93% of subjects had a Gleason Score of seven or greater, and all subjects had bone metastases. Fifty-five percent of subjects had bone only metastases, and the remaining had additional metastases. Primary outcomes were radiographic progression free survival, which
were statistically and clinically significant favoring apalutamide (Erleada). Head-to-head trials against abiraterone (Zytiga) have not occurred in this setting; however, the safety profile of abiraterone is further established at this time.

IX. Enzalutamide (Xtandi) was evaluated in metastatic, castration sensitive, prostate cancer in combination with ADE versus ADT alone. This study was not specifically in high risk disease; however, the majority of subjects (> 67%) had a Gleason score of 8 or greater – nearly 85% had bone metastases or bone and other metastases. Progression-free survival was 19 months for placebo plus ADT and was not reached for enzalutamide (Xtandi). Radiographic progression was experienced by 13.8% of those receiving enzalutamide (Xtandi) and 32.6% for placebo plus ADT. Head-to-head trials against abiraterone have not occurred in this setting; however, abiraterone provides a better value for the treatment of mCSPC at this time. Additionally, enzalutamide (Xtandi) was evaluated in a Phase III open-label trial in addition to ADT versus ADE alone in those that were castration naïve. The primary endpoint of OS was statistically significant in a group of 125 subjects (HR for death: 0.67, CI 0.52-0.86, p=0.002).

Investigational or Not Medically Necessary Uses

I. Therapies in this policy are being evaluated in other conditions; however, quality data indicating safety and efficacy in the following settings are not yet available:
   A. Cushing’s Syndrome
   B. Breast cancer
   C. Hepatocellular carcinoma
   D. Fallopian tube, ovarian, or uterine 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Require clinical rationale for use of generic abiraterone 500 mg instead of generic 250 mg</td>
<td>05/2022</td>
</tr>
<tr>
<td>Addition of Grade Group referenced with Gleason Score</td>
<td>05/2021</td>
</tr>
<tr>
<td>Additional of newly approved enzalutamide (Xtandi) 40 mg and 80 mg tablets</td>
<td>11/2020</td>
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<tr>
<td>Addition of enzalutamide (Xtandi) for castration sensitive prostate cancer given new FDA-approved indication. Removal of requirement upon renewal to change to generic abiraterone. Consolidation of requirements for agents in the setting of castration sensitive prostate cancer to streamline policy. Formatting updates</td>
<td>12/2019</td>
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<tr>
<td>Darolutamide (Nubeqa) new agent available, criteria converted to policy, and all agents combined into one policy. Requirement of generic abiraterone added unless contraindicated or not tolerated. Addition of use of GnRH therapy in metastatic castration sensitive disease included. Yonsa brand added. Erleada now FDA approved for castration sensitive disease.</td>
<td>08/2019</td>
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<tr>
<td>Generic abiraterone requirement added prior to use of branded 250 mg.</td>
<td>12/2018</td>
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<tr>
<td>Enzalutamide new indication of non-metastatic resistant prostate cancer added. Clinical notes added and appropriate routing through criteria.</td>
<td>08/2018</td>
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<tr>
<td>Apalutamide (Erleada) criteria created</td>
<td>04/2018</td>
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<tr>
<td>Abiraterone new indication of metastatic, high-risk castration sensitive prostate cancer added. LATITUDE trial information incorporated as well.</td>
<td>02/2018</td>
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<tr>
<td>Enzalutamide (Xtandi) criteria created</td>
<td>02/2018</td>
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<tr>
<td>Abiraterone (Zytiga) criteria created</td>
<td>09/2011</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
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<tbody>
<tr>
<td>dasatinib (Sprycel)</td>
<td>20 mg tablets</td>
<td>Philadelphia chromosome-positive (Ph+) Chronic myeloid leukemia (CML)/ Ph+ Acute lymphoblastic leukemia (ALL)</td>
<td>90 tablets/30 days</td>
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<tr>
<td></td>
<td>50 mg tablets</td>
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<td>30 tablets/30 days</td>
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<tr>
<td></td>
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<td>30 tablets/30 days</td>
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<td></td>
<td>100 mg tablets</td>
<td>Chronic phase CML</td>
<td>30 tablets/30 days</td>
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<tr>
<td></td>
<td>70 mg tablets</td>
<td>Gastrointestinal Stromal Tumors (GIST)</td>
<td>60 tablets/30 days</td>
</tr>
</tbody>
</table>

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
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

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*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.*

September 01, 2022
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 imatinib 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>02/2019</td>
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<td>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.</td>
<td>01/2018</td>
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<td>Previous Reviews</td>
<td>03/2017</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>decitabine/cedazuridine</td>
<td>35/100 mg tablet</td>
<td>Myelodysplastic Syndrome (MDS); Chronic myelomonocytic leukemia (CMML)</td>
<td>5 tablets/28 days</td>
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<td>(Inqovi)</td>
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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 hematopoesis 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 as 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.
References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>11/2020</td>
</tr>
</tbody>
</table>
Deflazacort (Emflaza) is an orally administered corticosteroid prodrug whose active metabolite exerts anti-inflammatory and immunosuppressive effects.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>deflazacort</td>
<td>6 mg tablets</td>
<td>Duchenne Muscular Dystrophy</td>
<td>0.9 mg/kg/day (round to nearest tablet size)</td>
</tr>
<tr>
<td></td>
<td>18 mg tablets</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>30 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>36 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.75 mg/mL oral suspension</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Deflazacort (Emflaza) 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. The member has a diagnosis of Duchenne Muscular Dystrophy (DMD); AND
      1. Member’s diagnosis has been confirmed by dystrophin genetic testing; AND
      2. Member is two years of age or older; AND
      3. Treatment with oral prednisone for six months or greater has been ineffective, is contraindicated, or not tolerated; AND
      4. Member’s current weight is documented

II. Deflazacort (Emflaza) is 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)
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 symptom improvement and/or stability of disease (e.g. improvements/preservation of muscle strength, pulmonary, and/or orthopedic function)

Supporting Evidence

I. 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 may still be confirmed by muscle biopsy and dystrophin analysis.

II. 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).
   - 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.

III. 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 found to not be statistically significant.

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.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>05/2020</td>
</tr>
<tr>
<td>Event</td>
<td>Date</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Revised to policy format, include use in pediatric patients down to two years of age.</td>
<td>07/2019</td>
</tr>
<tr>
<td>Update to criteria</td>
<td>01/2017</td>
</tr>
<tr>
<td>Criteria creation</td>
<td>05/2017</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Strips</td>
<td>Test Strips</td>
<td>Type 1 and type 2 diabetes mellitus</td>
<td>300 test strips/30 days</td>
</tr>
<tr>
<td>Glucometers</td>
<td></td>
<td></td>
<td>One meter/365 days</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>FreeStyle Lite, FreeStyle Freedom Lite, Contour Next, Contour Next EZ, and Contour Next One</th>
</tr>
</thead>
<tbody>
<tr>
<td>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:</td>
</tr>
</tbody>
</table>

- **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: N/A. Use pharmacy or phone options above
  - Abbott: 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, 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, 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:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rearranged questions to better capture intent and clarify path to coverage. Updated Glucometer table to more accurate billing information and website information</td>
<td>02/2022</td>
</tr>
<tr>
<td>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.</td>
<td>01/2021</td>
</tr>
<tr>
<td>Updated requirements language to be more consistent with plan’s standard language. Adjusted order of requirements to enhance clarity.</td>
<td>12/2020</td>
</tr>
<tr>
<td>Criteria transitioned into policy with medically not necessary and renewal evaluation sections added.</td>
<td>01/2020</td>
</tr>
<tr>
<td>Criteria created</td>
<td>01/2016</td>
</tr>
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</table>
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP121

Description
Dichlorphenamide (Keveyis®) is a carbonic anhydrase inhibitor; however, the mechanism by which dichlorphenamide (Keveyis®) exerts its therapeutic effects in periodic paralysis is unknown.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>dichlorphenamide</td>
<td>Primary periodic paralysis</td>
<td>50 mg tablets</td>
<td>120 tablets/30 days</td>
</tr>
</tbody>
</table>

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. 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:

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.
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.

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.

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 have 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 than other therapies that could be utilized. Given these factors dichlorphenamide (Keveyis) is not medically necessary for treatment of glaucoma.

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

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>07/2022</td>
</tr>
<tr>
<td>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.</td>
<td>12/2019</td>
</tr>
<tr>
<td>Policy created</td>
<td>09/2015</td>
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</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>dornase alfa (Pulmozyme)</td>
<td>2.5 mg/2.5 mL single-use ampule</td>
<td>Cystic fibrosis</td>
<td>30 single-use ampule/ 30 days</td>
</tr>
</tbody>
</table>

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 (Bethikis; 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

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.

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Updated criteria to policy format</td>
<td>11/2019</td>
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Policy Implementation/Update:

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<tr>
<td>Date Created</td>
<td>10/6/2017</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>droxidopa (Northera)</td>
<td>100 mg capsules</td>
<td>neurogenic orthostatic hypotension (nOH)</td>
<td>90 capsules /30 days</td>
</tr>
<tr>
<td></td>
<td>200 mg capsules</td>
<td></td>
<td>180 capsules /30 days</td>
</tr>
<tr>
<td></td>
<td>300 mg capsules</td>
<td></td>
<td>180 capsules/30 days</td>
</tr>
</tbody>
</table>

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**

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.

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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, light-headedness, 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


Policy Implementation/Update:

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<th>Date</th>
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<td>04/2021</td>
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<tr>
<td>Updated criteria to policy format; Added age limit, added attempted at least one non-pharmacologic intervention criteria</td>
<td>11/2019</td>
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<td>Policy created</td>
<td>11/2014</td>
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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: 12 months
• Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
</table>
| dupilumab    | Asthma (moderate to severe) | 100mg/0.67mL 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 |
|              | Atopic Dermatitis (moderate to severe); Atopic Dermatitis (moderate to severe) and comorbid Asthma (Moderate to severe) | 200 mg/1.14mL pen injector or prefilled syringe | Pediatric (6-11 years of age): 
No Loading Dose 
Maintenance: 
• 15 to less than 30 kg: 2 (100mg/0.67mL) syringes (1.34mL)/28 days; OR 1 (300mg/2mL) syringes/pens (2mL)/28 days 
• 30 kg or more: 2 (200mg/1.14mL) syringes/pens (2.28mL)/28 days |

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: 3 (200mg) syringes/pens (2.28 mL)/28 days 
• 60 kg or more: 3 (300mg) syringes/pens (4 mL)/28 days 
Maintenance: 
• 15 to less than 30 kg: 1 (300mg) syringes/pens (2 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.
### Initial Evaluation

I. **Dupilumab (Dupixent)** may be considered medically necessary when the following criteria below are met:
   - 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**
   - Must not be used in combination with another monoclonal antibody (e.g., benralizumab, mepolizumab, omalizumab, reslizumab, etc.); **AND**
   - A diagnosis of one of the following:
     1. **Atopic dermatitis (moderate to severe); AND**
        - Member is six months of age or older; **AND**
        - Body surface area (BSA) involvement of at least 10%; **OR**
        - Involves areas of the face, head, neck, hands, feet, groin, or intertriginous areas require documentation of severity; **AND**
        - Treatment with at least **two** of the following groups has been ineffective or not tolerated, unless ALL are contraindicated:
           - Group 1: Topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
           - Group 2: Topical calcineurin inhibitors (e.g. pimecrolimus cream, tacrolimus ointment)
           - Group 3: Topical PDE-4 inhibitors (e.g. crisaborole [Eucrisa]); **OR**
     2. **Asthma (moderate to severe); AND**
        - Member is 6 years of age or older;
        - Member has MODERATE asthma as defined by one of the following:

### Adult Dosage

<table>
<thead>
<tr>
<th>Condition</th>
<th>300 mg/2mL pen injector or prefilled syringe</th>
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</thead>
<tbody>
<tr>
<td>Chronic rhinosinusitis with nasal polyps</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td></td>
</tr>
</tbody>
</table>

- **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

- 2 (300mg) syringes/pens (4 mL)/28 days

- 4 (300mg) syringes/pens (8mL)/28 days

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*September 01, 2022*
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 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  

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  

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September 01, 2022
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. 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 12 years 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/mm², 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)

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
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:
   A. **Atopic dermatitis (moderate to severe); AND**
      Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, BSA involvement, pruritis symptoms);
      OR
   B. **Asthma (moderate to severe); AND**
      1. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **AND**
      2. Background controller medications (e.g., ICS/LABA product listed above) will be continued with the use of dupilumab (Dupixent), unless contraindicated; **OR**
   D. **Chronic rhinosinusitis with nasal polyposis (CRSwNP); AND**
      1. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in nasal congestion/obstruction severity, reduction in nasal polyps);
      **AND**
      2. 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**
   E. **Eosinophilic Esophagitis; AND**
      1. Member has exhibited improvement or stability of disease (e.g., improvement in dysphagia/vomiting/abdominal pain, reduction in eosinophils)

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, and as an add-on maintenance treatment for adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

II. The duration of initial approval at six months is derived from the evidence reported in the ICER reports for atopic dermatitis and asthma, as well as the dupilumab (Dupixent) trials for chronic rhinosinusitis with nasal polyposis, whose results were reported at 24 weeks (six months).
III. 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.

IV. **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.

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>Trial 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUPIXENT 300 mg Q2W</td>
<td>PBO</td>
<td>DUPIXENT 300 mg Q2W</td>
<td>PBO</td>
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<tr>
<td>N=224</td>
<td>N=224</td>
<td>N=233</td>
<td>N=236</td>
</tr>
<tr>
<td>% of patients with IGA 0 or 1</td>
<td>38%</td>
<td>10%</td>
<td>36%</td>
</tr>
<tr>
<td>% of patients with EASI-75</td>
<td>51%</td>
<td>15%</td>
<td>44%</td>
</tr>
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- **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.

<table>
<thead>
<tr>
<th>&lt;30 kg</th>
<th>&gt;30 kg</th>
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<tbody>
<tr>
<td>PBO + TCS N=61</td>
<td>Q4W + TCS N=63</td>
</tr>
<tr>
<td>13.1%</td>
<td>29.5%</td>
</tr>
<tr>
<td>p&lt;0.05</td>
<td>20.6%</td>
</tr>
<tr>
<td>PBO + TCS N=62</td>
<td>Q4W + TCS N=61</td>
</tr>
<tr>
<td>9.7%</td>
<td>36.1%</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>% of patients with IGA 0 or 1</td>
<td>% of patients with EASI-75</td>
</tr>
<tr>
<td>27.9%</td>
<td>75.4%</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
<td>60.3%</td>
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<tr>
<td>p&lt;0.0001</td>
<td>25.8%</td>
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<tr>
<td>p&lt;0.0001</td>
<td>63.9%</td>
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<td>p&lt;0.0001</td>
<td>74.6%</td>
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- **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 AD 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).

V. 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, 300 mg, 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 300 mg 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
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.

VI. **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 furoate 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.

VII. **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.

<table>
<thead>
<tr>
<th></th>
<th>Part A</th>
<th>Part B</th>
<th>Placebo</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-primary Endpoints</td>
<td>Dupixent 300mg QW</td>
<td>Placebo</td>
<td>Dupixent 300mg QW</td>
<td>Dupixent 300mg Q2W</td>
</tr>
<tr>
<td></td>
<td>N = 42</td>
<td>N = 39</td>
<td>N = 80</td>
<td>N = 81</td>
</tr>
<tr>
<td>Proportion of subjects achieving histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf), n (%)</td>
<td>25* (59.5)</td>
<td>2 (5.1)</td>
<td>47* (58.5)</td>
<td>49* (60.5)</td>
</tr>
<tr>
<td>Absolute change from baseline in DSQ score, LS mean (SE)</td>
<td>-21.9* (2.5)</td>
<td>-9.6 (2.8)</td>
<td>-23.8* (1.9)</td>
<td>-14.4 (1.86)</td>
</tr>
</tbody>
</table>

*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, peanut/tree nut, 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...
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.

Underlying and Eosinophilic Esophagitis (EoE)

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 sucralfose) 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.

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

<table>
<thead>
<tr>
<th>Potency Group</th>
<th>Corticosteroid</th>
<th>Vehicle type/form</th>
<th>Brand names</th>
<th>Available strength(s), percent (except as noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Super-high potency</td>
<td>Betamethasone dipropionate, augmented</td>
<td>Gel, lotion, ointment (optimized)</td>
<td>Diprolene</td>
<td>0.05</td>
</tr>
<tr>
<td>(Group 1)</td>
<td>Clobetasol propionate</td>
<td>Cream, gel, ointment, solution (scalp)</td>
<td>Temovate</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cream, emollient base</td>
<td>Temovate E</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lotion, shampoo, spray aerosol</td>
<td>Clobex</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Foam aerosol</td>
<td>Olux-E, Tovet</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solution (scalp)</td>
<td>Cormax</td>
<td>0.05</td>
</tr>
<tr>
<td>Fluocinonide</td>
<td>Cream</td>
<td></td>
<td>Vanos</td>
<td>0.1</td>
</tr>
<tr>
<td>Flurandrenolide</td>
<td>Tape (roll)</td>
<td></td>
<td>Cordran</td>
<td>4 mcg/cm^2</td>
</tr>
<tr>
<td>Halobetasol propionate</td>
<td>Cream, lotion, ointment</td>
<td></td>
<td>Ultravate</td>
<td>0.05</td>
</tr>
<tr>
<td>High potency</td>
<td>Amcinonide</td>
<td>Ointment</td>
<td>Cyclocort, Amcort</td>
<td>0.1</td>
</tr>
<tr>
<td>(Group 2)</td>
<td>Betamethasone dipropionate</td>
<td>Ointment</td>
<td>Diprostone</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cream, augmented formulation (AF)</td>
<td>Diprolene AF</td>
<td>0.05</td>
</tr>
<tr>
<td>High potency (Group 3)</td>
<td>Medium potency (Group 4)</td>
<td>Lower-mid potency (Group 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>-------------------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clobetasol propionate</td>
<td>Cream Impoyz 0.025</td>
<td>Betamethasone dipropionate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desoximetasone</td>
<td>Cream, ointment, spray</td>
<td>Lotion Bryhali 0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gel Topicort 0.25</td>
<td>Betamethasone dipropionate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diflorsone diacetate</td>
<td>Ointment ApexiCon¶, Florone¶ 0.05</td>
<td>Spray Sernivo 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluocinonide</td>
<td>Cream, gel, ointment, solution Lidex¶ 0.05</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Halcinonide</td>
<td>Cream, ointment, solution Halog 0.1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Halobetasol propionate</td>
<td>Lotion Bryhali 0.01</td>
<td>Fluocinolone acetonide</td>
<td></td>
<td></td>
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<tr>
<td>High potency (Group 3)</td>
<td></td>
<td>Aristocort HP¶, Kenalog¶, Triderm 0.5</td>
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<tr>
<td>Amcinonide</td>
<td>Cream Cyclocort¶, Amcort¶ 0.1</td>
<td>Betamethasone dipropionate</td>
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<tr>
<td>Betamethasone dipropionate</td>
<td>Cream, hydrophilic emollient Diprosone¶ 0.05</td>
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<tr>
<td>Betamethasone valerate</td>
<td>Ointment Valisone¶ 0.1</td>
<td>Fluticasone propionate</td>
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<tr>
<td></td>
<td>Foam Luxiq 0.12</td>
<td>Mometasone furoate</td>
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<tr>
<td>Desoximetasone</td>
<td>Cream Topicort LP¶ 0.05</td>
<td>Flurandrenolide</td>
<td></td>
<td></td>
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<tr>
<td>Diflorsone diacetate</td>
<td>Cream Florone¶ 0.05</td>
<td>Hydrocortisone valerate</td>
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<td></td>
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<tr>
<td>Diflucortolone valerate</td>
<td>Cream, oily cream, ointment Nerisone (Canada, United Kingdom, others) 0.1</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Fluocinonide</td>
<td>Cream aqueous emollient  Lidex-E¶ 0.05</td>
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<tr>
<td>Fluticasone propionate</td>
<td>Ointment Cutivate 0.005</td>
<td>Mometasone furoate</td>
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<td></td>
<td>Ointment Elocon 0.2</td>
<td>Triamcinolone acetonide</td>
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<tr>
<td>Triamcinolone acetonide</td>
<td>Cream, ointment Aristocort HP¶, Kenalog¶, Triderm 0.5</td>
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<tr>
<td></td>
<td>Ointment Kenalog¶ 0.1</td>
<td>Betamethasone dipropionate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ointment Kenalog¶ 0.1</td>
<td>Betamethasone valerate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ointment Trianex 0.05</td>
<td>Ethyl valerate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aerosol spray Kenalog 0.2 mg per 2 second spray</td>
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</tr>
<tr>
<td></td>
<td>Dental paste Oralone 0.1</td>
<td>Ethyl valerate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower-mid potency (Group 5)</td>
<td></td>
<td>Ethyl valerate</td>
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<tr>
<td>Betamethasone dipropionate</td>
<td>Lotion Diprosone¶ 0.05</td>
<td>Ethyl valerate</td>
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<tr>
<td>Betamethasone valerate</td>
<td>Cream Beta-Val, Valisone¶ 0.1</td>
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September 01, 2022
<table>
<thead>
<tr>
<th>Low pot</th>
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<tbody>
<tr>
<td>Desonide</td>
<td>Ointment</td>
</tr>
<tr>
<td>Gel</td>
<td>DesOwen</td>
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<tr>
<td>Fluocinolone acetonide</td>
<td>Cream</td>
</tr>
<tr>
<td>Flurandrenolide</td>
<td>Cream, lotion</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Cream, lotion</td>
</tr>
<tr>
<td>Hydrocortisone butyrate</td>
<td>Cream, lotion, ointment, solution</td>
</tr>
<tr>
<td>Hydrocortisone probutate</td>
<td>Cream</td>
</tr>
<tr>
<td>Hydrocortisone valerate</td>
<td>Cream</td>
</tr>
<tr>
<td>Prednicarbate</td>
<td>Cream</td>
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<tr>
<td>Triaminolone acetonide</td>
<td>Lotion</td>
</tr>
<tr>
<td>Ointment</td>
<td>Kenalog¶</td>
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<tr>
<td>Alclometasone dipropionate</td>
<td>Cream, ointment</td>
</tr>
<tr>
<td>Betamethasone valerate</td>
<td>Lotion</td>
</tr>
<tr>
<td>Desonide</td>
<td>Cream</td>
</tr>
<tr>
<td>Lotion</td>
<td>DesOwen, LoKara</td>
</tr>
<tr>
<td>Foam</td>
<td>Verdeso</td>
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<tr>
<td>Fluocinolone acetonide</td>
<td>Cream, solution</td>
</tr>
<tr>
<td>Shampoo</td>
<td>Capex</td>
</tr>
<tr>
<td>Oil (48% refined peanut oil)</td>
<td>Derma-Smoother/Fs Body, Derma-Smoother/Fs Scalp</td>
</tr>
<tr>
<td>Triaminolone acetonide</td>
<td>Cream, lotion</td>
</tr>
<tr>
<td>Hydrocortisone (base, ≥2%)</td>
<td>Cream, ointment</td>
</tr>
<tr>
<td>Lotion</td>
<td>Hytone, Ala Scalp, Scalacort</td>
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<td>Solution</td>
<td>Texacort</td>
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<td>Least pot</td>
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<td>Hydrocortisone (base, &lt;2%)</td>
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<tr>
<td>Cream</td>
<td>Cortaid¶, Cortizone 10, Hytone, Synacort</td>
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<tr>
<td>Gel</td>
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<td>Lotion</td>
<td>Aquanil HC, Sarnol-HC, Cortizone 10</td>
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<tr>
<td>Spray</td>
<td>Cortaid</td>
</tr>
<tr>
<td>Solution</td>
<td>Cortaid, Noble, Scalp Relief</td>
</tr>
<tr>
<td>Cream, ointment</td>
<td>Cortaid</td>
</tr>
<tr>
<td>Hydrocortisone acetate</td>
<td>Cream</td>
</tr>
<tr>
<td>Lotion</td>
<td>Nucort</td>
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</tbody>
</table>

¶ Inactive United States brand name for specific product; brand may be available outside United States

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September 01, 2022
References

19. Dellon et al. The Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Eosinophilic Esophagitis: Results from Part A of a Randomized, Placebo-Controlled Three-Part, Phase 3 Study. Poster presented at the 34th Annual Eastern Allergy Conference; Palm Beach, FL; June 2021.

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>08/2022</td>
</tr>
</tbody>
</table>

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September 01, 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 |
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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**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>duvelisib (Copiktra)</td>
<td>15 mg capsules</td>
<td>Relapsed/refractory chronic lymphocytic leukemia (CLL); Relapsed/refractory small lymphocytic lymphoma (SLL); Relapsed/refractory follicular lymphoma (FL)</td>
<td>56 capsules/28 days</td>
</tr>
<tr>
<td></td>
<td>25 mg capsules</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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:

Washington State Rx Services is administered by moda HEALTH
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. 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 regimens, 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 IIIB-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.

References

8. Verastem, Inc. A Double-Blind Study Evaluating Duvelisib in Subjects With Moderate to Severe Rheumatoid Arthritis and an Inadequate Response to Methotrexate Alone (ASPIRA). ClinicalTrials.gov Identifier: NCT0185170

**Policy Implementation/Update:**

<table>
<thead>
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<th>Action and Summary of Changes</th>
<th>Date</th>
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<td>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</td>
<td>2/2021</td>
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<td>Removed criteria: requirement for pneumocystis jirovecii pneumonia (PCP) prophylaxis and no history of allogenic stem cell transplant</td>
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<tr>
<td>Moved the follicular lymphoma indication to investigational uses</td>
<td></td>
</tr>
<tr>
<td>Criteria updated to policy format</td>
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<tr>
<td>Policy created</td>
<td>11/2018</td>
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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.
elagolix (Orilissa™, Oriahnn™)  
UMP POLICY

Policy Type: PA  Pharmacy Coverage Policy: UMP021

Description
Elagolix is an oral gonadotropin-releasing hormone (GnRH) antagonist.

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): Up to 12 months; maximum total (lifetime) fills should not exceed 24 28-day fills

Quantity limits

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
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<tbody>
<tr>
<td>elagolix (Orilissa)</td>
<td>150 mg tablets</td>
<td>Moderate to severe pain associated with endometriosis</td>
<td>30 tablets/30 days</td>
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<tr>
<td>Elagolix/estradiol/norethindrone acetate (Oriahnn)</td>
<td>200 mg tablets</td>
<td>Treatment of heavy menstrual bleeding associated with uterine fibroids</td>
<td>60 tablets/30 days</td>
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<tr>
<td>Elagolix/estradiol/norethindrone acetate (Oriahnn)</td>
<td>300 mg/1 mg/0.5 mg tablets</td>
<td>Treatment of heavy menstrual bleeding associated with uterine fibroids</td>
<td>56 tablets/28 days</td>
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</table>

Initial Evaluation
I. Elagolix (Orilissa) and elagolix/estradiol/norethindrone acetate (Oriahnn) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; AND
   B. 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
   C. Medication is prescribed by, or in consultation with, an obstetrician/gynecologist; AND
   D. A diagnosis of one of the following:
      1. Moderate-to-severe pain associated with endometriosis; AND
         i. Request is for elagolix (Orilissa); 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 continued use of estrogen containing contraceptives is planned in combination with elagolix (Orilissa), 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); 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; AND
   iv. Provider attestation that the member has not previously been treated with relugolix/estradiol/norethindrone (Myfembree).

II. Elagolix 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. 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

II. Elagolix/estradiol/norethindrone acetate (Oriahnn):
   A. Member has exhibited improvement in symptoms (reduction in menstrual blood loss, pain reduction, improved quality of life, etc.); AND
   B. Provider attestation the member has not previously received treatment with relugolix/estradiol/norethindrone (Myfembree); AND
      1. The member has not received treatment for more than 24 months
Supporting Evidence

I. 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.

II. 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.

III. 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.

IV. 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 antagonists (e.g., Lupron), GnRH agonists (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. 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/norethindone (Activella, Amabelz, Combipatch, Lopreeza, Mimvey Lo, and Mimvey).

XI. 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.

XII. Clinical trials 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. Studies have not yet been completed to evaluate elagolix (Orilissa) and elagolix/estradiol/norethindrone acetate (Oriahnn) in combination with bone loss prevention treatments.
XIII. Elagolix (Orilissa) and elagolix/estradiol/norethindrone acetate (Oriahnn) are contraindicated in pregnant patients due to an increased risk of early pregnancy loss.

Investigational or Not Medically Necessary Uses

I. Elagolix 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


Policy Implementation/Update:

<table>
<thead>
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<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
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<td>Removed criteria: &quot;Must be used in combination with a estradiol/norethindrone acetate product (Activella, CombiPatch, Mimvey Lo, etc.)&quot; from the indication heavy menstrual bleeding associated with uterine fibroids</td>
<td>12/2020</td>
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<td>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.</td>
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<td>Transition from criteria to policy</td>
<td>09/2019</td>
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<tr>
<td>Criteria created</td>
<td>10/2018</td>
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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.

September 01, 2022
eluxadoline (Viberzi®)
UMP POLICY

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

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<tr>
<td>eluxadoline (Viberzi)</td>
<td>75 mg tablets</td>
<td>Irritable bowel syndrome with diarrhea (IBS-D)</td>
<td>60 tablets/30 days</td>
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<td>100 mg tablets</td>
<td>with diarrhea (IBS-D)</td>
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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

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.

September 01, 2022
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


Policy Implementation/Update:

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<tr>
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<th>Date</th>
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<tr>
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<td>04/2020</td>
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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: 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

<table>
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<tr>
<th>Product Name</th>
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<th>Indication</th>
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<tr>
<td>Emicizumab-kxwh</td>
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<td>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</td>
<td>Up to 690 mg every 28 days</td>
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<td></td>
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* 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
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.

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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.

References

1. Hemlibra [Prescribing Information]. South San Francisco, CA: Genentech October 2018
Policy Implementation/Update:

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<th>Date Created</th>
<th>August 2019</th>
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<td>August 2019</td>
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<td>Last Updated</td>
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<td>New policy created for emicizumab-kxwh (Hemlibra)</td>
<td>08/2019</td>
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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. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy®) is a three-drug combination of bictegravir (BIC) 50mg, emtricitabine (FTC) 200 mg and tenofovir alafenamide (TAF) 25 mg indicated for the treatment of HIV-1 infection.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

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<th>Indication</th>
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<td>Treatment of HIV-1</td>
<td>30 tablets/30 days</td>
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<td>alafenamide (Biktarvy)</td>
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<td>30-120-15mg</td>
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<td>emtricitabine/tenofovir alafenamide</td>
<td>200-25 mg</td>
<td>Pre-Exposure Prophylaxis (PrEP);</td>
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Initial Evaluation

I. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) or emtricitabine/tenofovir alafenamide (Descovy) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an infectious disease or HIV specialist; AND
   B. Request is for emtricitabine/tenofovir alafenamide (Descovy) and member’s bodyweight is 17 kg (37.5lbs) or greater; OR
      1. Request is for bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy); AND
         i. Member meets one of the following criteria:
            a. Member weighs greater than, or equal to, 25 kg (56 lbs) and request is for the 50-200-25mg tablets; OR
            b. Member weighs between 14 kg (30 lbs) and 25 kg (56 lbs) and request is for the 30-120-15mg tablets; AND
         ii. Documentation of Hepatitis B virus (HBV) screening prior to initiation; AND
         iii. Member is treatment naïve; OR
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a. Member is virologically suppressed with HIV-1 RNA < 50 copies/mL; **AND**

b. Member has been on a stable ART regimen for at least the past 6 months with no history of treatment failure on current regimen; **AND**

c. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) will not be co-administered with dofetilide or rifampin; **AND**

C. One of the following is met:

1. A diagnosis of **HIV-1** when the following are met:
   i. Documentation that the member is not a candidate for a generic tenofovir disoproxil fumarate-based regimen due to contraindication or intolerance defined as any **ONE** of the following:
      a. Requires renal hemodialysis; **OR**
      b. Stabilized creatinine clearance (CrCl) less than 60mL/min within the prior 3 months; **OR**
      c. Stabilized creatinine clearance (CrCl) between 60-89 mL/min; **AND**
         i. Member has hypertension; **AND**
         ii. Member has one of the following:
            1. Diabetes
            2. Hepatitis C
            3. Vascular kidney disease (e.g., renal artery stenosis)
            4. Structural abnormalities (e.g., polycystic kidney, dysplastic kidney, renal mass)
            5. Member is African American with a family history of kidney disease; **OR**
      d. Member is high risk for bone complications as determined by a history of one of the following:
         i. Vertebral compression factor
         ii. Arm or hip fracture with minimal trauma
         iii. Member has chronic kidney disease with proteinuria, low phosphate or is grade 3 or worse
         iv. T score, less than, or equal to, -2.0 (DXA) at the femoral neck or spine
         v. Chronic, high dose glucocorticoid-therapy defined as more than 5 mg/day of prednisone, or equivalent, daily; **AND**
            1. Member has ongoing use of glucocorticoid therapy
            2. Documentation of the member’s current glucocorticoid regimen
            3. The expected duration of glucocorticoid therapy is greater than 2 months; **OR**
         ii. 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. Request is for emtricitabine/tenofovir alafenamide (Descovy); AND
ii. 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
iii. Member has a negative HIV-1 test no more than seven days prior to initiating treatment; AND
iv. Member's body weight is greater than, or equal to, 35 kg (77lbs); AND
v. 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)

IV. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) is considered investigational when used for all other conditions, including but not limited to:
    A. Use as a cure in those HIV-1
    B. Use for prevention of STI's, including, HIV-1

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:

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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. Request is for emtricitabine/tenofovir alafenamide (Descovy); AND
   b. 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
   c. Member has had a negative HIV-1 test within the last 3 months; AND
   d. 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

Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)

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. Severe acute exacerbations of Hepatitis B were reported in those who are positive for both Hepatitis B infection and HIV-1 and have discontinued products containing FTC and/or tenofovir disoproxil fumarate (TDF) and have discontinued bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy). It is important that after discontinuation of therapy those that are Hepatitis B positive be closely monitored and followed by an infectious disease specialist. Therefore, pre-treatment testing for HBV is recommended prior to the initiation of antiretroviral therapy. Additionally, patients with HIV and HBV coinfection should be monitored for several months following therapy discontinuation.

III. In clinical trials of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) , subjects with no antiretroviral treatment history who had eGFRs greater than 30 mL per minute, and in virologically suppressed subjects who had switched to bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) with eGFRs greater than 50 mL per minute, renal serious adverse events were encountered in less than 1% of subjects treated with bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) through week 48. Due to this, bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) is not recommended in patients with estimated creatinine clearance...
below 30 mL per minute. Furthermore, in patients taking tenofovir prodrugs who have impaired renal function and in those taking nephrotoxic agents including non-steroidal anti-inflammatory drugs are at increased risk of developing renal-related adverse reactions.

IV. In the clinical trials of adults with no antiretroviral treatment history, the primary safety assessment of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) was based on week 48 data from two randomized, double-blind, active-controlled trials, Trial 1489 and Trial 1490. Each trial enrolled 1274 HIV-1 infected adult subjects with no antiretroviral treatment history and gave 634 subjects one tablet of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) once daily. The most common adverse reactions reported in at least 5% of subjects in the bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) group in either Trial 1489 or Trial 1490 were diarrhea, nausea, and headache. Additional adverse reactions occurring in less than 2% of subjects who were administered bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) in Trials 1489 and 1490 included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression. Suicidal ideation, suicide attempt, and depression suicidal occurred in less than 1% of subjects; however, all events were serious and primarily occurred in subjects with a preexisting history of depression, prior suicide attempt, or psychiatric illness.

V. In the clinical trials of virologically suppressed adults, the safety of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) was based on week 48 data from 282 subjects in a randomized, double-blind, active-controlled trial (Trial 1844) in which virologically-suppressed subjects were switched from either DTG + ABC/3TC or ABC/DTG/3TC to bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy); and week 48 data from 290 subjects in an open-label, active-controlled trial in which virologically-suppressed subjects were switched from a regimen containing atazanavir (ATV) (given with cobicistat or ritonavir) or darunavir (DRV) (given with cobicistat or ritonavir) plus either FTC/TDF or ABC/3TC, to bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) (Trial 1878). However, the safety profile in virologically suppressed adult subjects in Trials 1844 and 1878 resulted in a similar safety profile to that in those with no antiretroviral treatment history.

VI. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy), a three-drug combination of bictegravir (BIC), has been shown to increase serum creatinine due to the inhibition of tubular secretion of creatinine without affecting renal glomerular function. Increases in serum creatinine, was seen by week 4 of treatment and remained stable through week 48. In Trials 1489 and 1490, the bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) group, saw a median (Q1, Q3) serum creatinine increase by 0.10 (0.03, 0.17) mg per dL from baseline to week 48, this was similar to that seen in the comparator groups who received ABC/DTG/3TC, or DTG + FTC/TAF. There were no discontinuations due to renal adverse events through week 48.

VII. In Trials 1489 and 1490, total bilirubin increases were observed in 12% of the subjects who were administered bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) through week 48. Increases were primarily Grade 1 (1.0 to 1.5 x ULN) (9%) and Grade 2 (1.5 to 2.5 x ULN) (3%). Graded bilirubin increases in the ABC/DTG/3TC, and DTG + FTC/TAF groups, were 4% and 6%, respectively. Increases were primarily Grade 1 (3% ABC/DTG/3TC and 5% DTG + FTC/TAF) or Grade 2 (1% ABC/DTG/3TC and 1% DTG + FTC/TAF). There were no discontinuations due to hepatic adverse events through Week 48.

VIII. As BIC inhibits organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE1) in vitro, coadministration of bictegravir/emtricitabine/tenofovir
Clarithromycin (Biktarvy) with drugs that are substrates of OCT2 and MATE1 (e.g., dofetilide) may increase their plasma concentrations and is not recommended. Additionally, coadministration with rifampin is contraindicated due to the effect of rifampin on the BIC component of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy).

IX. Safety and efficacy of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) in pediatric patients less than 18 years of age has not yet been established.

X. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) is not recommended in patients with severe renal impairment (estimated creatinine clearance (CrCL) below 30 mL per minute, estimated by Cockcroft-Gault (CG)), with no dosage adjustment of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) recommended in patients with CrCL greater than, or equal to, 30 mL per minute.

XI. No use or dosage adjustment of bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, as bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) has not yet been studied in patients with severe hepatic impairment (Child-Pugh Class C).

XII. Clinical trial results in HIV-1 subjects with no antiretroviral treatment history:

A. In Trial 1489, subjects were randomized in a 1:1 ratio to receive either bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) (N=314) or ABC/DTG/3TC (600 mg/50 mg/300 mg) (N=315) once daily. Subjects were aged between 18-71, with a mean age of 37, a mean baseline CD4+ cell count of 464 cells per mm3, allowing a range 0–1424; however, 11% of subjects had CD4+ cell count less than 200 cells per mm3, and 16% of subjects had a baseline viral load greater than 100,000 copies per mL. In Trial 1490, subjects were randomized in a 1:1 ratio to receive either bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) (N=320) or DTG + FTC/TAF (50 mg + 200 mg/25 mg) (N=325) once daily. In Trials 1489 and 1490, treatment outcomes were similar with the mean increase from baseline in CD4+ count at Week 48 was 233 and 229 cells per mm3 in the BIKTARVY and ABC/DTG/3TC groups, respectively, and 180 and 201 cells per mm3 in the BIKTARVY and DTG + FTC/TAF groups, respectively.

XIII. Clinical Trial Results in HIV-1 Virologically-Suppressed Subjects Who Switched to Biktarvy:

A. In Trial 1844, the efficacy and safety of switching from a regimen of DTG + ABC/3TC or ABC/DTG/3TC to bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) was evaluated in a randomized, double-blind trial of virologically-suppressed (HIV-1 RNA less than 50 copies per mL) HIV-1 infected adults (N=563, randomized and dosed). Prior to the trial entry, subjects had to have been stably suppressed (HIV-1 RNA less than 50 copies per mL) on their baseline regimen for at least 3 months and have had no history of treatment failure. Subjects were then randomized in a 1:1 ratio to either switch to bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) at baseline (N=282) or stay on their baseline antiretroviral regimen (N=281). Subjects were aged between 20–71, with a mean age of 54 and had a mean baseline CD4+ cell count of 723 cells per mm3 (range 124–2444). Results of trial 1844, was a mean change from baseline in CD4+ count at Week 48, -31 cells per mm3 in subjects who switched to bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) and 4 cells per mm3 in those who stayed on ABC/DTG/3TC.

B. In Trial 1878, the efficacy and safety of switching from either ABC/3TC or FTC/TDF (200/300 mg) plus ATV or DRV (given with either cobicistat or ritonavir) to
bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) were evaluated in a randomized, open-label study of virologically-suppressed HIV-1 infected adults (N=577, randomized and dosed). Prior to study entry subjects must have been stably suppressed on their baseline regimen for at least 6 months, must not have been previously treated with any INSTI, and must have not had a history of treatment failure. Subjects were then randomized in a 1:1 ratio to either switch to bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) (N=290) or stay on their baseline antiretroviral regimen (N=287). Subjects were aged between 20–79, with a mean age of 46 and had a mean baseline CD4+ cell count of 663 cells per mm3 (range 62–2582). At screening, 15% of subjects were receiving ABC/3TC plus ATV or DRV (given with either cobicistat or ritonavir) and 85% of subjects were receiving FTC/TDF plus ATV or DRV (given with either cobicistat or ritonavir). Results of trial 1878, was a mean change from baseline in CD4+ count at Week 48, 25 cells per mm3 in patients who switched to bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) and 0 cells per mm3 in patients who stayed on their baseline regimen.

**Emtricitabine/tenofovir alafenamide (Descovy)**

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 increase from baseline in CD4+ cell count 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 improved in patients assigned to the TAF group, while remaining stable in those who continued their initial TDF based regimen.
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. Bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Use as Pre-Exposure Prophylaxis (PrEP) in adults and adolescents at risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex
   B. Use as a preventive measure against other STI’s
   C. Use as a cure for those HIV-1 positive

II. 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>08/2022</td>
</tr>
<tr>
<td>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.</td>
<td>05/2022</td>
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<tr>
<td>Added 30/120/15mg Biktarvy tablet to policy and requirement of weight minimum.</td>
<td>12/2021</td>
</tr>
<tr>
<td>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</td>
<td>01/2021</td>
</tr>
<tr>
<td>Instead of tenofovir disoproxil fumarate (Truvada) requiring step through generic tenofovir disoproxil fumarate</td>
<td>12/2020</td>
</tr>
<tr>
<td>Policy created</td>
<td>07/2020</td>
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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.

Washington State Rx Services is administered by Moda Health
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>encorafenib (Braftovi)</td>
<td>50 mg capsule</td>
<td>Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy;</td>
<td>180 capsules/30 days</td>
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<tr>
<td></td>
<td>75 mg capsule</td>
<td>Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy</td>
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<tr>
<td>binimetinib (Mektovi)</td>
<td>15 mg tablet</td>
<td>Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy</td>
<td>180 tablets/30 days</td>
</tr>
</tbody>
</table>

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., dabrafenib, vemurafenib); AND

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September 01, 2022
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**
   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)

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**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

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September 01, 2022
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
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.

(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.

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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>06/2020</td>
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<tr>
<td>Prior authorization criteria transitioned to policy, updated criteria with the following: age edit, allowance of dermatologist prescribing, specialist requirement on renewal.</td>
<td>11/2019</td>
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<td>Criteria created</td>
<td>07/2018</td>
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Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP082

Split Fill Management*

Description
Entrectinib (Rozlytrek) is an orally administered selective kinase inhibitor.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>entrectinib (Rozlytrek)</td>
<td>100 mg capsules</td>
<td>Neurotrophic receptor tyrosine kinase gene fusion positive solid tumors</td>
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<tr>
<td></td>
<td>200 mg capsules</td>
<td>Non-small cell lung cancer, metastatic, ROS1-positive</td>
<td>90 capsules/30 days</td>
</tr>
</tbody>
</table>

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 12 years of age or older; **AND**
         ii. Member has metastatic disease, **OR** surgical resection is likely to result in severe morbidity (i.e., tumor is unresectable); **AND**
         iii. Member does not have an acquired resistance mutation; **AND**
         iv. 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. Prescribed by or in consultation with an oncologist; **AND**
   II. Medication will not be used in combination with any other oncolytic medication; **AND**
   III. Response to therapy as indicated by stabilization of disease or decrease in tumor size or spread; **AND**
   IV. Member does not have unacceptable medication toxicity (e.g., heart failure, hepatotoxicity, hyperuricemia, QT interval prolongation, vision disturbances, fracture, etc.).

**Supporting Evidence**

I. 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 which included 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.
II. Data for NTRK fusion-positive solid tumor FDA-approval included a pooled group of 54 subjects across the trials listed above. The primary outcome was an objective response rate (ORR) of: 57% (43-71), with 50% achieving partial response (PR) and 7.4% achieving complete response (CR).

III. Data for ROS1-positive NSCLC FDA-approved included a pooled 51 subjects across the trials listed above with the primary outcome of ORR: 78% (65-89), 73% with PR and 6% CR.

IV. 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). 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.

V. 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. Crizotinib (Xalkori) is FDA-approved, but has limited data for safety and efficacy and has not been shown to target CNS mets. 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. Entrectinib (Rozlytrek) has shown some CNS activity, and in clinical trials five of seven subjects with CNS metastases showed CNS response.

VI. 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.

VII. In all trials, entrectinib (Rozlytrek) was evaluated for safety and efficacy as monotherapy.

VIII. Specific resistance mutations have not been identified via label for entrectinib (Rozlytrek) as they have been for lorotrectinib (Vitrakvi).

IX. 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. Due to the mechanism of action, investigation in ALK-positive NSCLC is underway; however, safety and efficacy have not been defined.

II. Efficacy and safety of entrectinib (Rozlytrek) in solid tumors without NTRK fusions has not been sufficiently evaluated.

* 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.

Washington State Rx Services is administered by Moda Health.

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.

September 01, 2022
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

5. Vitrakvi [Prescribing Information]. Loxo Oncology, Inc. Stamford, CT. 2018
8. Clinicaltrials.gov

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tbody>
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<td>Added supporting evidence around stage IV metastatic disease and metastases.</td>
<td>10/2021</td>
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<td>Previous Reviews</td>
<td>09/2019 11/2019</td>
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Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitors (TKI)
UMP POLICY

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

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<th>Product Name</th>
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<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
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<td>80 mg tablets</td>
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<tr>
<td>dacomitinib (Vizimpro)</td>
<td>15 mg tablets</td>
<td>NSCLC</td>
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<td></td>
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<td>45 mg tablets</td>
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<td>erlotinib (Tarceva)</td>
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<td>NSCLC; Pancreatic cancer</td>
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<tr>
<td></td>
<td>150 mg tablets</td>
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<td>afatinib (Gilotrif)</td>
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</tr>
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<td>gefitinib (Iressa)</td>
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</table>

Initial Evaluation

I. Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), 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;

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.

September 01, 2022
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 **not** 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 **ONE** 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 **not** 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 **not** 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 not 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 (Iressa)
i. Metastatic (stage IV) non-small cell lung cancer; AND
ii. The member has not 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

II. Dacomitinib (Vizimpro) is considered not medically necessary 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 investigational when used for all other conditions, including but not limited to:
   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. The medication is prescribed by or in consultation with an oncologist; **AND**

II. 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**

III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**

IV. If the request is for brand erlotinib (Tarceva), generic erlotinib has been ineffective, contraindication, or not tolerated.

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.

I. 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.

II. 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.

III. 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.

IV. Erlotinib (Tarceva) was evaluated in the OPTIMAL, EURTAC, and ENSURE trials versus chemotherapy. Objective response rates (ORR) and PFS were favorable for erlotinib (Tarceva).

V. 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.

VI. 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.

VII. 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.

VIII. Gefitinib (Iressa) showed favorable PFS against chemotherapy in several RCTs.

IX. 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.

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. 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.

References

Policy Implementation/Update:

<table>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tbody>
<tr>
<td>Added supporting evidence around stage IV metastatic disease and metastases.</td>
<td>10/2021</td>
</tr>
<tr>
<td>Policy updated to include osimertinib (Tagrisso) indication of early stage, adjuvant treatment to surgical resection in NSCLC.</td>
<td>01/2021</td>
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<td>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.</td>
<td>07/2019</td>
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<td>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.</td>
<td>03/2018</td>
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<td>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</td>
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### 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**

<table>
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<tr>
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<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit*</th>
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*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 FGFR3 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 FGFR2 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 FGFR2 or FGFR3 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 FGFR2 fusion genetic alteration, and no patients that had FGFR2 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


Policy Implementation/Update:

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<td>August 2019</td>
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<tr>
<td>Last Updated</td>
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<th>Date</th>
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Washington State Rx Services is administered by moda HEALTH

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**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**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>darbepoetin alfa</td>
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<td></td>
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</tr>
<tr>
<td>(Aranesp)</td>
<td>25 mcg/mL vial</td>
<td>Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy</td>
<td>4 vials/syringes per 30 days</td>
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<td>40 mcg/mL vial</td>
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<td></td>
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<tr>
<td></td>
<td>150 mcg/mL vial</td>
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<tr>
<td></td>
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<td></td>
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<tr>
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<td>300 mcg/0.6 mL syringe</td>
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<tr>
<td></td>
<td>500 mcg/mL syringe</td>
<td></td>
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</tr>
<tr>
<td>epoetin alfa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Retacrit)</td>
<td>2000 units/mL vial</td>
<td>Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy</td>
<td>2,000U, 3,000U, 4,000U and 10,000U vials: 12 vials per 30 days</td>
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<tr>
<td></td>
<td>3000 units/mL vial</td>
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<tr>
<td></td>
<td>4000 units/mL vial</td>
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<td>10000 units/mL vial</td>
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<tr>
<td>(Procrit)</td>
<td>2000 units/mL vial</td>
<td>Chronic Kidney Disease With or Without Dialysis; Anemia due to zidovudine therapy; Allogeneic blood transfusion</td>
<td>20,000U and 40,000U vials: 4 vials per 30 days</td>
</tr>
<tr>
<td></td>
<td>3000 units/mL vial</td>
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</tbody>
</table>

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September 01, 2022
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

**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.

- Pfizer has communicated that Retacrit will experience a supply disruption during Q2-2022, with a return to supply in early Q4-2022. If Retacrit is not obtainable, as confirmed by FDA Drug shortage website located at: [http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm](http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm), or attested to by the provider, the above requirement is waived and coverage is provided for the originator brand.

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:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Hb and/or Hct Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia secondary to myelodysplastic syndrome (MDS)</td>
<td>Hemoglobin (Hb) &lt; 12 g/dL and/or Hematocrit (Hct) &lt; 36%</td>
</tr>
<tr>
<td>Anemia secondary to myeloproliferative neoplasms (MF, post-PV myelofibrosis, post-ET myelofibrosis)</td>
<td>Hemoglobin (Hb) &lt; 10 g/dL and/or Hematocrit (Hct) &lt; 30%</td>
</tr>
<tr>
<td>Reduction of allogeneic blood transfusions in elective, non-cardiac, non-vascular surgery</td>
<td>Hemoglobin (Hb) between 10 g/dL and 13 g/dL and/or Hematocrit (Hct) between 30% and 39%</td>
</tr>
<tr>
<td>Anemia secondary to chemotherapy treatment</td>
<td>Hemoglobin (Hb) &lt; 10 g/dL and/or Hematocrit (Hct) &lt; 30%</td>
</tr>
<tr>
<td>Anemia secondary to zidovudine treated, HIV-infected patients</td>
<td>Hemoglobin (Hb) &lt; 12 g/dL and/or Hematocrit (Hct) &lt; 36%</td>
</tr>
</tbody>
</table>
| 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


Policy Implementation/Update:

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<tr>
<th>Action and Summary of Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added Aranesp as a preferred product not requiring prior authorization; Updated formatting to align with current process;</td>
</tr>
<tr>
<td>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:”.</td>
</tr>
<tr>
<td>• Transitioned to policy format</td>
</tr>
<tr>
<td>• Added language regarding preferred product, Retacrit and removal of PA requirement</td>
</tr>
<tr>
<td>• 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)</td>
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<td>• Added coverage criteria for anemia associated with rheumatoid arthritis, anemia secondary to MDS, and anemia secondary to myelofibrosis</td>
</tr>
<tr>
<td>• Added specific renewal criteria</td>
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<tr>
<td>Previous reviews</td>
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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: Two 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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
</table>
| esketamine   | Treatment resistant depression (TRD), in conjunction with an oral antidepressant | 56 mg dose kit | Initial (two months):
|              |            |             | PA #1^: 56 mg – 2 devices per 3 days |
|              |            |             | PA #2: 35 devices per 56 days (to allow for 56mg or 84mg) |
|              |            |             | Renewal*: 12 devices per 28 days (to allow for 56mg or 84mg at weekly or every other week dosing) |
|              | Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior, in conjunction with an oral antidepressant | 84 mg dose kit | 24 devices per 28 days |

^Second dose for week one accounted for in PA#2
*Quantity exceptions are not allowed
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

I. Table 1: Quantity limits on per week level for the treatment of treatment resistant depression (TRD)

<table>
<thead>
<tr>
<th>Week</th>
<th>Cumulative Spravato Doses/Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>56 mg – 2 devices</td>
</tr>
<tr>
<td>Week 1 (twice weekly dosing)</td>
<td>56 mg (4 devices) or 84 mg (5 devices)</td>
</tr>
<tr>
<td>Week 2 (twice weekly dosing)</td>
<td>56 mg (8 devices) or 84 mg (11 devices)</td>
</tr>
<tr>
<td>Week 3 (twice weekly dosing)</td>
<td>56 mg (12 devices) or 84 mg (17 devices)</td>
</tr>
<tr>
<td>Week 4 (twice weekly dosing)</td>
<td>56 mg (16 devices) or 84 mg (23 devices)</td>
</tr>
<tr>
<td>Week 5 (once a week dosing)</td>
<td>56 mg (18 devices) or 84 mg (26 devices)</td>
</tr>
<tr>
<td>Week 6 (once a week dosing)</td>
<td>56 mg (20 devices) or 84 mg (29 devices)</td>
</tr>
<tr>
<td>Week 7 (once a week dosing)</td>
<td>56 mg (22 devices) or 84 mg (32 devices)</td>
</tr>
<tr>
<td>Week 8 (once a week dosing)</td>
<td>56 mg (24 devices) or 84 mg (35 devices)</td>
</tr>
<tr>
<td>Week 9 (every two weeks dosing or once weekly dosing)</td>
<td>56 mg (2 devices) or 84 mg (3 devices)</td>
</tr>
</tbody>
</table>

II. Table 2: Antidepressant Example (*please note list below is not comprehensive)

- Selective Serotonin Reuptake Inhibitors
  - paroxetine
  - fluvoxamine
  - escitalopram
  - sertraline
  - fluoxetine
  - citalopram

- Serotonin and Norepinephrine Reuptake Inhibitors
  - duloxetine
  - venlafaxine
  - desvenlafaxine
  - milnacipran
  - levomilnacipran

- Tricyclic antidepressant
  - amitriptyline
  - clomipramine
  - nortriptyline

- Other
  - bupropion
  - mirtazapine
  - vilazodone
  - vortioxetine
  - nefazodone

III. Table 3: Quantity limits for the treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

<table>
<thead>
<tr>
<th>Week</th>
<th>Cumulative Spravato Doses/Devices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>84mg (3 devices)</td>
</tr>
<tr>
<td>Week 1 (twice weekly)</td>
<td>56mg (5 devices) or 84mg (6 devices)</td>
</tr>
<tr>
<td>Week 2-4 (twice weekly)</td>
<td>56mg (12 devices) or 84mg (18 devices)</td>
</tr>
</tbody>
</table>
References

5. Alan J. Gelenberg, M.D., Marlene P. Freeman, M.D., et al. PRACTICE GUIDELINE FOR THE TREATMENT of Patients With Major Depressive Disorder. AMERICAN PSYCHIATRIC ASSOCIATION. 2010. Third edition


**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Removed requirement of augmentation with an additional antidepressant</td>
<td></td>
</tr>
<tr>
<td>• Updated renewal requirement for weekly dosing to require provider attestation that member is using least frequent dosing possible to maintain symptom control/remission</td>
<td></td>
</tr>
<tr>
<td>• 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</td>
<td></td>
</tr>
<tr>
<td>• Updated supporting evidence</td>
<td>5/2022</td>
</tr>
<tr>
<td>• Added new indication of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior and appropriate criteria</td>
<td></td>
</tr>
<tr>
<td>• 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</td>
<td></td>
</tr>
<tr>
<td>• Added major depressive disorder (MDD) symptoms, including suicidal ideation in patients who are at imminent risk for suicide as an investigational indication</td>
<td></td>
</tr>
<tr>
<td>• Added criteria:</td>
<td>10/2020</td>
</tr>
<tr>
<td>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);</td>
<td></td>
</tr>
<tr>
<td>o The member does not have a contraindication to and has not previously failed ketamine</td>
<td>03/2020</td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>o Medication is prescribed by, or in consultation with a psychiatrist</td>
<td></td>
</tr>
</tbody>
</table>

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*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.*

September 01, 2022
- Updated quantity limit to better align with dosing regimen
- 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, Lopreezea, 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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>everolimus (generic Afinitor)</td>
<td>2.5 mg tablet</td>
<td>Angiomyolipoma of the kidney, tuberous sclerosis syndrome;</td>
<td>28 tablets/28 days for subependymal giant cell astrocytoma: quantity associated with 4.5 mg/m² daily</td>
</tr>
<tr>
<td></td>
<td>5 mg tablet</td>
<td>Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.5 mg tablet</td>
<td>Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg tablet</td>
<td>Renal cell carcinoma, advanced disease;</td>
<td></td>
</tr>
<tr>
<td>everolimus (Afinitor)</td>
<td>2.5 mg tablet</td>
<td>Subependymal giant cell astrocytoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.5 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>everolimus (Afinitor Disperz)</td>
<td>2 mg tablet</td>
<td>Partial seizure, adjunct, tuberous sclerosis syndrome;</td>
<td>Quantity associated with 5 mg/m² daily for partial seizure, 4.5 mg/m² daily for subependymal giant cell astrocytoma.</td>
</tr>
<tr>
<td></td>
<td>3 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>everolimus (generic Afinitor Disperz)</td>
<td>2 mg tablet</td>
<td>Subependymal giant cell astrocytoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg tablet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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**
      
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.

Washington State Rx Services is administered by Moda Health

September 01, 2022
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 one anti-angiogenic therapy (e.g. pazopanib [Votrient], bevacizumab [Avastin], sunitinib [Sutent], axitinib [Inlyta]); **AND**
   iii. Everolimus will be used as monotherapy **OR** 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 **not medically necessary** when criteria above are not met and/or when used for:
   A. Carcinoid tumor

IV. Everolimus (Afinitor, Afinitor Disperz) is considered **investigational** when used for all other conditions, including but **not limited to**:
   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 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%).

V. 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.

VI. 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, Afinitor 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 macroglobulinemia

* 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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).</td>
<td>10/2021</td>
</tr>
<tr>
<td>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)</td>
<td>10/2020</td>
</tr>
<tr>
<td>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.</td>
<td>01/2020</td>
</tr>
<tr>
<td>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.</td>
<td>12/2019</td>
</tr>
<tr>
<td>Afinitor Disperz with indications added to criteria, formatting update and quantity limits changed to mirror available package sizes.</td>
<td>05/2018</td>
</tr>
<tr>
<td>Criteria created</td>
<td>05/2012</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprolix, coagulation factor IX (recombinant, Fc fusion protein)</td>
<td>250, 500, 1000, 2000, 3000, 4000 IU</td>
<td><strong>On-demand Treatment</strong>: 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. <strong>Routine Prophylaxis</strong>:</td>
<td>On-demand Treatment: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Routine Prophylaxis:</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>≥12 years</strong>: Up to 50 IU/kg once weekly or 100 IU/kg once every ten days</td>
<td><strong>≥12 years</strong>: Up to 315 IU/kg every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>&lt;12 years</strong>: Up to 60 IU/kg once weekly. More frequent or higher doses may be required</td>
<td><strong>&lt;12 years</strong>: Up to 255 IU/kg every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Perioperative Management</strong>:</td>
<td>Perioperative Management: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Minor surgery</strong>: Up to 80 IU/dL as a single infusion, then every 24 to 48 hours if needed until bleeding stops</td>
<td>Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Major surgery</strong>: 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</td>
<td></td>
</tr>
</tbody>
</table>

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.

September 01, 2022
| **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 IU | **On-demand Treatment**: Up to 80 IU/kg for the initial dose. Additional doses of 40 IU/kg can be given.  
**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  
**Perioperative Management**: Up to the number of doses requested for 28 days |

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4. Allows for +5% to account for assay and vial availability.

5. 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; pediatric (<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. Alprolix and Idelvion only: 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 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. 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 trials. Alprolix and Idelvion demonstrated effectiveness in reducing annualized bleeding rates when used prophylactically compared to on-demand treatment. Rebinyn has been shown to stop or prevent bleeding in the on-demand and perioperative settings.

VI. 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.

VII. 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

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>August 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>August 2019</td>
</tr>
<tr>
<td>Last Updated</td>
<td>August 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>08/2019</td>
</tr>
</tbody>
</table>

**Action and Summary of Changes**

| New policy created for extended half-life factor products | 08/2019 |
**Policy Type: PA/SP**

**Pharmacy Coverage Policy: UMP029**

**Description**

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**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adynovate, antihemophilic factor</strong>&lt;br&gt;(recombinant), PEGylated</td>
<td>250, 500, 750, 1000, 1500, 2000, 3000 IU</td>
<td><strong>On-demand Treatment</strong>: Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved&lt;br&gt;<strong>Routine Prophylaxis</strong>:&lt;br&gt;• ≥12 years: Up to 50 IU/kg two times per week&lt;br&gt;• &lt;12 years: 55 IU/kg two times per week with a maximum of 70 IU/kg&lt;br&gt;<strong>Perioperative Management</strong>:&lt;br&gt;• <em>Minor</em> (e.g. tooth extraction): Up to 50 IU/kg within one hour before surgery; Repeat after 24 hours as needed until bleeding is resolved&lt;br&gt;• <em>Major</em> (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 &lt;12 years of age) until adequate round healing</td>
<td><strong>On-demand Treatment</strong>: Up to the number of doses requested every 28 days&lt;br&gt;<strong>Routine Prophylaxis</strong>:&lt;br&gt;• ≥12 years: Up to 420 IU/kg every 28 days&lt;br&gt;• &lt;12 years: Up to 590 IU/kg every 28 days&lt;br&gt;<strong>Perioperative Management</strong>: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td>Drug</td>
<td>On-demand Treatment</td>
<td>Routine Prophylaxis</td>
<td>Perioperative Management</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| **Eloctate**, antihemophilic factor (recombinant), Fc fusion protein | **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  | • ≥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)  |
|                         |                                                                                     |                                                                                     |                                                                                           |
| **Esperoct**, antihemophilic factor (recombinant), glycopegylated | **On-demand Treatment:** Up to the number of doses requested every 28 days          | **Routine Prophylaxis:**  
  • ≥12 years: Up to 50 IU/kg per dose  
  • <12 years: Up to 65 IU/kg per dose | **Perioperative Management:**  
  Up to the number of doses requested for 28 days                                                                 |
|                         |                                                                                     | **Routine Prophylaxis:**  
  • ≥12 years: Up to 368 IU/kg every 28 days  
  • <12 years: Up to 546 IU/kg every 28 days | **Perioperative Management:**  
  Up to the number of doses requested for 28 days                                                                 |
<table>
<thead>
<tr>
<th>Jivi, antihemophilic factor (recombinant), PEGylated</th>
<th>On-demand Treatment: Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved</th>
<th>On-demand Treatment: Up to the number of doses requested every 28 days</th>
</tr>
</thead>
</table>
| 500, 1000, 2000, 3000 IU | Routine Prophylaxis:  
- ≥12 years: Up to 40 IU/kg two times per week  
- <12 years: Not FDA approved | Routine Prophylaxis:  
- ≥12 years: Up to 340 IU/kg every 28 days  
- <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 | 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**

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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.

September 01, 2022
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. Documentation that inhibitor testing has been performed within the last 12 months; AND
   i. if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; 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. Documentation that inhibitor testing has been performed within the last 12 months; AND
   1. 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 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 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 extended half-life products were established based on open-label, non-randomized trials. 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. 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.

Refer to the references for detailed information. The watched list of extended half-life factor VIII products is as follows:

- Adynovate® [Prescribing Information]. Westlake Village, CA: Shire; May 2018
- Afstyla® [Prescribing Information]. Kankakee, IL: CSL Behring; September 2017
- Eloctate® [Prescribing Information]. Waltham, MA: Bioverativ Therapeutics; December 2017
- Jivi® [Prescribing Information]. Whippany, NJ: Bayer; August 2018
- UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

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.
**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esperoct added to policy</td>
<td>05/2020</td>
</tr>
<tr>
<td>New policy created for extended half-life factor products</td>
<td>08/2019</td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit‡</th>
</tr>
</thead>
</table>
| Alphanate, antihemophilic factor/von Willebrand factor complex (human) | 250, 500, 1000, 1500, 2000 IU FVIII | **Control and prevention of bleeding – hemophilia A**: 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.  
**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  
**Control and prevention of bleeding and perioperative management – vWD**: 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 every 28 days | **Control and prevention of bleeding in hemophilia A**: Up to the number of doses requested every 28 days  
**Perioperative management in hemophilia A**: Up to the number of doses requested for 28 days  
**Control and prevention of bleeding and perioperative management in vWD**: Up to the number of doses requested for 28 days |
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
</table>
| 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 – hemophilia A**: Up to the number of doses requested every 28 days |
| | | **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**:  
- Loading: vWF:RCo target peak plasma level – 100 IU/dL; Target factor VIII:C activity – 80-100 IU/dL | **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 | **Perioperative management – vWD**: Up to the number of doses requested for 28 days |
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilate, von Willebrand factor/coagulation factor VIII complex (human)</td>
<td>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 &gt; 50%, for up to five to seven days</td>
<td>Control of bleeding episodes – vWD: Up to the number of doses requested every 28 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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 &gt; 50% and peak levels 100% until wound healing is achieved, up to six days or more</td>
<td>Perioperative management of bleeding – vWD: Up to the number of doses requested for 28 days</td>
<td></td>
</tr>
</tbody>
</table>

‡ 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)

γ 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

† 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.

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

Maintenance: 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.

*One IU of factor VIII activity per kg body weight will increase the circulating factor VIII level by approximately 2 IU/dL.

† 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

‡ 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)

γ 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

Washington State Rx Services is administered by moda HEALTH

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.

September 01, 2022
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 hematologist; 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 hematologist; 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**

1. **Alphanate** [Prescribing Information]. Los Angeles, CA: Grifols; June 2018
2. **Humate-P** [Prescribing Information]. Kankakee, IL; CSL Behring LLC; September 2017
3. **Wilate** [Prescribing Information]. Hoboken, NJ; Octapharm USA; September 2016


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>August 2019</th>
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<td>Date Effective</td>
<td>August 2019</td>
</tr>
<tr>
<td>Last Updated</td>
<td>August 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>08/2019</td>
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<table>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>New policy created for factor VIII/vWF complex products</td>
<td>08/2019</td>
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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**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>fedratinib (Inrebic)</td>
<td>Intermediate- or high-risk myelofibrosis</td>
<td>100 mg capsules</td>
<td>120 capsules/30 days</td>
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</table>

**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 investigative 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

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.

September 01, 2022
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.

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.

September 01, 2022
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


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

<table>
<thead>
<tr>
<th>Policy Name</th>
<th>Disease state</th>
</tr>
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<tbody>
<tr>
<td>ruxolitinib (Jakafi)</td>
<td>Intermediate- or high-risk myelofibrosis</td>
</tr>
<tr>
<td></td>
<td>Polycythemia vera</td>
</tr>
<tr>
<td></td>
<td>Graft versus-host disease (acute or chronic)</td>
</tr>
<tr>
<td>pacritinib (Vonjo)</td>
<td>Intermediate- or high-risk myelofibrosis</td>
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Policy Implementation/Update:

<table>
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<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>5/2022</td>
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<tr>
<td>Criteria created</td>
<td>9/2019</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit*</th>
</tr>
</thead>
<tbody>
<tr>
<td>fenfluramine</td>
<td>Dravet Syndrome</td>
<td>2.2 mg/ml solution</td>
<td>360 ml/30 days</td>
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<tr>
<td>(Fintepla)</td>
<td>Lennox-Gastaut Syndrome</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Monthly quantity (in mL) to allow for a maximum of 26 mg (12 mL) per day</td>
</tr>
</tbody>
</table>

*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. All 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
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, 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% CI -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% CI -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 hemiconic 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

<table>
<thead>
<tr>
<th>Weight-based Dosage</th>
<th>Maximum Total Daily Dosage</th>
<th>Weight-based Dosage</th>
<th>Maximum Total Daily Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without concomitant stiripentol</td>
<td>With concomitant stiripentol and clobazam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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.*

September 01, 2022
Initial Dosage

<table>
<thead>
<tr>
<th>Day</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>0.1 mg/kg twice daily</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.2 mg/kg twice daily</td>
</tr>
<tr>
<td>Day 7</td>
<td>0.15 mg/kg twice daily</td>
</tr>
<tr>
<td>Day 14</td>
<td>0.2 mg/kg twice daily</td>
</tr>
</tbody>
</table>

References

10. Lennox-gastaut syndrome. NORD (National Organization for Rare Disorders).

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

<table>
<thead>
<tr>
<th>Policy Name</th>
<th>Disease state</th>
</tr>
</thead>
<tbody>
<tr>
<td>cannabidiol (Epidiolex)</td>
<td>Lennox-Gastaut syndrome</td>
</tr>
<tr>
<td></td>
<td>Dravet syndrome</td>
</tr>
<tr>
<td></td>
<td>Tuberous Sclerosis Complex</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>stiripentol (Diacomit)</td>
<td>Dravet syndrome</td>
</tr>
<tr>
<td>vigabatrin (Sabril, Vigadrone)</td>
<td>Refractory complex partial epileptic seizure, adjunct therapy West syndrome (infantile spasms)</td>
</tr>
</tbody>
</table>

**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>08/2022</td>
</tr>
<tr>
<td>Policy created</td>
<td>11/2020</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>fentanyl citrate (Abstral)</td>
<td>100 mcg sublingual tablet</td>
<td>Chronic pain associated with cancer</td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>200 mcg sublingual tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>300 mcg sublingual tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>400 mcg sublingual tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>600 mcg sublingual tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>800 mcg sublingual tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td>fentanyl citrate (Actiq)</td>
<td>200 mcg lozenge handle</td>
<td>Chronic pain associated with cancer</td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>400 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>600 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
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<td></td>
<td>800 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>1200 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>1600 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td>fentanyl citrate (Fentora)</td>
<td>100 mcg buccal tablet</td>
<td>Chronic pain associated with cancer</td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>200 mcg buccal tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>400 mcg buccal tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>600 mcg buccal tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>800 mcg buccal tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td>fentanyl citrate (Lazanda)</td>
<td>100 mcg nasal spray</td>
<td>Chronic pain associated with cancer</td>
<td>15 bottles/30 days</td>
</tr>
<tr>
<td></td>
<td>400 mcg nasal spray</td>
<td></td>
<td>15 bottles/30 days</td>
</tr>
<tr>
<td>fentanyl citrate (Subsys)</td>
<td>100 mcg sublingual spray</td>
<td>Chronic pain associated with cancer</td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>200 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>400 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>600 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>800 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>1200 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>1600 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td>fentanyl citrate (fentanyl citrate)</td>
<td>200 mcg lozenge handle</td>
<td>Chronic pain associated with cancer</td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>400 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>600 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
</tbody>
</table>

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September 01, 2022
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®, fentanyl citrate) 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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Titration Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>fentanyl citrate (Abstral)</td>
<td><strong>Start</strong>: 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 half</td>
</tr>
</tbody>
</table>

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September 01, 2022
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*

<table>
<thead>
<tr>
<th>Current ACTIQ Dose (mcg)</th>
<th>Initial Abstral Dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mcg</td>
<td>100 mcg</td>
</tr>
<tr>
<td>400 mcg</td>
<td>200 mcg</td>
</tr>
<tr>
<td>600 mcg</td>
<td>200 mcg</td>
</tr>
<tr>
<td>800 mcg</td>
<td>200 mcg</td>
</tr>
<tr>
<td>1200 mcg</td>
<td>200 mcg</td>
</tr>
<tr>
<td>1600 mcg</td>
<td>400 mcg</td>
</tr>
</tbody>
</table>

**Product Name**

**Titration Dosing Schedule**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Titration Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>fentanyl citrate (Actiq)</td>
<td>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. <em>Note: No more than six units is allowed to be dispensed at one time until maintenance dose is found.</em></td>
</tr>
<tr>
<td>400 mcg lozenge handle</td>
<td>Same instructions as above <em>Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.</em></td>
</tr>
<tr>
<td>600 mcg lozenge handle</td>
<td>Same instructions as above <em>Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.</em></td>
</tr>
<tr>
<td>800 mcg lozenge handle</td>
<td>Same instructions as above <em>Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.</em></td>
</tr>
<tr>
<td>1200 mcg lozenge handle</td>
<td>Same instructions as above <em>Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.</em></td>
</tr>
<tr>
<td>1600 mcg lozenge handle</td>
<td>Same instructions as above <em>Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.</em></td>
</tr>
</tbody>
</table>
**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.*

<table>
<thead>
<tr>
<th>200 mcg buccal tablet</th>
<th>1x 200mg tab</th>
</tr>
</thead>
<tbody>
<tr>
<td>2x 100mcg, or</td>
<td></td>
</tr>
<tr>
<td>400 mcg buccal tablet</td>
<td>4x 100mcg, or</td>
</tr>
<tr>
<td></td>
<td>2x 200mg tab, or</td>
</tr>
<tr>
<td></td>
<td>1x 400mg tab</td>
</tr>
<tr>
<td>600 mcg buccal tablet</td>
<td>3x 200mcg, or</td>
</tr>
<tr>
<td></td>
<td>1x 600mg tab</td>
</tr>
<tr>
<td>800 mcg buccal tablet</td>
<td>4x 200mcg, or</td>
</tr>
<tr>
<td></td>
<td>1x 800mg tab</td>
</tr>
</tbody>
</table>

**Initial Dosing Recommendations for Patients on ACTIQ**

<table>
<thead>
<tr>
<th>Current ACTIQ Dose (mcg)</th>
<th>Initial Fentora Dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>100 mcg</td>
</tr>
<tr>
<td>400</td>
<td>100 mcg</td>
</tr>
<tr>
<td>600</td>
<td>200 mcg</td>
</tr>
<tr>
<td>800</td>
<td>200 mcg</td>
</tr>
<tr>
<td>1200</td>
<td>2x 200 mcg</td>
</tr>
<tr>
<td>1600</td>
<td>2x 200 mcg</td>
</tr>
</tbody>
</table>

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.

**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.*

<table>
<thead>
<tr>
<th>200 mcg nasal spray</th>
<th>2 x 100 mcg spray (1 in each nostril)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Note: Only comes in a 100mcg and 400mcg bottle, these strengths are achieved by intervals of 100mcg or 400mcg</td>
<td></td>
</tr>
<tr>
<td>400 mcg nasal spray</td>
<td>1 x 400 mcg</td>
</tr>
<tr>
<td>800 mcg nasal spray</td>
<td>2 x 400mcg (1 in each nostril)</td>
</tr>
<tr>
<td>Note: Only comes in a 100mcg and 400mcg bottle, these strengths are achieved by intervals of 100mcg or 400mcg</td>
<td></td>
</tr>
</tbody>
</table>

Washington State Rx Services is administered by moda HEALTH

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September 01, 2022
**fentanyl citrate (Subsys)**

<table>
<thead>
<tr>
<th>Dose</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mcg sublingual spray</td>
<td>1 × 100 mcg unit</td>
</tr>
<tr>
<td>200 mcg sublingual spray</td>
<td>1 × 200 mcg unit</td>
</tr>
<tr>
<td>400 mcg sublingual spray</td>
<td>1 × 400 mcg unit</td>
</tr>
<tr>
<td>600 mcg sublingual spray</td>
<td>1 × 600 mcg unit</td>
</tr>
<tr>
<td>800 mcg sublingual spray</td>
<td>1 × 800 mcg unit</td>
</tr>
<tr>
<td>1200 mcg sublingual spray</td>
<td>2 × 600 mcg unit</td>
</tr>
<tr>
<td>1600 mcg sublingual spray</td>
<td>2 × 800 mcg unit</td>
</tr>
</tbody>
</table>

*Please see chart below for conversion when switching from Actiq to Subsys.*

**Initial Dosing Recommendations for Patients on ACTIQ**

<table>
<thead>
<tr>
<th>Current ACTIQ Dose (mcg)</th>
<th>Initial Subsys Dose (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>100 mcg</td>
</tr>
<tr>
<td>400</td>
<td>200 mcg</td>
</tr>
<tr>
<td>600</td>
<td>200 mcg</td>
</tr>
<tr>
<td>800</td>
<td>400 mcg</td>
</tr>
<tr>
<td>1200</td>
<td>400 mcg</td>
</tr>
<tr>
<td>1600</td>
<td>400 mcg</td>
</tr>
</tbody>
</table>

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**

<table>
<thead>
<tr>
<th>Fentanyl citrate (fentanyl citrate)</th>
</tr>
</thead>
</table>

**Start:** 100 mcg, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100 mcg 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.*

<table>
<thead>
<tr>
<th>Dose</th>
<th>Unit</th>
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<tbody>
<tr>
<td>200 mcg lozenge handle</td>
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</tr>
<tr>
<td>400 mcg lozenge handle</td>
<td>1 × 400 mcg unit</td>
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<tr>
<td>600 mcg lozenge handle</td>
<td>1 × 600 mcg unit</td>
</tr>
<tr>
<td>800 mcg lozenge handle</td>
<td>1 × 800 mcg unit</td>
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<td>1200 mcg lozenge handle</td>
<td>1 × 1200 mcg unit</td>
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<tr>
<td>1600 mcg lozenge handle</td>
<td>2 × 1600 mcg unit</td>
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**References**


Policy Implementation/Update:

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<th>Date</th>
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</thead>
<tbody>
<tr>
<td>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.</td>
<td>06/2020</td>
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<tr>
<td>Converted to policy, added in REMS question, age limitation question, and clarified prescribing provider specialty needed for approval.</td>
<td>04/2020</td>
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<td>Previous reviews</td>
<td>11/15/13, 12/28/17</td>
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<td>Criteria created</td>
<td>12/2011</td>
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Policy Type: PA

Pharmacy Coverage Policy: UMP236

Description
Finerenone (Kerendia) is a selective, nonsteroidal mineralocorticoid receptor antagonist (MRA)

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

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<thead>
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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
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<tr>
<td>finerenone (Kerendia)</td>
<td>10 mg tablets</td>
<td>Adjunct therapy for chronic kidney disease in type 2 diabetes</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>20 mg tablets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Finerenone (Kerendia) 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 **Type 2 Diabetes Mellitus (T2DM)** when the following are met:
      1. Member has chronic kidney disease (CKD) based on **one** of the following:
         i. Estimated glomerular filtration rate (eGFR) is 60 mL/min/1.73m² or less for at least 3 months; **OR**
         ii. Persistent moderate to severe albuminuria (urine albumin-to-creatinine ratio [UACR] 30 mg/g or greater, or 0.113 mg/mmol or greater) for at least 3 months; **AND**
      2. Documentation that treatment with an Angiotensin Converting Enzyme inhibitor (ACEI, e.g., lisinopril) or an Angiotensin Receptor Blocker (ARB, e.g., losartan) has been tried, unless all agents in these classes are contraindicated; **AND**
         i. Provider attests that the treatment with an ACEI or ARB will be continued, unless all are contraindicated; **AND**
      3. Treatment with ONE Sodium Glucose Co-transporter-2 (SGLT2) inhibitor (e.g., empagliflozin (Jardiance), dapagliflozin (Farxiga)) has been ineffective, not tolerated, or all are contraindicated; **AND**
      4. Finerenone (Kerendia) will **not** be used in combination with a Sodium Glucose Co-Transporter-2 (SGLT2) inhibitor (e.g., empagliflozin (Jardiance), dapagliflozin (Farxiga)).

II. Finerenone (Kerendia) is considered **investigational** when used for all other conditions, including but not limited to:
A. Treatment of CKD in members less than 18 years of age
B. Treatment of hypertension
C. Treatment of cardiovascular disorder (e.g. myocardial infraction, heart failure)
D. Edema associated with nephrotic syndrome
E. Perioperative management of hyperaldosteronism

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
   A. Member has exhibited improvement or stability of disease symptoms (e.g. stabilization of eGFR, lack of hospitalization due to renal or cardiovascular disease); OR
   B. In the absence of improvement or stability of disease symptoms, the provider attests that continuation of therapy is medically necessary AND clinical rationale of medical necessity has been provided and reviewed by a health plan clinician.

Supporting Evidence

I. Finerenone (Kerendia) is a selective, nonsteroidal mineralocorticoid receptor antagonist (MRA) approved as an adjunct treatment to slow the progression of renal disease and to reduce the risk of cardiovascular (CV) outcomes in adult patients with chronic kidney disease (CKD) in type 2 diabetes (T2D). Efficacy and safety of finerenone (Kerendia) in the pediatric population has not been evaluated.

II. MR overactivation may lead to inflammation and fibrosis and contribute to cardiorenal risk in T2D via hemodynamic and metabolic mechanisms. These are considered major drivers of heart and kidney damage in patients with CKD in T2D. Finerenone (Kerendia) reduces inflammation and fibrosis by blocking MR overactivation promoted by cardiorenal disease or diabetes. Finerenone (Kerendia) is the first non-steroidal MRA for adjunct treatment for cardiorenal risk reduction for CKD in T2D. Place in therapy for finerenone (Kerendia) is anticipated as an alternative to SGLT2 inhibitors.

III. The KDIGO 2020 guideline for management of CKD in diabetes recommend control of hypertension and hyperglycemia, as well as use of renin-angiotensin blockers (e.g. ACEI, ARB). Additionally, SGLT2 inhibitors (SGLT2i) have been recently approved as adjunct therapy to reduce cardiorenal risk in patients with CKD in T2D. Specifically, utility of choice of anti-diabetic drug regimen depends largely on the stage (severity) of CKD. For example, a combination of metformin and SGLT2i for T2D, is recommended when eGFR is ≥ 30 mL/min. Renin–angiotensin system (RAS) inhibition is recommended for patients with albuminuria and hypertension. For members whose CKD progresses despite treatment with metformin, ACEI and/or ARB, and SGLT2i (e.g. eGFR reduction >30%, or progression to dialysis-dependence), additional antidiabetic therapy may be considered for glycemic control (e.g. GLP-1 agonist, DPP-4 inhibitors, insulin).
The clinical diagnosis of CKD in T2D is primarily based on the presence of albuminuria (urine-albumin-to-creatinine ratio [UACR] ≥ 30 mg/g) and/or eGFR < 60 mL/min/1.73 m² for ≥ 3 months, with the typical presentation generally considered to include a long duration of diabetes, albuminuria without hematuria, retinopathy, a gradually progressive decline in eGFR, and no other primary causes of kidney damage. Albuminuria is an essential marker for kidney disease, as well as a CV risk marker for myocardial infarction (MI) and stroke, in patients with T2D. Albuminuria is often the first clinical indicator of kidney disease, and frequently appears before a reduction in eGFR can be seen.

Two randomized, double-blind, placebo-controlled, Phase 3 trials for finerenone (Kerendia) have been completed. The new drug application (NDA) for finerenone (Kerendia) was submitted to the US-FDA based on data from one randomized, double-blind, placebo-controlled, Phase 3 trial (FIDELIO-DKD) in 5,734 patients with CKD in T2D. The primary endpoint for FIDELIO-DKD was a composite renal outcome consisting of kidney failure, a sustained decrease of ≥ 40% in eGFR, or death from renal causes. Composite CV outcomes were assessed as the key secondary endpoint. Another Phase 3 clinical trial (FIGARO-DKD) assessed composite CV outcomes as the primary endpoint, and composite renal outcomes as pre-specified secondary endpoint. Results for FIGARO-DKD are not published as of July 2021.

The FIDELIO-DKD participants consisted of adults (mean age 65) with diagnoses of T2D and CKD, with the majority of patients (52%) having an eGFR between 25 and 45 mL/min at baseline. All participants were pretreated with an ACEI, ARB, or both at maximum tolerated doses. Other baseline antihypertensive and antidiabetic medications (e.g. insulin, metformin, DPP-4 inhibitors) were also continued. Clinical trial data points to finerenone (Kerendia) as an adjunct to baseline therapy, specifically to ACEI or ARB. Although contraindication to all ACEI and ARB agents is rare, in such situations, coverage for finerenone (Kerendia) may be warranted without requiring concurrent therapy with an ACEI or ARB. Of note, adverse reactions to one agent in these therapeutic classes may not constitute as a class contraindication. Some examples of contraindication may include hypersensitivity reactions, severe angioedema, and persistent severe hyperkalemia.

The FIDELIO-DKD study demonstrated that, over a median follow-up period of 2.6 years, the primary composite renal outcomes was statistically significantly lower in the finerenone (Kerendia) group than the placebo group (17.8% [n= 504] vs 21.1% [n= 600]; HR: 0.82; (95% CI: 0.73, 0.93; p=0.001). Overall, 29 patients needed to be treated with finerenone (Kerendia) to prevent one primary outcome event (number needed to treat [NNT]; 95% CI: 16, 166) based on an absolute risk reduction of 3.4% (95% CI: 0.6, 6.2) after three years.

During the FIDELIO-DKD, only 4.3% (n= 124) participants were on SGLT2i at baseline and/or concurrently with finerenone (Kerendia). This trial was not powered to detect a difference in this subgroup (patients with and without concurrent SGLT2i use). Finerenone (Kerendia) did not provide renal risk reduction to this subgroup based on 14 primary endpoint events in the finerenone (Kerendia) arm versus 10 in the placebo arm (n=135); HR: 1.38 (95% CI: 0.61, 3.10). This indicates uncertainty around the effect size and clinical benefits of finerenone (Kerendia) in combination with SGLT2i in the real world setting. Although devoid of major safety concerns, additive efficacy, and applicability of finerenone (Kerendia) in combination with SGLT2 inhibitors remains uncertain.
Investigational or Not Medically Necessary Uses

I. There are ongoing clinical studies to assess efficacy and safety of finerenone (Kerendia) in other settings. Notably, clinical trials in the settings of diabetic nephropathy, heart failure with systolic and diastolic dysfunction (HFrEF, HfPpEF), non-diabetic kidney disease are underway. However, finerenone (Kerendia) does not have sufficient clinical evidence to support efficacy and safety, and has not been FDA-approved, for treatment of these conditions. Finerenone (Kerendia) is considered investigational when used for all other conditions, including but not limited to:
   A. Treatment of CKD in members less than 18 years of age
   B. Treatment of hypertension
   C. Treatment of cardiovascular disorder (e.g. myocardial infarction, heart failure)
   D. Edema associated with nephrotic syndrome
   E. Perioperative management of hyperaldosteronism

Appendix

Table 1. Examples of baseline therapies for Chronic Kidney Disease (CKD) in Type 2 Diabetes Mellitus (T2DM)

<table>
<thead>
<tr>
<th>Angiotensin-Converting Enzyme Inhibitors (ACEi)</th>
<th>Angiotensin II Receptor Blockers (ARB)</th>
<th>Sodium Glucose Co-Transporter-2 Inhibitors (SGLT2i)</th>
</tr>
</thead>
<tbody>
<tr>
<td>benazepril</td>
<td>azilsartan</td>
<td>canagliflozin (Invokana)</td>
</tr>
<tr>
<td>captopril</td>
<td>candesartan</td>
<td>dapagliflozin (Farxiga)</td>
</tr>
<tr>
<td>enalapril</td>
<td>eprosartan</td>
<td>empagliflozin (Jardiance)</td>
</tr>
<tr>
<td>fosinopril</td>
<td>irbesartan</td>
<td>ertugliflozin (Steglatro)</td>
</tr>
<tr>
<td>lisinopril</td>
<td>losartan</td>
<td></td>
</tr>
<tr>
<td>moexipril</td>
<td>olmesartan</td>
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</tr>
<tr>
<td>perindopril</td>
<td>telmisartan</td>
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<tr>
<td>quinapril</td>
<td>valsartan</td>
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<tr>
<td>ramipril</td>
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<td></td>
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<tr>
<td>trandolapril</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Combinations of SGLT2i with metformin and/or other antidiabetic agents:
- canagliflozin+metformin (Invokamet)
- dapagliflozin+metformin (Xigduo XR)
- dapagliflozin+saxagliptin (Qtern)
- empagliflozin+linagliptin (Glyxambi)
- empagliflozin+metformin (Synjardy)
- empagliflozin+linagliptin+metformin (Trijardy XR)

References


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.

September 01, 2022


**Policy Implementation/Update:**

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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: UMP204

Description
Fostemsavir (Rukobia) is an orally administered gp120 attachment inhibitor.

Length of Authorization
I. Initial: Three months
   • Renewal: 12 months

Quantity Limits

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<tr>
<th>Product Name</th>
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<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>fostemsavir (Rukobia)</td>
<td>600 mg extended-release tablets</td>
<td>Human immunodeficiency virus type 1 (HIV-1) infection</td>
<td>60 tablets/30 days</td>
</tr>
</tbody>
</table>

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

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

Policy Implementation/Update:

<table>
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<th>Date</th>
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</thead>
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<td>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.</td>
<td>03/2021</td>
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<td>Policy created</td>
<td>11/2020</td>
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Policy Type: PA

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

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</thead>
<tbody>
<tr>
<td>gabapentin ER (Gralise)</td>
<td>300 mg tablets</td>
<td>Postherpetic neuralgia</td>
<td>90 tablets/30 days</td>
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<td></td>
<td>600 mg tablets</td>
<td></td>
<td>33 tablets (1 pack)/30 days</td>
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<tr>
<td></td>
<td>300 mg-600mg tablets Blister/Starter Pack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gabapentin enacarbil (Horizant)</td>
<td>300 mg tablets</td>
<td>Postherpetic neuralgia; Restless leg syndrome</td>
<td>30 tablets/30 days</td>
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<tr>
<td></td>
<td>600 mg tablets</td>
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<td>60 tablets/30 days</td>
</tr>
</tbody>
</table>

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; 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**:

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.

September 01, 2022
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

5. Study of Safety and Effectiveness of GRALISE (Gabapentin) Tablets in the Treatment of Patients With Postherpetic Neuralgia in Clinical Practice. Clinicaltrials.gov. 2012 (NCT 01426230)
Policy Implementation/Update:

<table>
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<th>Date</th>
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</thead>
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<tr>
<td>Update to new policy format, addition of pregabalin as required agent to try and fail, removal of renal status related criteria</td>
<td>10/2020</td>
</tr>
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<td>Previous review</td>
<td>11/2011</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
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<tbody>
<tr>
<td>ganaxolone</td>
<td>Seizures associated with CDKL5</td>
<td>50 mg/mL oral</td>
<td>≤ 28 kg: Monthly quantity (in mL) to allow for a</td>
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<td>(Ztalmy)</td>
<td>Deficiency Disorder (CDD)</td>
<td>suspension</td>
<td>maximum of 63 mg/kg per day</td>
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<td>&gt; 28 kg: Monthly quantity (in mL) to allow for a</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>maximum of 1800 mg (36 mL) per day</td>
</tr>
</tbody>
</table>

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


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.

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<thead>
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<tr>
<td></td>
<td>Dravet Syndrome</td>
</tr>
<tr>
<td></td>
<td>Tuberous Sclerosis Complex</td>
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<tr>
<td>vigabatrin (Sabril®, Vigadone®) Policy</td>
<td>West Syndrome (Infantile Spasms)</td>
</tr>
<tr>
<td>stiripentol (Diacomit®) Policy</td>
<td>Refractory complex partial epileptic seizure, adjunct therapy</td>
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<td>fenfluramine (Fintepla®) Policy</td>
<td>Dravet Syndrome</td>
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Policy Implementation/Update:

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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: 6 months
- Renewal: Twelve months

Quantity limits

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<tr>
<td>gilteritinib (Xospata)</td>
<td>40 mg tablets</td>
<td>Relapse/Refractory FLT3 AML</td>
<td>90 tablets/30 days</td>
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</table>

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. Relapsed/refractory defined as those that fail to attain a complete remission (CR) with intensive induction chemotherapy; AND
      2. Xospata (gilteritinib) will be used as monotherapy; AND
      3. FLT3 mutation status has been detected by an FDA-approved test (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. 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. Relapsed/refractory FLT3-mutated AML
   A. Clinical documentation of response to treatment, such as stabilization or improvement in disease; AND
   B. Absence of disease progression after six months; AND
   C. Absence of unacceptable toxicity from the medication; AND
   D. Gilteritinib (Xospata) continues to be used as monotherapy

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. Gilteritinib (Xospata) was studied in a phase III, randomized controlled trial against salvage chemotherapy in those that had relapsed or were refractory (i.e., had not reached CR following treatment).

II. Subjects included were adults with confirmed FLT3-mutated AML as detected by an FDA-approved test. 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.

Investigational or Not Medically Necessary Uses

I. Newly diagnosed AML
   A. There is lack of evidence for the use of gilteritinib (Xospata)) in this setting.

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 evidence for the safety and efficacy of gilteritinib (Xospata) outside of the monotherapy setting. Clinical trials evaluated monotherapy only.

References

4. ClinicalTrials.gov

Policy Implementation/Update:

<table>
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<td></td>
<td>02/2019</td>
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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP206

Description
Glasdegib (Daurismo) is an orally administered hedgehog pathway inhibitor.

Length of Authorization
- Initial: six months
- Renewal: 12 months

Quantity limits

<table>
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<th>Glasdegib (Daurismo)</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
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<td>25 mg tablets</td>
<td>Acute myeloid leukemia</td>
<td>60 tablets/30 days</td>
<td>204939</td>
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<tr>
<td>100 mg tablets</td>
<td>Acute myeloid leukemia</td>
<td>30 tablets/30 days</td>
<td>204938</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Glasdegib (Daurismo) may be considered medically necessary when the following criteria are met:
   A. Prescribed by an oncologist or hematologist; **AND**
   B. A diagnosis of newly-diagnosed acute myeloid leukemia (AML) when the following are met:
      1. Age 75 years and older **OR**
      2. Have comorbidities that preclude use of intensive induction chemotherapy such as:
         i. Baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2
         ii. Severe cardiac comorbidity (i.e. LEVF <45%)
         iii. Baseline Scr >1.3 (CrCl ≥30 to <45 mL/min)
            **AND**
      3. Does not have hepatic or severe renal impairment (CrCl <30 mL/min); **AND**
      4. 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. Clinical documentation of response to treatment, such as stabilization or improvement of disease; **AND**
II. Absence of unacceptable toxicity from the medication

Supporting Evidence

Washington State Rx Services is administered by moda HEALTH

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.

September 01, 2022
I. 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.

II. Patients included in the trial were 55 years and older and met one of the following: at least 75 years old, severe cardiac disease, baseline Eastern Cooperative Oncology Group performance stats (ECOG PS) of 2, or a baseline serum creatinine > 1.3 mg/dL. 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.

III. Pivotal trial leading to glasdegib (Daurismo) approval met the primary efficacy outcome of overall survival, with median OS of 8.3 months in the combination arm versus 4.3 months with LDAC alone.

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. Trials are currently underway evaluating the use in combination with azacitidine or decitabine, data has not yet been published.

References


Policy Implementation/Update:

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<tr>
<td>Date Effective</td>
<td>February 2019</td>
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<tr>
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</table>
Glycopyrronium (Qbrexza™)

UMP POLICY

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

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<th>DDID</th>
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</thead>
<tbody>
<tr>
<td>glycopyrronium (Qbrexza)</td>
<td>Topical 2.4% single-use pre-moistened cloth</td>
<td>Primary axillary hyperhidrosis</td>
<td>30 cloths/30 days</td>
<td>203316 203275</td>
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</tbody>
</table>

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, glycopyrrrolate 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

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.

September 01, 2022
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

Policy Implementation/Update:

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<tr>
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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

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<tr>
<th>Product Name</th>
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<tbody>
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<td>Endometriosis</td>
<td>2 mg/mL nasal spray</td>
<td>16 mL/30 days</td>
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<td>Central Precocious Puberty</td>
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<tr>
<td>leuprolide acetate (Lupron)</td>
<td>Central Precocious Puberty</td>
<td>1 mg/0.2mL kit</td>
<td>1 kit/14 days</td>
<td>6 months</td>
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<tr>
<td>Leuprolide acetate (Lupron Depot)</td>
<td>Endometriosis, Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria</td>
<td>3.75 mg/syringe kit</td>
<td>1 syringe kit/30 days</td>
<td>6 months for all indications EXCEPT - 3 months for uterine leiomyoma - 2 months for Endometrial Thickness</td>
</tr>
<tr>
<td></td>
<td>Advanced Prostate Cancer, Central Precocious Puberty</td>
<td>7.5 mg/syringe kit</td>
<td>1 syringe kit/30 days</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>Advanced Prostate Cancer, Advanced Breast Endometrial Thickness, Uterine leiomyoma, Central Precocious Puberty, Gender Dysphoria</td>
<td>11.25 mg/syringe kit</td>
<td>1 syringe kit/90 days</td>
<td>6 months for all indications EXCEPT - 3 months for uterine Leiomyoma - 2 months for Endometrial Thickness</td>
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<td>Advanced Prostate Cancer</td>
<td>22.5 mg/syringe kit</td>
<td>1 syringe kit/90 days</td>
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<td>Advanced Prostate Cancer, Cancer Central Precocious Puberty</td>
<td>30 mg/syringe kit</td>
<td>1 syringe kit/120 days</td>
<td>6 months</td>
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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.

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<th>Leuprolide acetate (Lupron Depot-Ped)</th>
<th>Advanced Prostate Cancer</th>
<th>45 mg/syringe kit</th>
<th>1 syringe kit/180 days</th>
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<tr>
<td>Central Precocious Puberty</td>
<td>7.5 mg/syringe kit</td>
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<tr>
<td>Central Precocious Puberty</td>
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<tr>
<td>Central Precocious Puberty</td>
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<tr>
<td>Central Precocious Puberty</td>
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<tr>
<td>Leuprolide acetate (Lupron Depot-Ped)</td>
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<tr>
<td>Leuprolide acetate (Eligard)</td>
</tr>
<tr>
<td>Endometriosis</td>
</tr>
</tbody>
</table>

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.

September 01, 2022
<table>
<thead>
<tr>
<th>Leuprolide-norethindrone (Lupaneta)</th>
<th>Endometriosis</th>
<th>11.25-5 mg/syringe</th>
<th>1 syringe kit/90 days</th>
<th>6 months (MAX #1 renewal allow)</th>
</tr>
</thead>
</table>

**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**

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September 01, 2022
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 premenopausal 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 leiomyoma 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...
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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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10. Latronico AC. Challenges in monitoring GnRH analog treatment in central precocious puberty. Arch Endocrinol Metab. 2020;64(2):103-104.

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>05/2022</td>
</tr>
<tr>
<td>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 leiomyoma and endometrial thickness.</td>
<td>10/2019</td>
</tr>
<tr>
<td>Previous reviews</td>
<td>08/2017</td>
</tr>
<tr>
<td>Policy created</td>
<td>10/2014</td>
</tr>
</tbody>
</table>
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: 1 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

<table>
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<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>somatropin (Genotropin)</td>
<td>Growth hormone deficiency (GHD), children</td>
<td>5 mg/mL cartridge</td>
<td>Pediatric GHD: 0.24 mg/kg/week</td>
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<tr>
<td></td>
<td>Growth hormone deficiency (GHD), adults</td>
<td>12 mg/mL cartridge</td>
<td>Adult GHD: 0.08 mg/kg/week</td>
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<td>Idiopathic short stature</td>
<td>0.2 mg/0.25 mL syringe</td>
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<td>Prader-Willi syndrome</td>
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<td>Small for gestational age</td>
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<td>Turner syndrome</td>
<td>0.8 mg/0.25 mL syringe</td>
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<td></td>
<td>1 mg/0.25 mL syringe</td>
<td>Idiopathic short stature: 0.47 mg/kg/week</td>
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<td>Prader-Willi syndrome: 0.24 mg/kg/week</td>
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<td>Small for gestational age: 0.48 mg/kg/week</td>
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<table>
<thead>
<tr>
<th>Condition(s)</th>
<th>Dosage</th>
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<td>5 mg vial</td>
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<td>6 mg cartridge</td>
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<tr>
<td>• Idiopathic short stature</td>
<td>12 mg cartridge</td>
</tr>
<tr>
<td>• Short stature homeobox-containing gene (SHOX) deficiency</td>
<td>24 mg cartridge</td>
</tr>
<tr>
<td>• Small for gestational age</td>
<td></td>
</tr>
<tr>
<td>• Turner syndrome</td>
<td></td>
</tr>
<tr>
<td>2 mg/0.25 mL syringe</td>
<td>Turner syndrome: 0.33 mg/kg week</td>
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<tr>
<td>5 mg vial</td>
<td>Pediatric GHD: 0.3 mg/kg/week</td>
</tr>
<tr>
<td>6 mg cartridge</td>
<td>Adult GHD: 0.0875 mg/kg/week (0.0125 mg/kg/day)</td>
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<td>12 mg cartridge</td>
<td>Idiopathic short stature: 0.37 mg/kg/week</td>
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<td>24 mg cartridge</td>
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<td>• Growth hormone deficiency (GHD), adults</td>
<td>Adult GHD: 0.112 mg/kg/week (0.016 mg/kg/day)</td>
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<td>• Noonan syndrome</td>
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<td>• Small for gestational age</td>
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<tr>
<td>• Turner syndrome</td>
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<td>5 mg/2 mL pen injector</td>
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<td>• Turner syndrome</td>
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<td>• Small for gestational age</td>
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<td>• Turner syndrome</td>
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<td>somatropin (Sogroya)</td>
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Growth Hormone Therapy in Children and Adolescents

Initial Evaluation

Genotropin:
- There is no prior authorization required on this preferred agent, unless requesting over the allowed quantity limits noted above.

I. Growth hormone replacement 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
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. 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 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**

2. **Growth Hormone Deficiency; AND**
   i. Request is for Skytrofa; **AND**
      a. A trial with Genotropin 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 that is not expected to occur with Skytrofa; **OR**
   ii. Request for other growth hormone product; **AND**
      a. Treatment with Genotropin has been ineffective, contraindicated, or not tolerated; **AND**
      b. Treatment with Skytrofa has been ineffective, contraindicated, or not tolerated

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. Treatment with Genotropin has been ineffective, contraindicated, or not tolerated

**Growth Hormone Therapy in Adults**

**Initial Evaluation**

**Genotropin:**
- There is no prior authorization required on this preferred agent, unless requesting over the allowed quantity limits noted above.
II. **Growth hormone replacement** 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: hypopituitarism due to pituitary disease, hypothalamic disease, pituitary surgery, cranial radiation therapy, or traumatic brain injury; **AND**
         i. A subnormal response (less than 10 ng/ml) to any **TWO** of the following provocative growth hormone (GH) stimulation tests:
            1. Arginine
            2. Clonidine
            3. Glucagon
            4. Insulin induced hypoglycemia
            5. L-dopa
            6. Propranolol; **OR**
      b. 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**
      c. Idiopathic GH deficiency diagnosis; **AND**
         i. Diagnosis been confirmed by **BOTH** of the following:
            1. A subnormal response (less than 10 ng/ml) to any **TWO** of the following provocative growth hormone (GH) stimulation tests:
               a. Arginine
               b. Clonidine
               c. Glucagon
               d. Insulin induced hypoglycemia
               e. L-dopa
               f. 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 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
      d. Request is for Skytrofa; OR
e. Request for other growth hormone product; **AND**  
   i. Treatment with Genotropin has been ineffective, contraindicated, or not tolerated; **AND**  
   ii. Treatment with Skytrofa has been ineffective, contraindicated, or not tolerated; **OR**  

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**  
   d. Treatment with Genotropin has been ineffective, contraindicated, or not tolerated; **OR**  
      i. The request is for Humatrope or Zomacton for SHOX gene deficiency; **OR**  
      ii. The request is for Nutropin AQ for chronic renal insufficiency; **OR**  
      iii. The request is for Norditropin in Noonan Syndrome; **OR**  

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. Treatment with Genotropin has been ineffective, contraindicated, or not tolerated;  
      **AND**  
   b. 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. Other than device and FDA approved indications, there is little to no differentiation between these products. Skytrofa (lonapegsomatropin) is a 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 adults; however, efficacy results were based on a single trial in which numerical values compared to open-label Norditropin showed lower results. 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.

II. 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.

III. The diagnosis of GH deficiency is confirmed by measurement of GH secretion, commonly following stimulation by a provocative agent. The American Association of Clinical Endocrinologists (AACE) and the Growth Hormone Research Society (GHRS) all consider a growth hormone response of less than 10 ng/mL supportive of the diagnosis of GHD.

IV. 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.

V. Somatropin and somapacitan should not be used for growth promotion in pediatric patients with closed epiphyses.

VI. 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.

VII. 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.

VIII. 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.

IX. 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 presence of a low IGF-I also increases the likelihood that this diagnosis is correct.
FDA Approved Indications for Growth Hormone Products

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<thead>
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<th>Brand</th>
<th>GHD</th>
<th>TS</th>
<th>ISS</th>
<th>SGA</th>
<th>PWS</th>
<th>CKD</th>
<th>NS</th>
<th>SHOX</th>
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</table>

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

References

2. Somatropin. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/
8. Humatrope [Prescribing Information]. Indianapolis, IN: Lilly USA, LLC; Dec 2016.
### Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tr>
<td>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.</td>
<td>07/2022</td>
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<tr>
<td>Updated preferred product from Norditropin to Genotropin</td>
<td>01/2022</td>
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<tr>
<td>Addition of new product lonapegsomatropin in non-preferred position</td>
<td>08/2021</td>
</tr>
<tr>
<td>Addition of new product Sogroya in non-preferred position</td>
<td>02/2021</td>
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<td>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.</td>
<td>11/2020</td>
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<tr>
<td>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.</td>
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<tr>
<td>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.</td>
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<td>08/2014</td>
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**Hepatitis C**  
**UMP POLICY**

**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**

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<td>sofosbuvir (Sovaldi)</td>
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<td>400 mg oral tablet</td>
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<td>velpatasvir/sofosbuvir (Epclusa)</td>
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<td>150 mg / 37.5 mg oral pellets</td>
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<td>200 mg / 50 mg oral pellets</td>
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*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.*
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<tr>
<th>Drug Name (authorized generic)</th>
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<th>Genotype</th>
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<td>daclatasvir (Daklinza)</td>
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<td>velpatasvir/sofosbuvir/voxilaprevir (Vosevi)</td>
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<td>simeprevir (Olysio)</td>
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<td>1 box/28 days</td>
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*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 not medically necessary 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

References

Washington State Rx Services is administered by

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September 01, 2022
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Policy Implementation/Update:

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<tr>
<td>Review of age expansion for Mavyret and Epclusa, no policy update needed</td>
<td>07/2021</td>
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<tr>
<td>Updated to include specific scenarios for Vosevi approval</td>
<td>06/2021</td>
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<tr>
<td>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.</td>
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<td>Updated to remove provider specialty and F0 requirements</td>
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<td>Updated preferred products to only include Mavyret, sofosbuvir/velpatasvir (authorized generic to Epclusa), and Vosevi.</td>
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### Appendix:

Please note, Mavyret is the preferred agent for Uniform Medical Plan.

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<th>Genotype</th>
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<td>Treatment naïve + No cirrhosis</td>
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<table>
<thead>
<tr>
<th>Treatment</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment naïve + Cirrhosis</td>
<td>Mavyret x 8 weeks</td>
</tr>
<tr>
<td>Treatment experienced^+ No cirrhosis</td>
<td>Mavyret x 16 weeks</td>
</tr>
<tr>
<td>Treatment experienced^+ Cirrhosis</td>
<td>Mavyret x 16 weeks</td>
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<tr>
<td>Treatment experienced‡ + No cirrhosis</td>
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<tr>
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<tr>
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<td>Treatment experienced ‡ + Cirrhosis</td>
<td>Mavyret x 8 weeks</td>
</tr>
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<td>Genotype 2</td>
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<tr>
<td>Treatment naïve + No cirrhosis</td>
<td>Mavyret x 8 weeks</td>
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<tr>
<td>Treatment naïve + Cirrhosis</td>
<td>Mavyret x 8 weeks</td>
</tr>
<tr>
<td>Treatment experienced^+ No cirrhosis</td>
<td>Vosevi x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced^+ Cirrhosis</td>
<td>Vosevi x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced‡ + No cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced‡ + Cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
</tr>
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<td>Mavyret x 8 weeks</td>
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<tr>
<td>Treatment experienced‡ + Cirrhosis</td>
<td>Mavyret x 12 weeks</td>
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<tr>
<td>Genotype 3</td>
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<td>Mavyret x 8 weeks</td>
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<tr>
<td>Treatment experienced^+ No cirrhosis</td>
<td>Vosevi x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced^+ cirrhosis</td>
<td>Vosevi x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced‡ + No cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
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<table>
<thead>
<tr>
<th>Genotype 4</th>
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<th>Genotype 5</th>
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</thead>
<tbody>
<tr>
<td>Treatment naïve + No cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Mavyret x 8 weeks</td>
</tr>
<tr>
<td>Treatment naïve + Cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Mavyret x 8 weeks</td>
</tr>
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<td>Vosevi x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced^+ cirrhosis</td>
<td>Vosevi x 12 weeks</td>
<td>Vosevi x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced^+ No cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
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<td>Treatment experienced^+ Cirrhosis</td>
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</tr>
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<td>Mavyret x 12 weeks</td>
</tr>
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<td>Mavyret x 12 weeks</td>
</tr>
<tr>
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<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
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<td>Mavyret x 8 weeks</td>
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<tr>
<td>Treatment experienced^+ cirrhosis</td>
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<tr>
<td>Genotype 5</td>
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<td>Genotype 5</td>
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<tr>
<td>Treatment naïve + No cirrhosis</td>
<td>Mavyret x 8 weeks</td>
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<tr>
<td>Treatment naïve + Cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Mavyret x 8 weeks</td>
</tr>
<tr>
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<td>Vosevi x 12 weeks</td>
<td>Vosevi x 12 weeks</td>
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<tr>
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<td>Vosevi x 12 weeks</td>
<td>Vosevi x 12 weeks</td>
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<tr>
<td>Treatment experienced^+ No cirrhosis</td>
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<td>Mavyret x 8 weeks</td>
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<tr>
<td>Treatment experienced^+ cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Mavyret x 8 weeks</td>
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<table>
<thead>
<tr>
<th>Genotype 6</th>
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</thead>
<tbody>
<tr>
<td>Treatment naïve + No cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment naïve + Cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced(^{\dagger}) + No cirrhosis</td>
<td>Vosevi x 12 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced(^{\dagger}) + cirrhosis</td>
<td>Vosevi x 12 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced(^{\ddagger}) + No cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced(^{\ddagger}) + Cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced(^{\ddagger}) + No cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced(^{\ddagger}) + Cirrhosis</td>
<td>Mavyret x 12 weeks</td>
<td>Other:</td>
</tr>
</tbody>
</table>

\(^{\dagger}\)Treatment experienced after only NS5A (ledipasvir, velpatasvir, daclatasvir, elbasvir, ombitasvir) containing regimen  
\(^{\ddagger}\)Treatment experienced after only NS3/4A PI (simeprevir, boceprevir, telaprevir) containing regimen  
\(^{\ddagger\ddagger}\)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**
Hereditary Angioedema  
UMP POLICY

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 (Firazyrr), 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: Three months
- Renewal: Six months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 esterase inhibitor (Cinryze)</td>
<td>500 unit single use vial for IV administration</td>
<td>HAE prophylaxis</td>
<td>20 vials/30 days</td>
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<tr>
<td>C1 esterase inhibitor (Haegarda)</td>
<td>2000 unit single use vial for SQ administration</td>
<td></td>
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<tr>
<td></td>
<td>3000 unit single use vial for SQ administration</td>
<td></td>
<td></td>
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<tr>
<td>Lanadelumab (Takhzyro)</td>
<td>300 mg/2 mL single dose vial for SQ administration</td>
<td></td>
<td>4 mL/28 days</td>
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<tr>
<td></td>
<td>300 mg/2 mL prefilled syringe for SQ administration</td>
<td></td>
<td>2 syringes/28 day</td>
</tr>
<tr>
<td>Berotralstat (Orladeyo)</td>
<td>110 mg capsules</td>
<td></td>
<td>28 capsules/28 days</td>
</tr>
<tr>
<td></td>
<td>150 mg capsules</td>
<td></td>
<td></td>
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<tr>
<td>C1 esterase inhibitor (Berinert)</td>
<td>500 unit single use vial for IV administration</td>
<td>Treatment of acute HAE attacks</td>
<td>Weight based 20 iu/kg, refer to chart below</td>
</tr>
<tr>
<td>C1 esterase inhibitor (Ruconest)</td>
<td>2100 unit single use vial for IV administration</td>
<td></td>
<td>16 vials/30 days</td>
</tr>
<tr>
<td>Icatibant (Firazyrr)</td>
<td>30 mg/3 mL SQ prefilled syringe</td>
<td></td>
<td>9 syringes (27 mL)/30 days</td>
</tr>
<tr>
<td>Icatibant (generic Firazyr)</td>
<td>30 mg/3 mL SQ prefilled syringe</td>
<td></td>
<td>9 syringes (27 mL)/30 days</td>
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<tr>
<td>Icatibant (Sajazir)</td>
<td>30 mg/3 mL SQ prefilled syringe</td>
<td></td>
<td>9 syringes (27 mL)/30 days</td>
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<table>
<thead>
<tr>
<th>Medication</th>
<th>Body Weight (kg)</th>
<th>Vial Configuration</th>
<th>Vials per Dose</th>
<th>Number of Vials per 30 days</th>
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<tbody>
<tr>
<td>Haegarda</td>
<td>Up to 33 kg</td>
<td>2000 unit</td>
<td>1</td>
<td>8</td>
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<tr>
<td></td>
<td>34-50</td>
<td>3000 unit</td>
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<td>8</td>
</tr>
<tr>
<td></td>
<td>51-67</td>
<td>2000 unit</td>
<td>2</td>
<td>16</td>
</tr>
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</table>
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 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)
               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 has had a trial and failure or intolerance to one of the following or has a contraindication to ALL:
               i. danazol
               ii. aminocaproic acid

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iii. tranexamic acid; AND
d. “On demand” therapy (e.g., icatibant [Firazyr], icatibant [Sajazir], Berinert, Ruconest, Kalbitor) has been ineffective, contraindicated, or not tolerated; AND
e. The member is ≥ 6 years of age; AND
   i. The request is for 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
f. 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), OR Berinert is requested; OR
      a. Ruconest is requested; AND
      b. Treatment with Berinert AND generic icatibant/icatibant (Sajazir), have been ineffective, contraindicated, or not tolerated; 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; 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; 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 one of the following specialists: allergist, immunologist, dermatologist, hematologist, pulmonologist, medical geneticist; AND
IV. The member continues to be evaluated for potentially treatable triggers of HAE attacks and is being managed to avoid triggers; AND
V. The member has been seen and evaluated for medication efficacy and safety in the past 12 months; AND
VI. 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
VII. Documentation the member has experienced functional improvement AND improvement in the number, severity, or duration of attacks; AND
VIII. 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: Documentation that the dose will be de-escalated to 300 mg (2 mL) every four weeks OR documentation of medical necessity is provided for maintaining the dose at 300 mg (2 mL) every two weeks; OR
   D. The request is for Orladeyo; OR
IX. 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

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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 is 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. 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. Options for treatment include androgens (danazol), antifibrinolytics (aminocaproic acid, tranexamic acid), C1 esterase inhibitors (Cinryze, Haegarda), and kallikrein inhibitor (Takhzyro, Orladeyo). 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.

VIII. Androgens and antifibrinolytics are widely available and have been used historically with success in many patients. Danazol is FDA-approved 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. Antifibrinolytic therapies have a
more favorable safety profile compared to androgens (danazol) for the prophylactic treatment of HAE. Aminocaproic acid and tranexamic acid are both generally well tolerated, common adverse events include nausea, vomiting, and diarrhea.

IX. 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.

X. 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 every 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.

XI. 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
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.

XII. There are no direct head-to-head studies comparing lanadelumab (Takzhro) and berotralstat (Orladeyo) to establish superior safety or efficacy of one product over the other; however, lanadelumab (Takzhro) 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.

References

**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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)</td>
<td>10/2021</td>
</tr>
<tr>
<td>Added Orladeyo criteria for prophylactic treatment of HAE for P&amp;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.</td>
<td>02/2021</td>
</tr>
<tr>
<td>Age for Haegarda expanded down to six years of age (from previous 12)</td>
<td>10/2020</td>
</tr>
<tr>
<td>Added age restriction to Takhzyro of ≥ 12 years of age</td>
<td>03/2020</td>
</tr>
<tr>
<td>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.</td>
<td>10/2019</td>
</tr>
<tr>
<td>Takhzyro criteria created for P&amp;T.</td>
<td>10/2018</td>
</tr>
<tr>
<td>Criteria updated to include Cinryze prophylactic therapy for patients six years of age and older, a new FDA approved age range.</td>
<td>01/2018</td>
</tr>
<tr>
<td>HAE indication review completed, agents included in policy were updated and questions added to align with clinical appropriateness and medical criteria.</td>
<td>11/2017</td>
</tr>
<tr>
<td>Criteria created</td>
<td>10/2016</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>human chorionic gonadotropin (human chorionic gonadotropin)</td>
<td>10,000 unit vial</td>
<td>Hypogonadotropic hypogonadism; Ovulation induction*; Prepubertal cryptorchidism</td>
<td>5 vials/30 days</td>
</tr>
<tr>
<td>human chorionic gonadotropin (Novarel)</td>
<td>5,000 unit vial</td>
<td></td>
<td>10 vials/30 days</td>
</tr>
<tr>
<td>human chorionic gonadotropin (Pregnyl)</td>
<td>10,000 unit vial</td>
<td></td>
<td>5 vials/30 days</td>
</tr>
</tbody>
</table>

*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).

**References**


**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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</tbody>
</table>
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP212

Description
Hydrocortisone (Alkindi Sprinkle) is an orally administered corticosteroid.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>hydrocortisone (Alkindi Sprinkle)</td>
<td>0.5mg capsules</td>
<td>Adrenocortical insufficiency</td>
<td>10 mg/m²/day*</td>
</tr>
<tr>
<td></td>
<td>1mg capsules</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2mg capsules</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5mg capsules</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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:

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.

September 01, 2022
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 diagnosis 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 nMol/L) and high adrenocorticotropic hormone (ACTH) levels (≥ 66 pmol/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/m²) 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.

References


Policy Implementation/Update:

<table>
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<th>Action and Summary of Changes</th>
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<tr>
<td>Policy created</td>
<td>12/2020</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP175

Description
Hydroxyprogesterone caproate (Makena) is an injectable synthetic progestin with unknown mechanism in reducing the risk of recurrent preterm birth.

Length of Authorization
- Initial: Five or six months depending on gestational age of therapy initiation
- Renewal: no renewal

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydroxyprogesterone caproate (Makena,</td>
<td>Intramuscular solution: 250 mg/mL,</td>
<td>Preterm birth</td>
<td>Intramuscular solution: 250 mg/mL (4 vials/28 days), 1250 mg/5 mL (1 vial/35 days)</td>
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<td>hydroxyprogesterone caproate)</td>
<td>1250 mg/5 mL</td>
<td></td>
<td>Subcutaneous auto-injector: 275 mg/1.1mL</td>
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<td></td>
<td>Subcutaneous auto-injector: 275 mg/</td>
<td></td>
<td>Subcutaneous auto-injector: 4 auto-injectors/28 days</td>
</tr>
<tr>
<td></td>
<td>1.1mL</td>
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Initial Evaluation

I. Hydroxyprogesterone caproate (Makena) may be considered medically necessary when the following criteria are met:
   A. Member is 16 years of age or older; **AND**
   B. A diagnosis of **preterm birth** when the following are met:
      1. Member has a singleton pregnancy; **AND**
      2. Ultrasound confirming gestational age between 16 weeks, 0 days and 20 weeks, 6 days; **AND**
      3. Member will start dose **AT** as early as 16 weeks, 0 days of gestation; **AND**
      4. Member has a history of singleton spontaneous preterm birth or singleton premature rupture of membranes at less than 37 weeks of gestation; **AND**
   C. The request is for generic hydroxyprogesterone caproate vials; **OR**
      1. Documentation of treatment with generic hydroxyprogesterone caproate vial has been ineffective, contraindicated, or not tolerated; **AND**
   D. Provider attest that member’s pharmacy benefit will be billed.

II. Hydroxyprogesterone caproate (Makena) is considered **not medically necessary** when criteria above are not met and/or when used for:

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.
A. Multifetal gestation  
B. Major fetal anomalies  
C. Maternal complications (current or planned cerclage, hypertension requiring medication, or seizure disorder)  
D. Uterine anomalies  
E. Pediatric population (< 16 years of age)  
F. Therapy initiated after 21 weeks of gestation  
G. Breast cancer  
H. Adenocarcinoma of uterus  
I. Amenorrhea  
J. Endometrial disorder (production of secretory endometrium and desquamation)  

Supporting Evidence  

I. Hydroxyprogesterone caproate (Makena) was initially approved 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. An FDA Advisory Committee in August 2006 voted unanimously that an additional confirmatory clinical trial was required to further assess safety and efficacy.  

II. 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).  

III. 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. The inclusion criteria was: at least 18 years of age, pregnant with a singleton gestation, has a documented history (chart notations from previous pregnancy and not just oral history) of singleton spontaneous 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]).  

IV. In a clinical trial, the effectiveness of 17 alpha-hydroxyprogesterone caproate (17P) was demonstrated in patients as young as 16 years of age. Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks of gestation (incidence, 36.3 percent in the progesterone group vs. 54.9 percent in the placebo group; relative risk, 0.66 [95 percent confidence interval, 0.54 to 0.81]), delivery at less than 35 weeks of gestation (incidence, 20.6 percent vs. 30.7 percent; relative risk, 0.67 [95 percent confidence interval, 0.48 to 0.93]), and delivery at less than 32 weeks of gestation (11.4 percent vs. 19.6 percent; relative risk, 0.58 [95 percent confidence interval, 0.37 to 0.91]).
V. In order to assess for medical versus pharmacy billing, the criterion for provider attestation that member’s pharmacy benefit will be billed. Since we do not carry member’s medical benefit, this criterion is to ensure that the provider will not be double billing, medical and pharmacy.

Not Medically Necessary Uses

I. Hydroxyprogesterone caproate (Makena) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:

A. There is limited clinical evidence to suggest that hydroxyprogesterone caproate (Makena) is safe and efficacious in the setting of: multifetal gestation, major fetal anomalies, maternal complications (current or planned cerclage, hypertension requiring medication, or seizure disorder), uterine anomalies, pediatric population (< 16 years of age), and therapy initiated after 21 weeks of gestation

B. Although there may be a role for generic hydroxyprogesterone caproate in the setting of breast cancer, adenocarcinoma of uterus, amenorrhea and endometrial disorder (production of secretory endometrium and desquamation); for the purpose of this hydroxyprogesterone caproate (Makena) policy, only the indication of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth/premature rupture of membranes at less than 37 weeks would be considered medically necessary.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Criteria transitioned into policy format</td>
<td>02/2020</td>
</tr>
<tr>
<td>Criteria updated to remove question around contraindication, included package insert clinical notes, and new subcutaneous auto-injector formulation</td>
<td>04/2018</td>
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<tr>
<td>Criteria updated to truncate approval table to 20 weeks based on the most recent guideline from The Society for Maternal-Fetal Medicine.</td>
<td>10/2017</td>
</tr>
<tr>
<td>Previous reviews</td>
<td>09/2013, 10/2012,</td>
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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: UMP037

Split Fill Management*

Description
Ibrutinib (Imbruvica) is an orally administered Bruton's tyrosine kinase (BTK) inhibitor.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Ibrutinib (Imbruvica)</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>560 mg tablets</td>
<td>Mantle Cell Lymphoma, previously treated; Marginal Zone Lymphoma, relapsed/refractory</td>
<td>30 tablets/30 days</td>
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<tr>
<td>420 mg tablets</td>
<td>Chronic Graft versus Host Disease (refractory); Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; Waldenström Macroglobulinemia</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>280 mg tablet</td>
<td>Dose modification</td>
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Initial Evaluation

I. **Ibrutinib (Imbruvica)** 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 or hematologist; **AND**
   C. 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; **AND**
   D. Member has not experienced disease progression while on a BTK inhibitor [e.g. zanubrutinib (Brukinsa), acalabrutinib (Calquence)]; **AND**
   E. A diagnosis of one of the following:
      1. **Mantle Cell Lymphoma (MCL); AND**
         i. Member has received one prior therapy [e.g., lenalidomide, rituximab, stem cell transplant, etc.]; **AND**
         ii. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
2. **Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL); AND**
   i. The member does not have a 17p deletion or TP53 mutation confirmed by testing; **AND**
      a. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
      b. The request is for use in combination with bendamustine and rituximab in the relapsed/refractory setting; **OR**
   ii. The member has a 17p deletion or TP53 mutation confirmed by testing; **AND**
      a. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**

3. **Waldenström Macroglobulinemia (WM); AND**
   i. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
   ii. Ibrutinib (Imbruvica) will be used with rituximab; **OR**

4. **Chronic Graft versus Host Disease (cGVHD); AND**
   i. 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

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. Mantle cell lymphoma, frontline
   D. Mantle cell lymphoma, combination therapy
   E. Marginal zone lymphoma, monotherapy
   F. Marginal zone lymphoma, combination therapy
   G. Marginal zone lymphoma, frontline
   H. Diffuse large B cell lymphoma
   I. Relapsed/refractory multiple myeloma
   J. Hairy cell leukemia
   K. Primary CNS lymphoma
   L. Esophagogastric carcinoma
   M. Glioblastoma
   N. Non-small-cell lung carcinoma
   O. T-cell lymphoma

**Renewal Evaluation**

I. Treatment is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
II. 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; AND

III. 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

IV. 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. In the setting of MCL, ibrutinib (Imbruvica) was studied in one open-label, multi-center, single-arm trial of 111 previously treated patients that received at least one prior therapy. The primary endpoint of overall response rate (ORR) was 67% (23% complete response), with a median duration of response of 17.5 months. 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).

III. 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 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.

IV. 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).

V. In the setting of cGVHD, ibrutinib (Imbruvica) was studied in an open-label, multi-center, single-arm trial of 42 patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy. Therapy with ibrutinib (Imbruvica) results 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 includes but is not limited to mycophenolate mofetil, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), and sirolimus.

VI. 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:

   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. Chronic lymphocytic leukemia/small lymphocytic lymphoma in the first line setting in combination with obinutuzumab
   i. 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.

C. Relapsed/refractory Hodgkin lymphoma
   i. Subject of current ongoing trials.

D. Mantle cell lymphoma, frontline
   i. Ibrutinib (Imbruvica) is being investigated as a first-line treatment for patients with MCL in the Phase 3 SHINE trial (NCT01776840), evaluating the safety and efficacy of ibrutinib plus bendamustine and rituximab in older patients with newly diagnosed MCL who are not eligible for stem cell transplant. SHINE has fully enrolled but there are no data available yet.
   ii. 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.

TRIANGLE has fully enrolled but there are no data available yet.

iii. 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.

E. Mantle cell lymphoma, combination therapy.

i. 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.

ii. 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.

iii. 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.

F. Marginal zone lymphoma, monotherapy

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 primary endpoint of ORR was 46% with ibrutinib (Imbruvica) therapy. Secondary endpoints were DOR and OS – not reached, and median PFS of 14.2 months. Treatment of MZL with ibrutinib (Imbruvica) remains experimental and investigational. The quality of evidence is considered low due to observational nature of the 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 MZL.

G. Marginal zone lymphoma, combination therapy

i. Ibrutinib (Imbruvica) has not been studied in combination with other oncolytic agents for the treatment of MZL. NCCN guidelines do not support the use of ibrutinib (Imbruvica) in combination with other agents for MZL.

H. Marginal zone lymphoma, frontline

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. 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).

I. Diffuse large B cell lymphoma
   i. 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 needed and are currently underway, as ibrutinib (Imbruvica) is the subject of several ongoing phase 2 trials in the relapsed/refractory setting.
   
   ii. The addition of ibrutinib (Imbruvica) 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.

J. Relapsed/refractory multiple myeloma
   i. 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.

K. Hairy cell leukemia
   i. 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.

L. Primary CNS lymphoma
   i. 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.

M. Esophagogastric carcinoma
   i. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

N. Glioblastoma
   i. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

O. Non-small-cell lung carcinoma
   i. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

P. T-cell lymphoma
i. 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.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
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<tr>
<td>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 naive CLL/SLL to investigational or not medically necessary uses section.</td>
<td>01/2022</td>
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<td>Event</td>
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<td>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.</td>
<td>06/2020</td>
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<td>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.</td>
<td>03/2019</td>
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<td>Updated formatting, extended initial approval from 3 months to 6 months.</td>
<td>01/2018</td>
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<td>08/2014</td>
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<td>Criteria created</td>
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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

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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

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.
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 idelisib (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. Idelisib (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 idelisib (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 idelisib (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. Idelisib (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

References
1. Zydelig (idelalisib) [prescribing information]. Gilead Science, Inc, Foster City(CA). February 2022
2. ClinicalTrials.gov. A Randomized, Double-Blind, Placebo-Controlled Study of Idelalisib in Combination With Rituximab for Previously Treated Chronic Lymphocytic Leukemia (CLL). NCT01539512.

Policy Implementation/Update:

<table>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Moved FL and SLL to E/I section following voluntary withdraw of these indications by the manufacturer.</td>
<td>03/2022</td>
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<tr>
<td>Policy updated to require use of one prior therapy for CLL; removed history of toxic epidermal necrolysis</td>
<td>02/2020</td>
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</tbody>
</table>

Washington State Rx Services is administered by Moda Health

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.

September 01, 2022
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: 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**

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<thead>
<tr>
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<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>imatinib</td>
<td>100 mg tablet</td>
<td>Chronic eosinophilic leukemia;</td>
<td>90 tablets/30 days</td>
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<td></td>
<td>Dermatofibrosarcoma protuberans, unresectable, recurrent, and/or metastatic;</td>
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<td></td>
<td>400 mg tablet</td>
<td>Gastrointestinal stromal tumor, Kit (CD117)-positive, adjuvant treatment;</td>
<td>30 tablets/30 days</td>
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<td>Gastrointestinal stromal tumor, Kit (CD117)-positive, unresectable or metastatic disease;</td>
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<td>Hypereosinophilic syndrome;</td>
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<td></td>
<td>Myelodysplastic syndrome, PDGFR gene rearrangement;</td>
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<tr>
<td>imatinib (Gleevec)</td>
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<td>Myelodysplastic syndrome, chronic, PDGFR gene rearrangement;</td>
<td>90 tablets/30 days</td>
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<td></td>
<td>Philadelphia chromosome-positive acute lymphoblastic leukemia, newly diagnosed, in combination with chemotherapy;</td>
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<tr>
<td></td>
<td>400 mg tablet</td>
<td>Philadelphia chromosome-positive acute lymphoblastic leukemia, relapsed/refractory;</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Philadelphia chromosome positive chronic myelogenous leukemia, accelerated phase or blast crisis;</td>
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</table>
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 leukencephalopathy
   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

References

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### Action and Summary of Changes

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<td>Prior authorization criteria transitioned to policy format, new indications added/specifed, age edit added, addition of specialist provider, and limitation of dual oral therapy.</td>
<td>11/2019</td>
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<td>Generic imatinib preferred therapy indicated for initial and continuation of therapy, unless medical necessity for brand met.</td>
<td>11/2018</td>
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<td>Criteria questions rearranged and clarified.</td>
<td>08/2017</td>
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<tr>
<td>Criteria updated to prefer generic imatinib for initial approval.</td>
<td>05/2017</td>
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<td>Criteria updated for new disease states.</td>
<td>02/2016</td>
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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP241

**Description**

Infgratinib (Truseltiq) is a selective inhibitor of fibroblast growth factor receptor 1-4 (FGFR).

**Length of Authorization**

- N/A

**Quantity Limits**

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</thead>
<tbody>
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<td>infgratinib (Truseltiq)</td>
<td>50 mg dose: 25 mg capsules (1 blister card)</td>
<td>Previously treated adults with unresectable, locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement</td>
<td>42 capsules/28 days</td>
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<td>75 mg dose: 25 mg capsules (2 blister cards)</td>
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<td>63 capsules/28 days</td>
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<td></td>
<td>100 mg dose: 100 mg capsules (1 blister card)</td>
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<td>21 capsules/28 days</td>
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<tr>
<td></td>
<td>125 mg dose: 25 mg/100 mg capsules (1 blister pack)</td>
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<td>42 capsules/28 days</td>
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</table>

**Initial Evaluation**

I. **Infgratinib (Truseltiq)** is considered investigational when used for all conditions, including but not limited to unresectable, locally advanced or metastatic cholangiocarcinoma with an FGFR2 fusion or other rearrangement.

**Renewal Evaluation**

I. N/A

**Supporting Evidence**

I. Infgratinib (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 a 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 infgratinib (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. Infgratinib (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. Infgratinib (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 erythrodyasesthesia syndrome (31%), and arthralgia (29%). Serious adverse events occurred in 34 patients (31%), most frequent being anemia, pyrexia, hypercalceremia, 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


Policy Implementation/Update:

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<th>Action and Summary of Changes</th>
<th>Date</th>
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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

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<th>inotersen (Tegsedi)</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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<tbody>
<tr>
<td>284 mg/1.5 mL syringe</td>
<td>hereditary transthyretin-mediated amyloidosis</td>
<td>6 mL/28 days</td>
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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 10^9/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**

5. Center for Drug Evaluation and Research. Tegsedi (inotersen) Summary Review. Application Number: 211172Orig1s000. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211172Orig1s000SumR.pdf.

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Interferon Gamma-1B (Actimmune®)

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

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<td>Interferon Gamma-1B (Actimmune®)</td>
<td>100mcg (2 million IU)/0.5ml vial</td>
<td>Severe Malignant Osteopetrosis (SMO); Chronic Granulomatous Disease (CGD)</td>
<td>BSA* over 0.5 m²: 50mcg/m² Three times weekly</td>
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<td>BSA* equal to or less than 0.5m²: 1.5mg/kg/dose Three times weekly</td>
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*maximum dose: 50mcg/m² 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
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.

References
1. “Chronic Granulomatous Disease” National Organization for Rare Diseases (NORD) 2018 Chronic Granulomatous Disease - NORD (National Organization for Rare Disorders) [rarediseases.org]
2. “Osteopetrosis” National Organization for Rare Diseases (NORD) 2018 Osteopetrosis - NORD (National Organization for Rare Disorders) [rarediseases.org]
3. ACTIMMUNE [Prescribing Information]. Horizon therapeutics Ireland DAC. Dublin Ireland, US License NO 2022

9. “Horizon Pharma plc Announces Topline Results from Phase 3 Study of ACTIMMUNE (interferon gamma-1b) in Friedreich’s Ataxia” Horizon Pharma plc Announces Topline Results from Phase 3 Study of ACTIMMUNE® (interferon gamma-1b) in Friedreich's Ataxia | Horizon Therapeutics plc 12/08/2016

Policy Implementation/Update:

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<td>10/2021</td>
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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

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<td>(Nourianz)</td>
<td>40 mg tablets</td>
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<td>30 tablets/30 days</td>
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Initial Evaluation

I. Istradefylline (Nourianz) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by or in consultation with a neurologist; AND
   B. A diagnosis of Parkinson’s Disease when the following are met:
      1. Member is currently on an oral levodopa regimen at least four times per day; AND
      2. Member is experiencing at least two hours of daily OFF time; AND
      3. Prescriber attests that member will be using istradefylline (Nourianz) in combination with carbidopa/levodopa; AND
      4. 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; AND
      5. 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)

II. Istradefylline (Nourianz) is considered investigational when used for all other conditions, including but not limited to:
A. Parkinson’s disease WITHOUT documentation of motor fluctuations, “wearing off”

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. 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 all four studies, patients treated with istradefylline (Nourianz) experienced a statistically significant decrease from baseline in daily “off” time compared to patients receiving a placebo. 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%).
II. 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).
III. 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 don’t recommend one adjunctive therapy approach over another.

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.

References


Policy Implementation/Update:

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Ivabradine (Corlanor®)
UMP POLICY

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

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<td>5 mg tablets</td>
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<td>7.5 mg tablets</td>
<td>Heart Failure in Pediatric Patients;</td>
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<td></td>
<td>5 mg/5 mL solution</td>
<td>Inappropriate Sinus Tachycardia</td>
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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 \( \leq 35\% \), who are in sinus rhythm with resting heart rate \( \geq 70 \) beats per minute and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use.


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

3. Ferrari R, Fox K. The role of heart rate may differ according to pathophysiology setting: from SHIFT to SIGNIFY. Eur Heart J. 2015;36:2042–2046
Policy Implementation/Update:

<table>
<thead>
<tr>
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<td>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.</td>
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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.
Ivosidenib (Tibsovo®); Enasidenib (Idhifa®)

**UMP POLICY**

**Policy Type:** PA/SP  
**Pharmacy Coverage Policy:** UMP123

Split Fill Management* (applies to ivosidenib [Tibsovo] only)

**Description**

Ivosidenib (Tibsovo) inhibits the isocitrate dehydrogenase 1 (IDH1) enzyme. It limits the proliferation of the 2-HG oncometabolite, a competitive inhibitor of the normal metabolite, and promotes cell differentiation.

Enasidenib (Idhifa) inhibits the isocitrate dehydrogenase 2 (IDH2) enzyme. It specifically targets IDH2 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)
- Renewal: 12 months

**Quantity Limits**

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<td>50 mg tablets</td>
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<td>30 tablets/30 days</td>
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<td>enasidenib (Idhifa)</td>
<td>100 mg tablets</td>
<td>Acute myeloid leukemia, relapsed/refractory</td>
<td>30 tablets/30 days</td>
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<tr>
<td>ivosidenib (Tibsovo)</td>
<td>250 mg capsule</td>
<td>Acute myeloid leukemia, relapsed/refractory; Acute myeloid leukemia, newly diagnosed; Cholangiocarcinoma, advanced/metastatic</td>
<td>60 capsules/30 days</td>
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**Initial Evaluation**

I. **Enasidenib (Idhifa) or ivosidenib (Tibsovo)** 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. Will not be used in combination with other oncologic agents (i.e. as monotherapy); **AND**

D. A diagnosis of one of the following:

   1. **Relapsed or refractory acute myeloid leukemia (AML); AND**

      i. Treatment with the following has been ineffective, contraindicated, or not tolerated:

         a. Systemic chemotherapy; **OR**

         b. Allogenic hematopoietic stem cell transplant; **AND**

      ii. Presence of IDH-1 mutation as detected by an FDA-approved test; **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.*
The 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. **Newly diagnosed AML; AND**
   - Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
   - Member is 75 years of age or older; **OR**
     - 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**
   - Request is for ivosidenib (Tibsovo); **OR**
   - Presence of IDH-2 mutation as detected by an FDA-approved test; **AND**
   - Request is for enasidenib (Idhifa); **OR**

3. **Locally advanced or metastatic cholangiocarcinoma; AND**
   - Request is for ivosidenib (Tibsovo); **AND**
   - Provider attests that the member is not a candidate for surgery (i.e., unresectable cholangiocarcinoma); **AND**
   - Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
   - Member has had disease progression on, or after, at least one systemic therapy (e.g., gemcitabine, or 5-fluorouracil).

II. Enasidenib (Idhifa) and/or ivosidenib (Tibsovo) is/are considered investigational when used for all other conditions, including but not limited to:

   A. Enasidenib (Idhifa) and/or ivosidenib (Tibsovo) used in combination with another oncology therapy
   B. Advanced cholangiocarcinoma without IDH-1 mutation
   C. Chondrosarcomas
   D. 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) 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 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.

III. 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.

IV. Ivosidenib (Tibsovo):
   1. Ivosidenib (Tibsovo) was studied in an open-label, single-arm, multicenter clinical trial in 174 adult patients with relapsed or refractory AML with an IDH1 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 a IDH1 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.

- 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.
Investigational or Not Medically Necessary Uses

I. Enasidenib (Idhifa) and/or ivosidenib (Tibsovo) are used in combination with another oncology therapy
   A. Current clinical trial data leading to FDA approval are in the monotherapy setting. Safety and efficacy have not been established for specific combination regimens.

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. 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 ivosidenib (Tibsovo) and enasidenib (Idhifa) 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

### Policy Implementation/Update:

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<tr>
<td>Update to include expanded indication for ivosidenib (Tibsovo) for cholangiocarcinoma; updated supporting evidence; added split fill requirement for Tibsovo.</td>
<td>10/2021</td>
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<td>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.</td>
<td>02/2020</td>
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<td>Policy created. Tibsovo and Idhifa was combined into one policy.</td>
<td>12/2019</td>
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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.

ixazomib (Ninlaro®)

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

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<td>Previously treated multiple myeloma, in combination with lenalidomide and dexamethasone</td>
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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


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<td>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.</td>
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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: 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

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<td>lapatinib (Tykerb)</td>
<td>250 mg</td>
<td>Breast cancer, HER2 overexpression, advanced or metastatic in combination</td>
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<td></td>
<td>tablets</td>
<td>with capecitabine after prior therapy</td>
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<td>Breast cancer, HR-positive, HER2 overexpression, in postmenopausal women,</td>
<td>168 tablets/28</td>
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<td></td>
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<td>in combination with letrozole</td>
<td>days</td>
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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 capecitabine 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 capecitabine for those with advanced or metastatic, HER2(+) disease.

IV. Lapatinib (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**


Policy Implementation/Update:

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<tr>
<td>Added criteria to prefer generic lapatinib over brand Tykerb unless contraindicated or not tolerated</td>
<td>06/2021</td>
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<td>Criteria transitioned to policy. Policy updated to include the following requirement: specialist prescriber, age, concurrent therapies, specified place in therapy.</td>
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<td>Previous Reviews</td>
<td>09/2013, 08/2013, 08/2011, 10/2008</td>
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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**

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<td>larotrectinib</td>
<td>25 mg capsule</td>
<td>Neuotrophic receptor tyrosine kinase gene fusion</td>
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<td>100 mg capsule</td>
<td>positive solid tumor, metastatic</td>
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<td>20 mg/1 mL solution</td>
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<td>Quantity calculated to 100 mg/m2 of body surface area</td>
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**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 included 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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<td>Last Reviewed</td>
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Action and Summary of Changes

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
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<tbody>
<tr>
<td>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.</td>
<td>12/2019</td>
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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:
  - Lenalidomide (Revlimid)
    1. Follicular lymphoma/Marginal zone lymphoma: 12 months
    2. All other indications: Six months
  - Pomalidomide (Pomalyst) and thalidomide (Thalomid)
    1. All indications: Three months
- Renewal:
  - Lenalidomide (Revlimid)
    1. Follicular lymphoma/Marginal zone lymphoma: Cannot be renewed
    2. All other indications: 12 months
  - Pomalidomide (Pomalyst)
    1. All indications: 12 months
  - Thalidomide (Thalomid)
    1. Cutaneous manifestations of moderate to severe Erythema Nodosum Leprosum (ENL): 12 months
    2. Multiple myeloma: 12 months

Quantity limits

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<td>21 capsules/28 days</td>
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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.

<table>
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<tr>
<th>Drug</th>
<th>Strengths</th>
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<tr>
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<td>Multiple Myeloma</td>
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<td>50 mg capsules 100 mg capsules 150 mg capsules 200 mg capsules</td>
<td>Erythema Nodosum Leprosum</td>
<td>60 capsules/30 days</td>
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**Initial Evaluation**

I. **Lenalidomide (Revlimid)** 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 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**

   C. 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**

   D. 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
E. 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
F. 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; 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 response to treatment defined by improvement or stabilization of disease or symptoms; AND

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.

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September 01, 2022
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. Pomaliidomide (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.
  - 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.

References

Addition of new indication for Kaposi Sarcoma for Pomalyst as experimental and investigational

- 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

Added pomalidomide (Pomalyst) and thalidomide (Thalomid) agents to policy; removed black box warnings and precautions readily available in compendia; removed laboratory criteria.

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.

Excluded package insert/monitoring question and removed renewal question regarding regular hematological laboratory tests, extended initial approval from 3 months to 6 months.

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.
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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.
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).

Length of Authorization
- Initial: up to 100 days post-transplant
- Renewal: no renewal

Quantity limits

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<tr>
<td>Letermovir (Prevymis)</td>
<td>240 mg tablet</td>
<td>Prophylaxis for CMV Infection</td>
<td>30 tablets/30 days</td>
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<td>480 mg tablet</td>
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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. Member is cytomegalovirus (CMV)-seropositive; AND
   E. Member is an allogeneic hematopoietic stem cell transplant (HSCT) recipient with a high risk of CMV reactivation; AND
   F. Documentation of transplant date has been recorded in chart notes; AND
   G. If the request is for Letermovir (Prevymis) 240 mg, it will be used in combination with cyclosporine.

II. Letermovir (Prevymis) is considered investigational when used for all other conditions, including but not limited to:
   A. Prevention of CMV infection or disease in all other settings EXCEPT HSCT
   B. Treatment for CMV infection or disease
Supporting Evidence

I. Per label, 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). Safety and efficacy in the pediatric population has not been established.

II. Considering the complexity of care for patients receiving HSCT, the agent requested must be prescribed by, or in consultation with, an oncologist, hematologist, infectious disease, or transplant specialist.

III. 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)].

IV. A review by Chen et al. 2018 demonstrated that among the six antiviral therapies studied, ganciclovir and letermovir 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 has an excellent safety profile with no myelosuppression, and its use should be considered for this indication in patients at risk. Letermovir 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.

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
   B. Treatment for CMV infection or disease

References


Policy Implementation/Update:

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<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Removed requirement of valacyclovir or ganciclovir trial given reduced efficacy and/or safety in comparison to letermovir</td>
<td>10/2020</td>
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<td>Policy created</td>
<td>11/2019</td>
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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: 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**

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>levodopa (Inbrija)</td>
<td>42 mg capsules</td>
<td>Parkinson’s Disease</td>
<td>120 capsules/30 days*</td>
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*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\textsuperscript{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\textsuperscript{SM}-PD trial

IV. Due to the safety concerns, patients with chronic respiratory disease are excluded from the SPAM\textsuperscript{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


Policy Implementation/Update:

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<th>Date</th>
</tr>
</thead>
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<tr>
<td>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.</td>
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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP254

Description

Levoketoconazole (Recorlev®), the 2S,4R enantiomer of ketoconazole, is an orally administered steroidogenesis inhibitor that reduces endogenous cortisol levels.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

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<th>Product Name</th>
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<tr>
<td>levoketoconazole (Recorlev®)</td>
<td>150 mg tablets</td>
<td>Cushing’s Syndrome</td>
<td>240 tablets/30 days</td>
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Initial Evaluation

I. 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 is not a candidate for pituitary surgery; OR
         i. Cortisol levels remain abnormal following attempted resection; 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)*

II. Levoketoconazole (Recorlev) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Treatment of fungal infections

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.
III. Levoketoconazole (Recorlev) is considered investigational when used for all other conditions, including but not limited to:
   A. Exogenous (iatrogenic) Cushing’s syndrome
   B. Use in combination with osilodrostat (Isturisa), pasireotide diaspartate (Signifor), and/or mifepristone (Korlym)

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 cortisol levels remained elevated despite at least a three-month trial of a therapeutic dose of oral ketoconazole; OR
   a. Documentation of serious adverse effect or allergy with oral ketoconazole; AND

IV. Member has exhibited improvement or stability of cortisol levels and disease symptoms [e.g., improvement in cushingoid appearance, acne, hirsutism, psychiatric symptoms, body weight].

Supporting Evidence

I. 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.

II. The safety and efficacy of levoketoconazole (Recorlev) has been studied in patients 18 years of age or older, and there is no published data to support its use in pediatric patients.

III. Cushing’s syndrome is a disorder that leads to excess cortisol (hypercortisolemia) and is usually due to a corticotropin (ACTH)-producing pituitary or adrenal tumor. Hallmark symptoms of high levels of cortisol include clinical features such as weight gain, hypertension, high blood glucose, and depression. Goals of treatment include the reversal of clinical manifestations by normalizing cortisol secretion, damaging tumor eradication, and avoidance of permanent hormone deficiency which can result in dependence upon medications. 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.

IV. 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.

V. Systemic therapy options for Cushing’s syndrome 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, and pasireotide are FDA-approved to treat Cushing’s syndrome/disease in patients who pituitary surgery is not an option or has not been curative. Ketoconazole, metyrapone, mitotane, etomidate, and cabergoline are used off-label for Cushing’s syndrome.

VI. 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 March 2022, guidelines have not been updated with regard to place in therapy for levoketoconazole for the treatment of Cushing’s syndrome.

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, trial of all of these regimens is required prior to use of levoketoconazole (Recorlev).

VIII. 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. Retrospective studies and clinical trials evaluated treatment response at 6-months while patients were maintained on a stable therapeutic dose. In absence of strong evidence to support a preferred treatment algorithm, trial of oral ketoconazole at a maximally tolerated therapeutic dose for at least three-months is required prior to assessing treatment failure.

IX. Levoketoconazole (Recorlev) has not been evaluated against ketoconazole for the treatment of hypercortisolemia in patients with Cushing’s syndrome therefore comparative safety and 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. Further, 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.

X. Levoketoconazole (Recorlev) has been studied in two phase 3 studies for the treatment of endogenous hypercortisolism 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 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.

- 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.

- The overall quality of evidence for levoketoconazole (Recorlev) is considered low due to open-label study design, lack of a comparator 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.

Investigational or Not Medically Necessary Uses

I. Levoketoconazole (Recorlev) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. 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.
   B. Exogenous (iatrogenic) Cushing’s syndrome
      i. Safety and efficacy has only been established for endogenous Cushing’s syndrome, there is currently limited evidence to suggest the use of levoketoconazole in the setting of exogenous (iatrogenic) Cushing’s syndrome.
   C. Used in combination with osilodrostat (Isturisa), pasireotide diaspargate (Signifor), and/or mifepristone (Korlym)
      i. In practice, ketoconazole has been used in combination with metyrapone or with 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).
      ii. Levoketoconazole (Recorlev) has not been studied in combination with osilodrostat (Isturisa), pasireotide diaspargate (Signifor), and/or mifepristone (Korlym).

Appendix

I. 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.
II. 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 hepatotoxicity 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.

III. 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.

References


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.

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<th>Disease state</th>
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<tr>
<td>pasireotide diaspertate (Signifor®)</td>
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<td></td>
<td>Acromegaly Cushing’s disease</td>
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<tr>
<td>mifepristone (Korlym®)</td>
<td>Hyperglycemia secondary to hypercortisolism in Cushing’s syndrome</td>
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Policy Implementation/Update

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<td>Policy created</td>
<td>03/2022</td>
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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

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<td>Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults</td>
<td>224 tablets/14 days</td>
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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

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. 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


Policy Implementation/Update:

<table>
<thead>
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<th>Action and Summary of Changes</th>
<th>Date</th>
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<td>Transitioned to policy format</td>
<td>10/2020</td>
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<td>Previous Reviews</td>
<td>07/2018</td>
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Iomtitapide (Juxtapid®)
UMP POLICY

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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>Lomitapide (Juxtapid)</td>
<td>5 mg capsules</td>
<td>Homozygous familial hypercholesterolemia (HoFH)</td>
<td>30 capsules /30 days</td>
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<td>10 mg capsules</td>
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<td>40 mg capsules</td>
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<td>60 mg capsules</td>
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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. Treated LDL-C ≥ 300 mg/dL with one 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 **plus** 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

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. 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

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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.

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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

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:

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<td>Date Effective</td>
<td>May 2013</td>
</tr>
<tr>
<td>Last Updated</td>
<td>December 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>11/2015, 12/2019</td>
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<table>
<thead>
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<th>Date</th>
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<tbody>
<tr>
<td>• Transitioned to policy format</td>
<td></td>
</tr>
<tr>
<td>• Removed mipomersen (Kynamro) from policy due to discontinuation status as of 5/31/2018</td>
<td></td>
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<tr>
<td>• Added requirement for specialty prescriber</td>
<td></td>
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<tr>
<td>• Added minimum age requirement</td>
<td></td>
</tr>
<tr>
<td>• Added details regarding confirmation of a diagnosis of HoFH</td>
<td></td>
</tr>
<tr>
<td>• Clarified that use must be concurrent with standard lipid-lowering agents</td>
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<tr>
<td>• Indicated that combination of lomitapide (Juxtapid) with PCSK9 inhibitors or use for hypercholesterolemia without HoFH is considered investigational</td>
<td>12/2019</td>
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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

<table>
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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>Lonafarnib (Zokinvy)</td>
<td>50 mg capsules</td>
<td>Hutchinson-Gilford Progeria Syndrome (HGPS); processing-deficient Progeroid Laminopathies (PL)</td>
<td>Initial: Maximum 230mg/m^2/day</td>
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<tr>
<td></td>
<td>75 mg capsules</td>
<td></td>
<td>Renewal: Maximum 300mg/m^2/day</td>
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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 experimental and investigational 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 m² to 0.75 m². 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 0.39m².
III. Hutchinson-Gilford Progeria Syndrome (HGPS) 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
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.

V. The safety and efficacy of lonafarnib (Zokinvy) have been studied in an 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/m² twice daily and after four months of treatment patients who were tolerating treatment had a dose increase to 150 mg/m² 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/m² 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.

References


Policy Implementation/Update:

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<td>Policy created</td>
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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

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<tr>
<th>Pegfilgrastim</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>Pegfilgrastim (Neulasta)</td>
<td>Prophylactic use in patients with non-myeloid malignancy;</td>
<td>Two prefilled syringes per 28-day supply</td>
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<tr>
<td>Pegfilgrastim (Neulasta Onpro)</td>
<td>Neutropenic complications from prior cycle;</td>
<td>Two kits per 28-day supply</td>
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<tr>
<td>Pegfilgrastim-jmdb (Fulphila)</td>
<td>Exposure to myelosuppressive doses of radiation;</td>
<td>Two prefilled syringes per 28-day supply</td>
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<tr>
<td>Pegfilgrastim-cbqv (Udenyca)</td>
<td>Bone marrow transplantation failure or engraftment delay;</td>
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<tr>
<td>Pegfilgrastim-bmez (Ziextenzo)</td>
<td>Peripheral progenitor cell (PBPC) mobilization and transplant</td>
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<tr>
<td>Pegfilgrastim-apgf (Nyvepria)</td>
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Initial Evaluation

I. Pegfilgrastim-bmez (Ziextenzo) 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. Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome); OR
      5. Prophylactic use in patients with non-myeloid malignancy; AND
         i. Patient is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 20% or greater; OR

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ii. Patient is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 10% or greater AND meeting one or more of the following:
   a. Age 65 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. Patient 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 >2.0 mg/dL); OR
   l. Chronic immunosuppression in the post-transplant setting including organ transplant

II. Pegfilgrastim (Neulasta, Neulasta Onpro), pegfilgrastim-cbqv (Udenyca), and pegfilgrastim-apgf (Nyvepria) 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-bmez (Ziextenzo) have been ineffective, contraindicated, or not tolerated.

Renewal Evaluation
   I. Same as initial prior authorization policy criteria

Supporting Evidence
   I. Indication listed under section I supported by FDA-labeled indication(s) or recommended per Compendia
   II. Expected incidence of febrile neutropenia percentages for myelosuppressive chemotherapy regimens can be found in the NCCN Myeloid Growth Factors Clinical Practice Guideline at NCCN.org.

References
11. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) filgrastim.
   National Comprehensive Cancer Network, 2018. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc.” To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2018. Moda Health Plan, Inc. Medical Necessity Criteria Page 4/6

Policy Implementation/Update:

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<td>04/2022</td>
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<td>Updated pegfilgrastim-jmdb (Fulphila) as preferred product; removed pegfilgrastim-cbqv (Udenyca) from preferred products. (Effective 7/1/2021)</td>
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<td>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.</td>
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<tr>
<td>Updated policy to allow for 28 days supply</td>
<td>02/2020</td>
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<tr>
<td>Added Ziextenzo, biosimilar to Neulasta; update quantity limits to allow for 30 days supply</td>
<td>12/2019</td>
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<tr>
<td>Added Udenyca, biosimilar to Neulasta</td>
<td>01/2019</td>
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<tr>
<td>Neulasta, Neulasta Onpro preferred GCSF</td>
<td>12/2018</td>
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<tr>
<td>Added Fulphila, biosimilar to Neulasta</td>
<td>07/2018</td>
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Washington State Rx Services is administered by Moda Health.

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: 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

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<th>Product Name</th>
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<td>mannitol (Bronchitol)</td>
<td>40 mg capsules</td>
<td>Cystic Fibrosis</td>
<td>560 capsules/28 days</td>
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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**

*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. 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


Policy Implementation/Update:

<table>
<thead>
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<th>Action and Summary of Changes</th>
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</tr>
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<tr>
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</tbody>
</table>
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

Description
Maralixibat (Livmarli™) is an orally administered reversible ileal bile acid transporter (IBAT) inhibitor.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
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<tbody>
<tr>
<td>maralixibat (Livmarli)</td>
<td>9.5 mg/mL solution</td>
<td>Cholestatic pruritis in patients with Alagille Syndrome one year of age and older</td>
<td>Monthly quantity to allow for a maximum of 380 mcg/kg/day (maximum of 3 mL)</td>
</tr>
</tbody>
</table>

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, colestervelam); AND
   3. Rifampin; AND
   4. Opioid antagonist (e.g., naltrexone); AND
   5. Serotonin reuptake inhibitor (e.g., sertraline)

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 genetic 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:

<table>
<thead>
<tr>
<th>ALGS in a first degree relative</th>
<th>Paucity</th>
<th>JAG1 or NOTCH2 mutation*</th>
<th>Number of criteria needed**</th>
</tr>
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<td>Present or absent</td>
<td>Present</td>
<td>Identified</td>
<td>Any or no features</td>
</tr>
<tr>
<td>None (proband)</td>
<td>Present</td>
<td>Not identified</td>
<td>3 or more features</td>
</tr>
<tr>
<td>None (proband)</td>
<td>Absent or unknown</td>
<td>Not identified</td>
<td>4 or more features</td>
</tr>
<tr>
<td>None (proband)</td>
<td>Absent or unknown</td>
<td>Identified</td>
<td>1 or more features</td>
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<td>Present</td>
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<td>2 or more features</td>
</tr>
<tr>
<td>Present</td>
<td>Absent or unknown</td>
<td>Identified</td>
<td>Any or no features</td>
</tr>
</tbody>
</table>

*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

Washington State Rx Services is administered by moda HEALTH

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September 01, 2022
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).

- **Sertraline** - 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).

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 ICH 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: 283µmol/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 Hepatoporoenterostomy (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 one 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
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(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

<table>
<thead>
<tr>
<th>Member weight (kg)</th>
<th>Days 1-7 (190 mcg/kg/day)</th>
<th>Beginning Day 8 (380 mcg/kg/day)</th>
<th>PA#1: quantity per 28-day supply for month one (mL)</th>
<th>PA#2: quantity per 28-day supply for month two through six (mL)</th>
<th>Renewal: quantity per 28-day supply</th>
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<tr>
<td>Volume QD (mL)</td>
<td>Volume QD (mL)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 6</td>
<td>0.1</td>
<td>0.2</td>
<td>4.9</td>
<td>5.6</td>
<td>5.6</td>
</tr>
<tr>
<td>7 to 9</td>
<td>0.15</td>
<td>0.3</td>
<td>7.4</td>
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<tr>
<td>10 to 12</td>
<td>0.2</td>
<td>0.45</td>
<td>10.9</td>
<td>12.6</td>
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<td>13 to 15</td>
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<td>16 to 19</td>
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<tr>
<td>20 to 24</td>
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<td>0.5</td>
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<td>35 to 39</td>
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References


Policy Implementation/Update:

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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

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<td>Post-transplant CMV infection/disease that is</td>
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<tr>
<td>(Livtencity)</td>
<td></td>
<td>refractory to other treatments</td>
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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, lettermovir [Preymis]); **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 **not medically necessary** 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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<td>02/2022</td>
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mavacamten (Camzyos™)
UMP POLICY

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

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<td>30 capsules/30 days</td>
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<td>5 mg capsule</td>
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<td>15 mg capsule</td>
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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 (pVO2) 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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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

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<td>2.5 mg tablet</td>
<td>Moderately severe to severe hypertension</td>
<td>300 tablets/30 days</td>
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<td></td>
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<td>Uncomplicated malignant hypertension</td>
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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

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. 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. Gilles 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 vasodilator) 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

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September 01, 2022
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


Policy Implementation/Update:

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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: 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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
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<td>mecasermin (Increlex)</td>
<td>40 mg/4 mL multiple dose vial</td>
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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/m²); 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

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.

Washington State Rx Services is administered by moda HEALTH

September 01, 2022
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


Policy Implementation/Update:

<table>
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<tr>
<th>Date Created</th>
<th>September 2008</th>
</tr>
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<tbody>
<tr>
<td>Date Effective</td>
<td>October 2008</td>
</tr>
<tr>
<td>Last Updated</td>
<td>November 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>12/2008, 11/2019</td>
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</table>

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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>11/2019</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>mechlorethamine (Valchlor)</td>
<td>0.016% topical gel/jelly</td>
<td>Mycosis fungoides-type cutaneous T-cell lymphoma, in those that have received prior skin-directed therapy</td>
<td>60 grams (1 tube)/30 days</td>
</tr>
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</table>

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
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.

References


Policy Implementation/Update:

<table>
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<tr>
<th>Date Created</th>
<th>January 2014</th>
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<tr>
<td>Date Effective</td>
<td>March 2014</td>
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<tr>
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<td>Last Reviewed</td>
<td>11/2019</td>
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<thead>
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<th>Date</th>
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</thead>
<tbody>
<tr>
<td>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.</td>
<td>11/2019</td>
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</table>
Medications for Colonoscopy Preparation
UMP POLICY

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>All therapies with the FDA approval for use in colonoscopy preparation</td>
<td>Multiple</td>
<td>Colonoscopy preparation</td>
</tr>
</tbody>
</table>

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


Policy Implementation/Update:

<table>
<thead>
<tr>
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<th>Date</th>
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<tbody>
<tr>
<td>Updated requirement for medication used to cover all use for colonoscopy prep instead of just in the setting of colorectal cancer screening</td>
<td>08/2021</td>
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<tr>
<td>Criteria transitioned to policy format</td>
<td>05/2021</td>
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<tr>
<td>Criteria created</td>
<td>07/2016</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>mepolizumab (Nucala)</td>
<td>100 mg/mL syringe,</td>
<td>Asthma (severe)</td>
<td>1 syringe/autoinjector/28 days</td>
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<tr>
<td></td>
<td>100 mg/mL autoinjector</td>
<td>Eosinophilic granulomatosis with polyangitis</td>
<td>3 syringes/autoinjectors/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypereosinophilic Syndrome</td>
<td>3 syringes/autoinjectors/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic Rhinosinusitis with Nasal Polyps</td>
<td>1 syringe/autoinjector/28 days</td>
</tr>
<tr>
<td></td>
<td>40mg/0.4mL prefilled syringe</td>
<td>Asthma (severe)</td>
<td>1 syringe/28 days</td>
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Provider Administered Agents*, **

<table>
<thead>
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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>mepolizumab (Nucala)</td>
<td>100 mg/vial</td>
<td>Asthma (severe)</td>
<td>1 vial/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eosinophilic granulomatosis with polyangitis</td>
<td>3 vials/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypereosinophilic Syndrome</td>
<td>3 vials/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic Rhinosinusitis with Nasal Polyps</td>
<td>1 vial/28 days</td>
</tr>
</tbody>
</table>

*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 **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**
   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 **ALL** 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. 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-
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.

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.

<table>
<thead>
<tr>
<th>Scores (range)</th>
<th>Placebo n=201</th>
<th>Mepolizumab (Nucala) n=206</th>
<th>Mean Difference vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline Mean (SD)*</td>
<td>Mean Change (SE)*</td>
<td>Mean Baseline Mean (SD)*</td>
</tr>
<tr>
<td>NPS (0-8)</td>
<td>5.6 (1.41)</td>
<td>0.06 (0.14)</td>
<td>5.4 (1.17)</td>
</tr>
<tr>
<td>Nasal obstruction VAS</td>
<td>9.02 (0.83)</td>
<td>-2.54 (0.25)</td>
<td>8.92 (0.83)</td>
</tr>
</tbody>
</table>

* 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Added 40mg prefilled syringe</td>
<td>02/2022</td>
</tr>
<tr>
<td>Policy updated to reflect the new CRSwNP indication.</td>
<td>09/2021</td>
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</table>

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.

New Policy

06/2019

10/2019
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>metoclopramide</td>
<td>15 mg intranasal</td>
<td>Acute and recurrent diabetic gastroparesis</td>
<td>10 ml/28 days</td>
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<tr>
<td>(Gimoti)</td>
<td>spray</td>
<td></td>
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</tr>
</tbody>
</table>

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] 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.

September 01, 2022
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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tr>
<td>Policy created</td>
<td>11/2020</td>
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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: 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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>metreleptin (Myalept)</td>
<td>11.3 mg powder (5 mg/mL) vial</td>
<td>Congenital Lipodystrophy; Acquired Generalized Lipodystrophy</td>
<td>60 mL/30 days</td>
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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

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.

September 01, 2022
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


Policy Implementation/Update:

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<th>Date Created</th>
<th>September 2014</th>
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<tr>
<td>Date Effective</td>
<td>September 2014</td>
</tr>
<tr>
<td>Last Updated</td>
<td>October 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>10/2019</td>
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<table>
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<th>Date</th>
</tr>
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<tbody>
<tr>
<td>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.</td>
<td>10/2019</td>
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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP201

Description
Metyrosine (Demser) is an orally administered tyrosine hydroxylase inhibitor.

Length of Authorization
- Initial: Three months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>metyrosine (generic Demser)</td>
<td>250 mg capsule</td>
<td>pheochromocytoma</td>
<td>480 capsules/30 days</td>
</tr>
<tr>
<td>metyrosine (Demser)</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

Initial Evaluation

I. Metyrosine (Demser) 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. 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 (Demser) is considered investigational when used for all other conditions, including but not limited to:
   A. Velocardiofacial syndrome-associated psychosis
   B. Bipolar disorder
   C. Schizophrenia
   D. Gilles de la Tourette’s syndrome

September 01, 2022
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

Supporting Evidence

I. Pheochromocytoma is a rare neuroendocrine tumor that hypersecrete one or more catecholamines (epinephrine, norepinephrine, and dopamine) and if left untreated, cardiovascular morbidity and mortality are high. Once diagnosed, patients should undergo surgical resection of the pheochromocytoma following appropriate medical preparation. Preoperative 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 (Demser) 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 (Demser) 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 Demser 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 (Demser) 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 (Demser) 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 (Demser) 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 (Demser) derivative is subject of ongoing trials, currently recruiting, in this setting.

References

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>11/2020</td>
</tr>
</tbody>
</table>
midostaurin (Rydapt®)
UMP POLICY

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

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<tr>
<td>midostaurin</td>
<td>25 mg capsule</td>
<td>Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with cytarabine/daunorubicin induction and cytarabine consolidation</td>
<td>56 capsules/28 days</td>
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<tr>
<td>(Rydapt)</td>
<td></td>
<td>Systemic mast cell disease: aggressive systemic mastocytosis, systemic mastocytosis with hematological neoplasm, mast cell leukemia</td>
<td>224 capsules/28 days</td>
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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

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. **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


Policy Implementation/Update:

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<thead>
<tr>
<th>Date Created</th>
<th>July 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>August 2017</td>
</tr>
<tr>
<td>Last Updated</td>
<td>November 2019</td>
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<td>November 2019</td>
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<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>11/2019</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP095

Description
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>mifepristone</td>
<td>300 mg tablets</td>
<td>Hyperglycemia secondary to hypercortisolism in Cushing’s syndrome</td>
<td>120 tablets/30 days</td>
</tr>
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</table>

Initial Evaluation

I. 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. A diagnosis of hyperglycemia secondary to hypercortisolism in members with endogenous Cushing’s syndrome when the following are met:
      1. Member has a diagnosis of type 2 diabetes OR glucose intolerance; AND
      2. Baseline hemoglobin A1c (HbA1c) has been provided in this request; AND
      3. Member has had an inadequate response to pituitary surgery or is not a candidate for surgery; AND
      4. Treatment with TWO of the following has been ineffective, not tolerated, or all are contraindicated:
         i. Ketoconazole; OR
         ii. Cabergoline (Dostinex); OR
         iii. Metyrapone (Metopirone); OR
         iv. Mitotane (Lysodren)

II. Mifepristone (Korlym) is considered not medically necessary 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

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.

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September 01, 2022
III. Mifepristone (Korlym) is considered investigational when used for all other conditions, including but not limited to:
   A. Exogenous (iatrogenic) Cushing’s syndrome
   B. Type 2 diabetes related hyperglycemia

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 reduction in HbA1c from baseline; AND
IV. Member has exhibited improvement in Cushing’s syndrome manifestation (e.g., cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight)

Supporting Evidence

I. 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.
   A. The primary efficacy analysis for the diabetes cohort was an analysis of responders (patient who had a ≥25% reduction from baseline in glucose AUC). The primary efficacy analysis was conducted in the modified intent-to-treat population (n=25); 15 of 25 patients (60%) were treatment responders (95% CI: 39%, 78%).
   B. 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).
   C. 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.
II. According to the Endocrine Society Clinical Practice Guideline, first line treatment is transsphenoidal surgery (TSS) regardless of the cause. Although surgical treatment is optimal, medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Medical therapy options within guidelines consist of steroidogenesis inhibitors (i.e. ketoconazole, metyrapone, mitotane, etomidate), pituitary-directed treatments (i.e. cabergoline, pasireotide), and glucocorticoid antagonists (i.e. mifepristone). Guidelines do not prefer one medical therapy over another; however, guidelines do recommend glucocorticoid antagonists (i.e. mifepristone) in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after TSS.
Investigational or Not Medically Necessary Uses

I. Hypertension associated with Cushing’s syndrome
   A. In the clinical trial, 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).

II. Termination of pregnancy and induction of labor
   A. Although the active ingredient (mifepristone) at a lower strength is indicated for both termination of pregnancy and induction of labor, mifepristone (Korlym) has not been approved by the FDA or studied in those indications.

III. Exogenous (iatrogenic) Cushing’s syndrome
   A. Safety and efficacy has only been established for endogenous Cushing’s syndrome, there is currently limited evidence to suggest the use of mifepristone (Korlym) in the setting of exogenous (iatrogenic) Cushing’s syndrome.

IV. Type 2 diabetes related hyperglycemia
   A. Safety and efficacy 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.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Changed criteria regarding previous therapy to require treatment with two agents to have been ineffective, not tolerated, or contraindicated</td>
<td>08/2020</td>
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<td>Updated renewal language to reflect new standard language</td>
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<tr>
<td>Updated supporting evidence</td>
<td></td>
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<td>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.</td>
<td>10/2019</td>
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<td>09/2012</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>migalastat</td>
<td>123 mg capsule</td>
<td>Fabry disease</td>
<td>15 capsules/30 days</td>
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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

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.

September 01, 2022
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

Policy Implementation/Update:

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<th>September 2018</th>
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<tr>
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<td>November 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>09/2019</td>
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</table>

**Action and Summary of Changes**

| 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 |
miglustat (Zavesca®); eliglustat (Cerdelga®)  
UMP POLICY

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>miglustat</td>
<td>100 mg capsules</td>
<td>Mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option</td>
<td>90 capsules/30 days</td>
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<td>(generic Zavesca)</td>
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<tr>
<td>miglustat</td>
<td>100 mg capsules</td>
<td>Type 1 Gaucher disease; CYP2D6 extensive metabolizers (EMs) or intermediate metabolizers (IMs)</td>
<td>56 capsules/28 days</td>
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<td>(Zavesca)</td>
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<tr>
<td>eliglustat</td>
<td>84 mg capsules</td>
<td>Type 1 Gaucher disease; CYP2D6 poor metabolizers (PMs)</td>
<td>28 capsules/28 days</td>
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<tr>
<td>(Cerdelga)</td>
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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**

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.

September 01, 2022
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 naïve 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>11/2020</td>
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<tr>
<td>Miglustat (Zavesca) criteria created</td>
<td>05/2018</td>
</tr>
<tr>
<td>Eliglustat (Cerdelga) criteria created</td>
<td>11/2014</td>
</tr>
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</table>
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.

### Migraine Abortive Therapies, Quantity Exception

**Policy Type: QE**

**Pharmacy Coverage Policy: UMP160**

**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

<table>
<thead>
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<th>Product Name</th>
<th>Dosage Form</th>
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<td>12 tablets/30 days</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>10 mg tablet</td>
<td>12 tablets/30 days</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>10 mg ODT</td>
<td>12 tablets/30 days</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>rizatriptan (Maxalt)</td>
<td>5 mg tablet</td>
<td>12 tablets/30 days</td>
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</tr>
<tr>
<td></td>
<td>10 mg tablet</td>
<td>12 tablets/30 days</td>
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</tr>
<tr>
<td>rizatriptan (Maxalt-MLT)</td>
<td>10 mg tablet</td>
<td>12 tablets/30 days</td>
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</tr>
<tr>
<td>sumatriptan (oral)</td>
<td>25 mg tablet</td>
<td>9 tablets/30 days</td>
<td>20 tablets/30 days</td>
</tr>
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<td></td>
<td>50 mg tablet</td>
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<td>20 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>100 mg tablet</td>
<td>9 tablets/30 days</td>
<td>20 tablets/30 days</td>
</tr>
<tr>
<td>sumatriptan (Imitrex) (oral)</td>
<td>25 mg tablet</td>
<td>9 tablets/30 days</td>
<td>20 tablets/30 days</td>
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<tr>
<td></td>
<td>50 mg tablet</td>
<td>9 tablets/30 days</td>
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</tr>
<tr>
<td></td>
<td>100 mg tablet</td>
<td>9 tablets/30 days</td>
<td>20 tablets/30 days</td>
</tr>
<tr>
<td>sumatriptan/naproxen (oral)</td>
<td>85-500 mg tablet</td>
<td>9 tablets/30 days</td>
<td>20 tablets/30 days</td>
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<tr>
<td>sumatriptan/naproxen (oral)</td>
<td>85-500 mg tablet</td>
<td>9 tablets/30 days</td>
<td>20 tablets/30 days</td>
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Washington State Rx Services is administered by Moda Health

September 01, 2022
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Formulation</th>
<th>Dose/Package</th>
<th>Days/Package</th>
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<tbody>
<tr>
<td>Naproxen (Treximet)</td>
<td>(oral)</td>
<td>5 mg spray</td>
<td>6 doses (1 box)/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg spray</td>
<td>18 doses (3 boxes)/30 days</td>
</tr>
<tr>
<td>Sumatriptan (nasal)</td>
<td></td>
<td>5 mg spray</td>
<td>6 doses (1 box)/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg spray</td>
<td>18 doses (3 boxes)/30 days</td>
</tr>
<tr>
<td>Sumatriptan (Imitrex) (nasal)</td>
<td></td>
<td>11 mg powder</td>
<td>8 doses (1 kit/16 nosepieces)/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 doses (2 kits/32 nosepieces)/30 days</td>
</tr>
<tr>
<td>Sumatriptan (Onzetra Xsail) (nasal)</td>
<td></td>
<td>10 mg spray</td>
<td>6 doses (1 box)/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 doses (3 boxes)/30 days</td>
</tr>
<tr>
<td>Sumatriptan (Tosymra) (nasal)</td>
<td></td>
<td>4 mg/0.5 mL</td>
<td>4 mL (4 kits, 8 doses)/30 days</td>
</tr>
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<td></td>
<td>6 mg/0.5mL</td>
<td>8 mL (8 kits, 16 doses)/30 days</td>
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<tr>
<td>Sumatriptan (SQ)</td>
<td></td>
<td>4 mg/0.5 mL Kit</td>
<td>4 mL (4 kits, 8 doses)/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mg/0.5 mL solution</td>
<td>8 mL (8 kits, 16 doses)/30 days</td>
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<tr>
<td>Sumatriptan (Imitrex) (SQ)</td>
<td></td>
<td>4 mg/0.5 mL solution</td>
<td>4 mL (4 kits, 8 doses)/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 mg/0.5 mL refill</td>
<td>8 mL (8 kits, 16 doses)/30 days</td>
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<tr>
<td>Sumatriptan (Zomig/ZMT) (nasal)</td>
<td></td>
<td>3 mg/0.5 mL solution</td>
<td>4 mL (4 kits, 8 doses)/30 days</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>8 mL (8 kits, 16 doses)/30 days</td>
</tr>
<tr>
<td>Zolmitriptan (oral)</td>
<td></td>
<td>2.5 mg tablet</td>
<td>9 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg tablet</td>
<td>20 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5 mg ODT</td>
<td></td>
</tr>
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<td></td>
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<td>5 mg ODT</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan (Zomig/ZMT) (oral)</td>
<td></td>
<td>2.5 mg tablet</td>
<td>9 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5mg tablet</td>
<td>20 tablets/30 days</td>
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<tr>
<td></td>
<td></td>
<td>2.5 mg ODT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg ODT</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan (Zembrace Symtouch) (SQ)</td>
<td></td>
<td>2.5 mg spray</td>
<td>6 doses/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 mg spray</td>
<td>18 doses (3 boxes)/30 days</td>
</tr>
<tr>
<td>Lasmiditan (Reyvow)</td>
<td></td>
<td>50 mg tablet</td>
<td>4 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100 mg tablet</td>
<td>8 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 tablets/30 days</td>
<td></td>
</tr>
<tr>
<td>Ubrogepant (Ubrelyv)</td>
<td></td>
<td>50 mg tablet</td>
<td>8 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 tablets/30 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>32 tablets/30 days</td>
<td></td>
</tr>
<tr>
<td>Celecoxib (Elyxyb)</td>
<td></td>
<td>120 MG/4.8 ML oral solution</td>
<td>43.2 mL (9 doses)/30 days</td>
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<td></td>
<td></td>
<td></td>
<td>56.4 mL (18 doses)/30 days</td>
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<tr>
<td>Diclofenac potassium (Cambia)</td>
<td></td>
<td>50 mg packet</td>
<td>9 packets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 packets/30 days</td>
</tr>
</tbody>
</table>

**Initial Evaluation**

1. 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:

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.

September 01, 2022
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

### Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added in celecoxib (Elyxyb) oral solution and Cambia oral packets and respective quantity limits</td>
<td>12/2021</td>
</tr>
<tr>
<td>Removed Nurtec from current policy as this was moved to Aimovig, Emgality, Ajovy/CGRP policy instead</td>
<td>04/2021</td>
</tr>
<tr>
<td>Corrected quantity limit for Nurtec to reflect manufacturer guidance and allowance of 8/30 or 16/30</td>
<td>07/2020</td>
</tr>
<tr>
<td>New FDA-approved migraine therapies added to policy: lasmiditan (Reyvow), ubrogepant (Ubrelvy), rimegepant (Nurtec ODT).</td>
<td>04/2020</td>
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<tr>
<td>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.</td>
<td>12/2019</td>
</tr>
<tr>
<td>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.</td>
<td>05/2018</td>
</tr>
<tr>
<td>Updated with clinical note regarding pediatric strength of Treximet.</td>
<td>10/2016</td>
</tr>
<tr>
<td>Updated with Onzentra Xsail.</td>
<td>05/2016</td>
</tr>
<tr>
<td>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.</td>
<td>01/2016</td>
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<td>Previous Reviews</td>
<td>08/2014, 01/2013, 08/2012, 04/2012</td>
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<td>09/2011</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>miltefosine (Impavido)</td>
<td>50 mg capsules</td>
<td>Visceral leishmaniasis, Cutaneous leishmaniasis, Mucosal leishmaniasis</td>
<td>30 to 44 kg: 56 capsules/28 days, OR ≥ 45 kg: 84 capsules/28 days</td>
</tr>
</tbody>
</table>

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:  

**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**

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:**

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<tr>
<th>Date Created</th>
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<tr>
<td>Date Effective</td>
<td>August 2016</td>
</tr>
<tr>
<td>Last Updated</td>
<td>October 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>4/2016, 10/2019</td>
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</tr>
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<tbody>
<tr>
<td>Transitioned criteria into policy with the following additions: supporting evidence, investigational section and CDC diagnostic recommendations.</td>
<td>10/2019</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>mitapivat (Pyrukynd)</td>
<td>Hemolytic anemia in patients with pyruvate kinase deficiency</td>
<td>5 mg tablets</td>
<td>56 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg tablets</td>
<td>50 tablets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg tablets</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>5 mg tablet taper pack</td>
<td>7 tablets/7 days*</td>
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<td></td>
<td></td>
<td>20 mg and 5 mg taper pack</td>
<td>14 tablets/14 days*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 mg and 20 mg taper pack</td>
<td>14 tablets/14 days*</td>
</tr>
</tbody>
</table>

*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


Related Policies

There are no related policies.

Policy Implementation/Update:

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<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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</thead>
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<td>Policy created</td>
<td>05/2022</td>
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</table>
mobocertinib (Exkivity™)

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>mobocertinib (Exkivity)</td>
<td>40 mg capsules</td>
<td>Metastatic non-small-cell lung cancer with exon 20 insertion mutation after progression on platinum-based chemotherapy</td>
<td>120 capsules/30 days</td>
</tr>
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Initial Evaluation

I. Mobocertinib (Exkivity) is considered investigational 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 (Ryrevant). 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 (Ryrevant) 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) 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


Policy Implementation/Update:

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<thead>
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<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Policy created</td>
<td>11/2021</td>
</tr>
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</table>
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

<table>
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<tr>
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<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>cladribine (Mavenclad)</td>
<td>Relapsing forms of multiple sclerosis (MS)</td>
<td>10 mg tablets (box of 4 tablets)</td>
<td>1 box (4 tablets)/26 days*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg tablets (box of 5 tablets)</td>
<td>1 box (5 tablets)/26 days*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg tablets (box of 6 tablets)</td>
<td>1 box (6 tablets)/26 days*</td>
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<tr>
<td></td>
<td></td>
<td>10 mg tablets (box of 7 tablets)</td>
<td>1 box (7 tablets)/26 days*</td>
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<tr>
<td></td>
<td></td>
<td>10 mg tablets (box of 8 tablets)</td>
<td>1 box (8 tablets)/26 days*</td>
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<tr>
<td></td>
<td></td>
<td>10 mg tablets (box of 9 tablets)</td>
<td>1 box (9 tablets)/26 days*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg tablets (box of 10 tablets)</td>
<td>1 box (10 tablets)/26 days*</td>
</tr>
<tr>
<td>daclizumab (Zinbryta)</td>
<td></td>
<td>150mg/mL single-dose PFS</td>
<td>1 syringe/28 days</td>
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<tr>
<td>dimethyl fumarate (Tecfidera, dimethyl fumarate)</td>
<td></td>
<td>30 day starter pack</td>
<td>1 starter pack/30 days (60 capsules/30 days)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120 mg capsule</td>
<td>60 capsules/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>240 mg capsule</td>
<td>60 capsules/30 days</td>
</tr>
<tr>
<td>monomethyl fumarate (Bafiertam)</td>
<td></td>
<td>95 mg capsule</td>
<td>120 capsules/30 days</td>
</tr>
<tr>
<td>diroximel fumarate (Vumerity)</td>
<td></td>
<td>231 mg capsule</td>
<td>120 capsules/30 days</td>
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<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dose/Strength</th>
<th>Packaging/Duration</th>
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<tbody>
<tr>
<td>fingolimod (Gilenya)</td>
<td>Relapsing forms of MS</td>
<td>0.25 mg capsule</td>
<td>30 capsules/30 days</td>
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<tr>
<td></td>
<td></td>
<td>0.5 mg capsule</td>
<td>30 capsules/30 days</td>
</tr>
<tr>
<td>glatiramer acetate (Copaxone, Glatopa, glatiramer acetate)</td>
<td></td>
<td>20 mg/mL single dose PFS</td>
<td>30 syringes per/30 days</td>
</tr>
<tr>
<td>glatiramer acetate (Copaxone, Glatopa, glatiramer acetate)</td>
<td></td>
<td>40 mg/mL single dose PFS</td>
<td>12 syringes/28 days</td>
</tr>
<tr>
<td>interferon beta-1a (Avonex)</td>
<td>Relapsing forms of multiple sclerosis (MS)</td>
<td>30 mcg/0.5mL PFS</td>
<td>4 syringes (1 kit)/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 mcg/0.5mL pen</td>
<td>4 pens/28 days</td>
</tr>
<tr>
<td>interferon beta-1a (Plegridy)</td>
<td></td>
<td>1 starter pack – (Pen Injector or PFS)</td>
<td>1 starter pack/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>125 mcg/0.5mL (Pen Injector or PFS)</td>
<td>2 pens (or PFS)/28 days</td>
</tr>
<tr>
<td>interferon beta-1a (Rebif)</td>
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<td>22 mcg/0.5mL (Auto-injector or PFS)</td>
<td>12 syringes/28 days</td>
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<td></td>
<td></td>
<td>44 mcg/0.5mL (Auto-injector or PFS)</td>
<td>12 syringes/28 days</td>
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<td></td>
<td></td>
<td>Titration Pack (PFS or Solution)</td>
<td>1 pack (12 syringes)/28 days</td>
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<tr>
<td>interferon beta-1b (Betaseron)</td>
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<td>0.3 mg powder for reconstitution</td>
<td>14 syringes/28 days</td>
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<tr>
<td>interferon beta-1b (Extavia)</td>
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<td>0.3 mg powder for reconstitution</td>
<td>15 syringes/30 days</td>
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<tr>
<td>ofatumumab (Kesimpta)</td>
<td>Relapsing forms of multiple sclerosis (MS); Ulcerative colitis**</td>
<td>20 mg/0.4mL Auto-injector</td>
<td>Initial: 3 pens/28 days Maintenance: 1 pen/28 days</td>
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<tr>
<td>ozanimod (Zeposia)</td>
<td></td>
<td>0.23 mg capsules</td>
<td>4 tablets/4 days</td>
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<td></td>
<td></td>
<td>0.46 mg capsules</td>
<td>3 tablets/3 days</td>
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<tr>
<td></td>
<td></td>
<td>0.92 mg capsules</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>ponesimod (Ponvory)</td>
<td></td>
<td>2-10 mg starter pack</td>
<td>Initial: 14 tablets/14 days Maintenance: 30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20 mg tablet</td>
<td></td>
</tr>
<tr>
<td>siponimod (Mayzent)</td>
<td>Relapsing forms of multiple sclerosis (MS)</td>
<td>0.25 mg starter pack (Titrato to 2 mg dose)</td>
<td>12 tablets/5 days</td>
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<td></td>
<td></td>
<td>0.25 mg tablets</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25 mg starter pack (Titrato to 1 mg dose)</td>
<td>7 tablets/4 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 mg tablet</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 mg tablets</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7 mg tablets</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 mg tablets</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td>teriflunomide (Aubagio)</td>
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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.
*Maximum of 2 boxes/331 days

PFS: Prefilled Syringe

Initial Evaluation

Interferon beta-1a (Avonex), generic dimethyl fumarate, fingolimod (Gilenya), glatiramer acetate (Glatopa), generic glatiramer acetate, and teriflunomide (Aubagio) are the preferred agents.

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

*Brand Copaxone and Tecfidera are noncovered drugs given generic availability, nonformulary multi-source brand requirements apply

I. Cladribine (Mavenclad), daclizumab (Zinbryta), diroximel fumarate (Vumerity), interferon beta-1a (Plegridy), interferon beta-1a (Rebif), interferon beta-1b (Betaseron), 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), dimethyl fumarate, fingolimod (Gilenya), glatiramer acetate/Glatopa, or teriflunomide (Aubagio)

II. 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 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 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 Tecfidera:** Documentation of treatment with all four (1, 2, 3, and 4) of the following have been ineffective, contraindicated, or not tolerated:
   1. interferon beta-1a (Avonex)
   2. fingolimod (Gilenya)
   3. glatiramer acetate (Glatopa) or generic glatiramer acetate
   4. teriflunomide (Aubagio); OR

E. **For Brand Copaxone:** Documentation of treatment with all four (1, 2, 3, and 4) of the following have been ineffective, contraindicated, or not tolerated:
   1. interferon beta-1a (Avonex)
   2. fingolimod (Gilenya)
   3. dimethyl fumarate
   4. teriflunomide (Aubagio)

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 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. 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**

III. Unless Brand has been previously approved through this health plan, if the request is for **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 complications 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**

IV. 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-titrat 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 as 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>
<thead>
<tr>
<th>MS with a relapsing-remitting course</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissemination in time (Development/appearance of new CNS lesions over time)</th>
<th>Dissemination in space (Development of lesions in distinct anatomical locations within the CNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥ 2 clinical attacks; OR</td>
<td>• ≥ 2 lesions; OR</td>
</tr>
<tr>
<td>• 1 clinical attack AND one of the following:</td>
<td>• 1 lesion AND one of the following:</td>
</tr>
<tr>
<td>o 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</td>
<td>o Clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location</td>
</tr>
<tr>
<td>o CSF-specific oligoclonal bands</td>
<td>o 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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary progressive MS course</th>
</tr>
</thead>
<tbody>
<tr>
<td>• MS course characterized by steadily increasing objectively documented neurological disability independent of relapses. Fluctuations, periods of stability, and superimposed</td>
</tr>
</tbody>
</table>

Washington State Rx Services is administered by Moda HEALTH

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.

September 01, 2022
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.

**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**

1. daclizumab (Zinbryta) [Prescribing Information]. Biogen Inc. Cambridge, MA. May 2016
2. teriflunomide (Aubagio) [Prescribing Information]. Sanofi. Cambridge, MA. January 2016
4. Interferon beta-1a (Rebif) [Prescribing Information]. Serono, Inc. September 2005
6. Interferon beta-1b (Betaseron) [Prescribing Information]. Berlex Laboratories. Revised October 2006
7. Interferon beta-1b (Extavia) [Prescribing Information]. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ. Revised November 2017
8. glatiramer acetate (Copaxone) [Prescribing Information]. Teva Pharmaceuticals, Inc., Revised February 2004
11. fingolimod (Gilenya) [Prescribing Information]. East Hanover, NJ: Novartis Corp. Revised August 2015
12. dimethyl fumarate (Tecfidera) [Prescribing Information]. Biogen Idec Inc. Cambridge, MA. January 2013
group phase 3 OPTIMUM study [oral presentation]. Presented at: The 35th European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress; September 11-13, 2019; Stockholm, SE.

27. monomethyl fumarate (Bafiertam) [Prescribing Information]. High Point, NC; Banner Life Sciences LLC. April 2020.

### Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added 0.25 (1mg) starter pack and 1 mg dose of Mayzent to policy</td>
<td>04/2022</td>
</tr>
<tr>
<td>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.</td>
<td>11/2021</td>
</tr>
<tr>
<td>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</td>
<td>05/2021</td>
</tr>
<tr>
<td>Adding loading dose to QL table for Kesimpta</td>
<td>02/2021</td>
</tr>
<tr>
<td>Addition of brand Copaxone into policy aligning with requirements for brand Tecfidera requiring medical necessity for brand over generic.</td>
<td>12/2020</td>
</tr>
<tr>
<td>Addition of ofatumumab (Kesimpta) and ponesimod to policy within non-preferred position. Addition of brand Tecfidera criteria requiring medical necessity for brand over generic.</td>
<td>11/2020</td>
</tr>
<tr>
<td>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.</td>
<td>09/2020</td>
</tr>
<tr>
<td>Updated to include ozanimod (Zeposia) as a non-preferred product</td>
<td>04/2020</td>
</tr>
<tr>
<td>Updated fingolimod (Gilenya) as a preferred product effective 4/1/2020 per WA PDL update</td>
<td>03/2020</td>
</tr>
<tr>
<td>Updated to add non-preferred Vumerity</td>
<td>11/2019</td>
</tr>
<tr>
<td>Updated to include box around preferred agents not requiring prior authorization</td>
<td>10/2019</td>
</tr>
<tr>
<td>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).</td>
<td>08/2019</td>
</tr>
<tr>
<td>Policy created from criteria</td>
<td>11/2017</td>
</tr>
</tbody>
</table>
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: Three months
- Renewal: 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenvatinib (Lenvima)</td>
<td>Unresectable Hepatocellular Carcinoma; Advanced Renal Cell Carcinoma; Recurrent, High-risk or Metastatic Endometrial Carcinoma; Locally Recurrent or Metastatic Progressive Thyroid Cancer</td>
<td>4 mg capsule therapy pack</td>
<td>30 capsules/30 days*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 mg capsule therapy pack</td>
<td>30 capsules/30 days*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14 mg capsule therapy pack</td>
<td>60 capsules/30 days*</td>
</tr>
<tr>
<td></td>
<td>Unresectable Hepatocellular Carcinoma</td>
<td>8 mg capsule therapy pack</td>
<td>60 capsules/30 days*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 mg capsule therapy pack</td>
<td>90 capsules/30 days*</td>
</tr>
<tr>
<td></td>
<td>Advanced Renal Cell Carcinoma; Recurrent, High-risk or Metastatic Endometrial Carcinoma</td>
<td>18 mg capsule therapy pack</td>
<td>90 capsules/30 days*</td>
</tr>
<tr>
<td></td>
<td>Locally Recurrent or Metastatic Progressive Thyroid Cancer</td>
<td>24 mg capsule therapy pack</td>
<td>90 capsules/30 days*</td>
</tr>
<tr>
<td></td>
<td>Advanced Renal Cell Carcinoma; Advanced Soft Tissue Sarcoma</td>
<td>200 mg tablets</td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>Unresectable Liver Carcinoma; Advanced Renal Cell Carcinoma</td>
<td>200 mg tablets</td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>Locally Recurrent or Metastatic Progressive Thyroid Cancer</td>
<td>200 mg tablets</td>
<td>120 tablets/30 days</td>
</tr>
</tbody>
</table>

*Quantity limits are based on recommended daily dose of lenvatinib (Lenvima) for each indication; QL exceptions allowed only for dose reductions.
Initial Evaluation

I. Lenvatinib (Lenvima), pazopanib (Votrient), or sorafenib (Nexavar) 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); 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:

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.
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); 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)

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 investigation when used for all other conditions, including but not limited to:
   A. Gastrointestinal Stromal Tumor
   B. Adipocytic Sarcoma/Liposarcoma
   C. Sorafenib (Nexavar) for the treatment of desmoid tumors (aggressive fibromatosis)
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

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
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.

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.

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. Desmoid fibromatosis:
      i. Sorafenib (Nexavar) received a category 1 recommendation from NCCN for the treatment of desmoid tumors (aggressive fibromatosis) based on the data from a phase-3, double-blind, randomized, placebo-controlled, crossover clinical trial (N=87). However, sorafenib is not FDA-approved for this indication. Primary endpoint for this study was progression-free survival rate (PFSR), which was estimated (based on Kaplan-Meier curve) at 89% (95% CI, 80.99) as compared to that for placebo 36% (95% CI; 22, 57). 54% of participants had newly diagnosed, untreated desmoid tumors. Although primary outcome was statistically significant, clinical meaningfulness of this data is uncertain due to high withdrawal rates from the trial (62%), significant response rates observed in placebo arm, and lack of patient quality of life (HRQoL) measures. It should be noted that desmoid tumors are slow growing benign tumors, which often regress spontaneously without treatment. hence, efficacy of therapeutic intervention in an untreated patient population, on the basis of PFSR, may not be conclusive.
   D. 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/or 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

8. Olivier Mir MD et al. PAZOGIST trial, Lancet Oncology; 2016; 17 (55) 632-641.

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<tbody>
<tr>
<td>Added requirement to trial generic sorafenib tosylate prior to branded Nexavar</td>
<td>06/2022</td>
</tr>
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</table>

Washington State Rx Services is administered by moda

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.

September 01, 2022
<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>02/2022</td>
<td>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</td>
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<tr>
<td>10/2021</td>
<td>Moved “Sorafenib (Nexavar) for the treatment of desmoid tumors (aggressive fibromatosis)” out of the “Not Medically Necessary” section to “Investigational Use” section; Changed policy name from “lenvatinib (Lenvima™), pazopanib (Votrient®), sorafenib (Nexavar®)” to “Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)”</td>
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<tr>
<td>09/2021</td>
<td>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-naive allowing coverage in first-line as well as 2nd-line settings, added requirement for Child-Pugh class A/B7. Updates to supporting evidence sections.</td>
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<tr>
<td>04/2021</td>
<td>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)</td>
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<tr>
<td>12/2020</td>
<td>Updated supporting evidence for investigational indication of endometrial carcinoma for Lenvima</td>
</tr>
<tr>
<td>10/2020</td>
<td>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</td>
</tr>
<tr>
<td>10/2018</td>
<td>Previous reviews</td>
</tr>
<tr>
<td>06/2017</td>
<td>• Lenvima: Updated indication to include advanced renal cell carcinoma (2017), updated indication to include unresectable hepatocellular carcinoma (2018)</td>
</tr>
<tr>
<td>03/2016</td>
<td>• Votrient: Updated to reflect FDA approved indications and quantity limits (2016)</td>
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<tr>
<td>10/2020</td>
<td>• Nexavar: Updated to reflect FDA approved indications (2016)</td>
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<tr>
<td>03/2016</td>
<td>Criteria created</td>
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<tr>
<td>03/2015</td>
<td>• Lenvima: 2015</td>
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<td>02/2012</td>
<td>• Votrient: 2012</td>
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<td>03/2012</td>
<td>• Nexavar: 2012</td>
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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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>neratinib (Nerlynx)</td>
<td>40 mg tablets</td>
<td>Breast cancer, early stage, HER2-positive, following trastuzumab</td>
<td>180 tablets/30 days</td>
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<td></td>
<td></td>
<td>Breast cancer, advanced or metastatic HER2-positive</td>
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</table>

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
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. 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Addition of new indication for advanced or metastatic breast cancer. Addition of split fill management.</td>
<td>07/2020</td>
</tr>
<tr>
<td>Criteria transitioned to policy, with updates to newest format: inclusion of specialty provider, clarification on concurrent therapies, age requirement.</td>
<td>10/2019</td>
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<tr>
<td>Criteria created</td>
<td>09/2017</td>
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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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<tr>
<td>nilotinib</td>
<td>50 mg capsules</td>
<td>Newly diagnosed OR resistant/intolerant Ph+ CML in chronic phase</td>
<td>112 capsules/28 days</td>
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<td></td>
<td>150 mg capsules</td>
<td>Newly diagnosed Ph+ CML in chronic phase</td>
<td>112 capsules/28 days</td>
</tr>
<tr>
<td></td>
<td>200 mg capsules</td>
<td>Resistant or intolerant Ph+ CML Gastrointestinal Stromal Tumors (GIST)</td>
<td>112 capsules/28 days</td>
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</table>

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


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<tr>
<td>Date Effective</td>
<td>August 2010</td>
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<tr>
<td>Last Updated</td>
<td>December 2019</td>
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<td>Last Reviewed</td>
<td>03/2012, 07/2012, 08/2012, 01/2013, 05/2018, 12/2019</td>
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Action and Summary of Changes

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<tr>
<td>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.</td>
<td>12/2019</td>
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<tr>
<td>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).</td>
<td>05/2018</td>
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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

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
</table>
| 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
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, an 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.

Policy Implementation/Update:

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<thead>
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<tr>
<td>Policy created</td>
<td>10/2020</td>
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</table>
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

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<tr>
<th>Product Name</th>
<th>Indication</th>
<th>Dosage Form</th>
<th>Quantity Limit</th>
</tr>
</thead>
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<tr>
<td>nintedanib (Ofev)</td>
<td>Idiopathic pulmonary fibrosis (IPF); Systemic sclerosis-associated interstitial lung disease (SSc-ILD); Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype</td>
<td>100 mg capsules</td>
<td>60 capsules/30 days</td>
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<td>150 mg capsules</td>
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<tr>
<td>pirfenidone (generic Esbriet)</td>
<td>Idiopathic Pulmonary Fibrosis (IPF)</td>
<td>267 mg capsules or tablets</td>
<td>270 capsules or tablets/30 days</td>
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<td>534 mg tablets</td>
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<td></td>
<td></td>
<td>801 mg tablets</td>
<td>90 tablets/30 days</td>
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<tr>
<td>pirfenidone (Esbriet)</td>
<td>Idiopathic Pulmonary Fibrosis (IPF)</td>
<td>267 mg capsules or tablets</td>
<td>270 capsules or tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>801 mg tablets</td>
<td>90 tablets/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

1. **Nintedanib (Ofev) and pirfenidone (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 any form of smoking; 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; OR
         a. Generic pirfenidone has not been tolerated or is 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 (e.g. decline in %FVC with worsening respiratory symptoms or increasing extent of fibrotic changes on chest imaging)

II. Nintedanib (Ofev) and prifenidone (Esbriet) are considered investigational when used for all other conditions, including but not limited to:
   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

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.
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 prfenidone (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:

   ● Idiopathic pulmonary fibrosis (IPF); AND
     i. The request is for generic pirfenidone; OR
        a. Generic pirfenidone has not been tolerated or is contraindicated; OR
   
   ● Systemic sclerosis-associated interstitial lung disease (SSc-ILD); AND
     i. Request is for nintedanib (Ofev); OR
   
   ● 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)
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. 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:

<table>
<thead>
<tr>
<th>End Points</th>
<th>INPULSIS-1</th>
<th></th>
<th></th>
<th>INPULSIS-2</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nintedanib (N=307)</td>
<td>Placebo (N=204)</td>
<td>95% CI; ( P ) value</td>
<td>Nintedanib (N=327)</td>
<td>Placebo (N=217)</td>
<td>95% CI; ( P ) value</td>
</tr>
<tr>
<td>Adjusted absolute mean change from baseline in FVC (mL)</td>
<td>-95.1</td>
<td>-205.0</td>
<td>109.9 (71.3, 148.6; ( P &lt; 0.001 ))</td>
<td>-95.3</td>
<td>-205.0</td>
<td>109.8 (70.9, 148.6; ( P &lt; 0.001 ))</td>
</tr>
<tr>
<td>Adjusted absolute mean change from baseline in FVC (% predicted)</td>
<td>-2.8%</td>
<td>-6.0%</td>
<td>3.2% (2.1, 4.3; ( P &lt; 0.001 ))</td>
<td>-3.1%</td>
<td>-6.2%</td>
<td>3.1% (1.9, 4.3; ( P &lt; 0.001 ))</td>
</tr>
<tr>
<td>FVC response at week 52 (%): FVC decline ≤ 5%</td>
<td>52.8%</td>
<td>38.2%</td>
<td>1.85% (1.28, 2.66; ( P &lt; 0.001 ))</td>
<td>53.2%</td>
<td>39.3%</td>
<td>1.79% (1.23, 2.55; ( P &lt; 0.001 ))</td>
</tr>
<tr>
<td>FVC response at week 52 (%): FVC decline ≤ 10%</td>
<td>70.6%</td>
<td>56.9%</td>
<td>1.91% (1.32, 2.79; ( P &lt; 0.001 ))</td>
<td>69.6%</td>
<td>63.9%</td>
<td>1.29% (0.89, 1.86; ( P &lt; 0.001 ))</td>
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</tbody>
</table>

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), esophageal 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 treatment.
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


Policy Implementation/Update:

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<th>Date</th>
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<tr>
<td>Added generic pirfenidone 534mg tablets to QL table</td>
<td>08/2022</td>
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<tr>
<td>Added new generic pirfenidone, requiring trial of generic pirfenidone prior to brand Esbriet</td>
<td>06/2022</td>
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<tr>
<td>• Added nintedanib (Ofev) to the Moda Split Fill program</td>
<td>06/2020</td>
</tr>
<tr>
<td>• 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)].</td>
<td>06/2020</td>
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<tr>
<td>• Added criteria for baseline assessment [eg. forced vital capacity (%FVC) or carbon monoxide diffusing capacity (DLCO) or six minute walking distance (6MWD)]</td>
<td>06/2020</td>
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<tr>
<td>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.</td>
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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: UMP139**

**Split Fill Management***

**Description**
Niraparib (Zejula) is an orally administered poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment, or maintenance therapy, of ovarian, fallopian tube, or primary peritoneal cancer.

**Length of Authorization**
- Initial: Six months
- Renewal: 12 months

**Quantity limits**

<table>
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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>niraparib (Zejula)</td>
<td>100 mg capsules</td>
<td>Treatment for: advanced ovarian, fallopian tube, or primary peritoneal cancer</td>
<td>90 capsules/30 days</td>
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<tr>
<td></td>
<td></td>
<td>Maintenance for: recurrent or advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer</td>
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</table>

**Initial Evaluation**

I. Niraparib (Zejula) 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. Niraparib (Zejula) will be used as monotherapy; **AND**
   D. Member has **not** progressed on prior PARP inhibitor (e.g. olaparib [Lynparza], rucaparib [Rubraca]) therapy; **AND**
   E. Provider is requesting niraparib (Zejula) for **Treatment** (and not maintenance therapy); **AND**
      1. Member has a diagnosis of **advanced (stage III or IV) ovarian, fallopian tube, or primary peritoneal cancer**; **AND**
         i. Member has been treated with **three** or more prior **lines** of chemotherapy (e.g. cisplatin, carboplatin, paclitaxel, doxorubicin, bevacizumab, gemcitabine); **AND**
            a. Member has homologous recombination deficiency (HRD) positive tumor (i.e., tBRCAm); **OR**

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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. Member without BRCA mutations and progressed at least six months after their last dose of platinum-based chemotherapy regimen (e.g. cisplatin, oxaliplatin, carboplatin); OR

F. Provider is requesting niraparib (Zejula) for Maintenance therapy; AND
   1. Member is in complete or partial response to their last platinum-based chemotherapy regimen (i.e., platinum-sensitive) (e.g. cisplatin, oxaliplatin, carboplatin); AND
   2. 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); AND
   3. 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
         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)

II. Niraparib (Zejula) is 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. Prostate Cancer
   D. Lung Cancer
   E. Advance Solid Tumors
   F. Melanoma
   G. Pancreatic cancer
   H. Gastroesophageal 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. Member has exhibited a response to therapy such as stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

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. The safety of niraparib (Zejula) for the treatment of advanced ovarian cancer after three or more chemotherapies was studied in a single arm trial with the investigator assessment of objective response rate (ORR) as the efficacy outcome measure. That trial included 98 patients with advanced ovarian cancer positive for homologous recombination deficiency (HRD) tumors, also known as BRCAmut positive tumors. Those patients were required to have been treated with three or more prior lines of chemotherapy, and those with history of PARP inhibitors were excluded. Additionally, patients without BRCA mutations must have progressed at least six months after their last dose of platinum-based chemotherapy regimen.

IV. HRD (BRCAmut) positive ORR was 24% with 95% CI (16, 34) without BRCAmut, ORR was 20% with 95% CI (8, 37). Efficacy and safety of niraparib (Zejula) 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. gBRCAm) 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. gBRCAm) 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; gBRCAm) 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.

V. 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.

VI. 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.

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

* 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


Policy Implementation/Update:

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<thead>
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<tbody>
<tr>
<td>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</td>
<td>09/2020</td>
</tr>
<tr>
<td>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 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.</td>
<td>11/2019</td>
</tr>
<tr>
<td>Criteria created</td>
<td>08/2017</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>nitisinone</td>
<td>2 mg capsule</td>
<td>Hereditary tyrosinemia type 1</td>
<td>2 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>5 mg capsule</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>10 mg capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitisinone</td>
<td>2 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg tablet</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>10 mg tablet</td>
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<td></td>
</tr>
<tr>
<td>nitisinone</td>
<td>2 mg capsule</td>
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<tr>
<td></td>
<td>5 mg capsule</td>
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<td></td>
<td>10 mg capsule</td>
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<tr>
<td></td>
<td>20 mg capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 mg/mL suspension</td>
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</table>

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

### Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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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.
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If you think we did not offer these services or discriminated, you can file a written complaint. Please mail or fax it to:
Washington State Rx Services
Attention: Appeal Unit
PO Box 40168
Portland, OR 97240-0168
Fax: 1-866-923-0412

You can also file a civil rights complaint with:
The U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue, SW Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD).

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html


Complaint forms are available at https://fortress.wa.gov/oic/onlineservices/cc/pub/complaintinformation.aspx
ATENCIÓN: Si habla español, hay disponibles servicios de ayuda con el idioma sin costo alguno para usted. Llame al 1-888-361-1611 (TRS: 711).

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Đ, dịch vụ hỗ trợ ngôn ngữ miễn phí cho bạn. Gọi 1-888-361-1611 (TRS: 711)

توجه: در صورتي كه فارسی صحبت می کنید، خدمات ترجمه به صورت رایگان برای شما موجود است. با تماس به‌گرید.

1-888-361-1611 (TRS: 711)

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