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

Updates effective 07/01/2021

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: UMP050

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
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
abemaciclib (Verzenio)	50 mg tablets	Breast cancer, HER2-negative, HR-positive, advanced or metastatic (women)	56 tablets/28 days
	100 mg tablets		
	150 mg tablets		
	200 mg tablets		
palbociclib (Ibrance)	75 mg capsules/tablets*	Breast cancer, HER2-negative, HR-positive, advanced or metastatic (men and women)	21 capsules or tablets/28 days
	100 mg capsules/tablets*		
	125 mg capsules/tablets*		
ribociclib (Kisqali)	200 mg tablet dose pack	Breast cancer, HER2-negative, HR-positive, advanced or metastatic (women)	21 tablets/28 days
	400 mg tablet dose pack		42 tablets/28 days
	600 mg tablet dose pack		63 tablets/28 days
ribociclib/letrozole (Kisqali/Femara)	200 mg and 2.5 mg tablet dose pack		49 tablets/28 days
	400 and 2.5 mg tablet dose pack		70 tablets/28 days
	600 and 2.5 mg tablet dose pack		91 tablets/28 days

Initial Evaluation

I. Abemaciclib (Verzenio), palbociclib (Ibrance), 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. 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. fulvestrant); **AND**
D. Member has not previously progressed on, or after treatment with another CDK4/6 inhibitor (e.g. ribociclib [Kisqali], abemaciclib [Verzenio]); **AND**
E. Diagnosis of **breast cancer** when the following are met:
    1. The Member has hormone receptor-positive (HR+) and HER2-negative (HER2-) disease; **AND**
    2. Disease is advanced (stage III) or metastatic (stage IV); **AND**
    3. Request is for treatment as first line chemotherapy in combination with an aromatase inhibitor (e.g. letrozole, anastrozole, exemestane); **AND**
        i. The member is a postmenopausal female (natural or pharmacotherapy induced [e.g. GnRH therapy [e.g. Lupron] used concomitantly]); **OR**
        ii. The member is male; **AND**
            a. The request is for palbociclib (Ibrance); **AND**
            b. Palbociclib (Ibrance) will be administered in combination with a GnRH analog (e.g. goserelin, leuprolide); **OR**
    4. Request is for treatment as a second line or subsequent-line chemotherapy; **AND**
        i. The member has progressed after first line endocrine therapy (e.g. aromatase inhibitor, or estrogen receptor modulator [e.g. tamoxifen]); **AND**
            a. The medication will be administered in combination with fulvestrant (Faslodex); **AND**
            b. The member is a postmenopausal female (natural or pharmacotherapy induced [e.g. GnRH therapy [e.g. Lupron] used concomitantly]); **OR**
            c. The member is male; **AND**
                i. The request is for palbociclib (Ibrance); **OR**
        ii. The member has previously progressed following endocrine therapy and chemotherapy; **AND**
            a. The member's current disease stage is metastatic (stage IV); **AND**
            b. The member is female; **AND**
            c. Member received endocrine therapy and chemotherapy (not containing a CDK 4/6 inhibitor) in the metastatic (stage IV) setting; **AND**
            d. 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; **AND**
II. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
III. The medication is prescribed by, or in consultation with, an oncologist; **AND**
IV. 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 fulvestrant (Faslodex); **AND**
V. 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) was evaluated in adult, female subjects with HR+, HER2-, advanced or metastatic breast cancer. The following studies were pivotal trials for the approved indications:
    - 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.
    - 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.

i. The OS data from this trial was reported in September 2019. There was statistically significant OS in favor of abemaciclib (Verzenio) in combination with fulvestrant versus placebo by 9.4 months.

- 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. Initial FDA-approval of palbociclib (Ibrance) was for women only and was evaluated in adults with breast cancer with the following characteristics: HR+, HER2-, advanced (stage III) or metastatic (stage IV) disease. There were two settings evaluated: initial endocrine based therapy in combination with an aromatase inhibitor and treatment in combination with fulvestrant after progression on initial endocrine therapy.

V. Palbociclib (Ibrance) was further 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. Guidelines recommend that men on an aromatase inhibitor and palbociclib (Ibrance) be administered a GnRH analog concurrently. Available evidence suggests that those treated with aromatase inhibitor monotherapy have been associated with inferior outcomes; likely due to inadequate estradiol suppression.

VI. 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. Concomitant therapy with GnRH agonist (goserelin) was utilized in order to induce menopause in all participants. 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).

i. Overall survival data was reported in September 2019 (HR: 0.74 [p=0.00455]) in favor of ribociclib (Kisqali).

VII. Clinical trials to date have not included significant numbers of subjects previously treated with other CDK4/6 inhibitors; thus, safety and efficacy of subsequent administration is unknown at this time. Additionally, CKD4/6 inhibitors have been evaluated as monotherapy, and sufficient safety and efficacy evidence, in combination with therapies outside of aromatase inhibitors and fulvestrant, remain unknown. The 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."

VIII. Endocrine therapies include, but may not be limited to, the following: tamoxifen, anastrozole, letrozole, exemestane. Chemotherapy regimen include, but may not be limited to, the following: doxorubicin, paclitaxel, capecitabine, gemcitabine, cyclophosphamide, carboplatin, docetaxel, cisplatin, and combinations of these therapies.

IX. There is lack of scientific evidence from randomized controlled trials supporting the safety and/or efficacy for increased dosing or frequency of palbociclib (Ibrance). The dosing recommendation is one capsule once daily, with various doses for tolerability and dose adjustments for safety considerations, in 21 out of 28-day cycles. Increasing the dose beyond 125 mg per day, or dosing more than 21 out of every 28 days has not been evaluated.

X. Postmenopausal status may be reached in women via ovarian suppression through GnRH therapy (pharmacotherapy-induced) for several weeks prior to palbociclib (Ibrance) administration, bilateral oophorectomy (surgically-induced), ovarian irradiation, or natural menopause. Any of these routes is considered acceptable for aforementioned criteria.

XI. The NCCN Guidelines do not currently distinguish a preference between currently available CDK4/6 inhibitors (abemaciclib, palbociclib ribociclib) and no evidence is currently available indicating that one of these agents is superior than 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 and 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.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of wording related to GnRH therapy to induce menopause in order to clarify the FDA approval for Kisqali in pre/perimenopausal setting	03/2021
Transitioned criteria to policy format and merged into one policy	12/2020

Previews reviews • Verzenio: Updated to include age, specialist, limit concurrent therapy, with renewal criteria to align with current practice and removal of subgroup analysis exclusions, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2019); added new indication: first-line treatment in combination with an aromatase inhibitor (2018); clarified use of concomitant medication (2017) • Kisqali: Updated to include age, specialist, limit concurrent therapy, with renewal criteria to align with current practice (2019); updated product availability with Kisqali-Femara dose pack, added new indication for pre/perimenopausal setting in combination with aromatase inhibitor, as well as postmenopausal setting in combination with fulvestrant as first or second line endocrine therapy, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2018) • Ibrance: Updated QL box to inform about transition to tablets (2020), Added new indication and FDA-approval of breast cancer in men, added criteria to avoid combination use or use after progression on another CDK4/6 inhibitor (2019); updated criteria to allow treatment after disease progression on prior endocrine therapy (2016)	03/2020 10/2019 05/2019 09/2018 08/2018 03/2018 09/2017 01/2016
Criteria created • Verzenio • Kisqali • Ibrance	 10/2019 04/2017 02/2015

acalabrutinib (Calquence®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP108

Description

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

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

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

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 <u>not</u> experienced disease progression while on a BTK inhibitor [e.g. zanubrutinib (Brukinsa®), ibrutinib (Imbruvica®)]; **AND**
   D. A diagnosis of one of the following:
      1. **Mantle cell lymphoma (MCL)**; **AND**
         i. Treatment with least one first-line therapy for MCL [e.g., rituximab, bendamustine + rituximab, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) - based regimen, Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, and dexamethasone), bortezomib or carfilzomib, stem-cell transplant, lenalidomide, etc.] has been ineffective, contraindicated, or not tolerated; **OR**
      2. **Chronic Lymphocytic Leukemia (CLL) or small lymphocytic lymphoma (SLL)**; **AND**
         i. Medication is used in <u>**one**</u> of the following settings:
            a. Previously untreated CLL/SLL; **AND**

i. Medication will be used as monotherapy or in combination with obinutuzumab (Gazyva); **OR**

b. Relapsed or refractory after at least one prior systemic therapy; **AND**

i. Member has **not** experienced disease progression while on venetoclax (Vencelxta) or a phosphoinositide-3 kinase inhibitor [e.g. duvelisib (Copiktra), idelalisib (Zydelig)]; **AND**

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

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

A. Diffuse Large B-Cell Lymphoma
B. Head and neck squamous cell carcinoma
C. Ovarian cancer
D. Non-small cell lung cancer (NSCLC)
E. Severe Chronic Graft Versus Host Disease
F. 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. 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); **OR**
- Acalabrutinib (Calquence) will be used in combination with obinutuzumab (Gazyva) in the setting of previously untreated CLL/SLL; **AND**

V. 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. MCL, 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. Acalabrutinib (Calquence) was studied in an open-label, phase 2 study in patients with relapsed or refractory mantle cell lymphoma. Oral acalabrutinib (100 mg twice per day) was given until disease progression or unacceptable toxicity. 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.

V. 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, 3 arm trial of acalabrutinib in combination with obinutuzumab, acalabrutinib 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.

VI. 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 of MCL and 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. Diffuse Large B-Cell Lymphoma
   B. Head and neck squamous cell carcinoma
   C. Ovarian cancer
   D. Non-small cell lung cancer (NSCLC)
   E. Severe Chronic Graft Versus Host Disease
   F. Waldenström's macroglobulinemia (WM)

References

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Policy Implementation/Update:

Date Created	January 2018
Date Effective	February 2018
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	**Date**
Updated criteria to policy format. Addition of age requirement to ages 18 and older. Require member has not experienced disease progression while on a BTK inhibitor. Added new indication of CLL/SLL.	12/2019
Criteria created	01/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP001

Description

Alirocumab (Praluent) and evolocumab (Repatha) are subcutaneous Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) inhibitors.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
alirocumab (Praluent)	75 mg/mL pen injector	Heterozygous familial hypercholesterolemia; Homozygous familial hypercholesterolemia; Atherosclerotic cardiovascular disease	2 mL (2 injections)/28 days
	150 mg/mL pen injector		
evolocumab (Repatha)	140 mg/mL auto injector; prefilled syringe		2 mL (2 injections)/28 days
	420 mg/mL solution cartridge		3.5 mL (1 injection)/28 days

Initial Evaluation

I. Alirocumab (Praluent) or evolocumab (Repatha) may be considered medically necessary when the following criteria below are met:
   A. Therapy is prescribed by, or in consultation with, a provider specializing in lipid management (e.g., cardiology, lipidology, endocrinology); **AND**
   B. The member has a LDL-cholesterol level greater than or equal to 70 mg/dL while on maximally tolerated statin therapy; **AND**
   C. If the request is for alirocumab (Praluent): Treatment with evolocumab (Repatha) has been ineffective, contraindicated, or not tolerated; **AND**
   D. Therapy with a high intensity statin (greater than or equal to atorvastatin [Lipitor] 40 mg or rosuvastatin (Crestor) 20 mg) for at least an 8 week duration has been ineffective; **AND**
      1. The member will continue statin therapy in combination with alirocumab (Praluent) or evolocumab (Repatha); **OR**
   E. There is documentation of statin failure defined by one of the following:
      1. Treatment with maximally tolerated doses of any statin (e.g., simvastatin [Zocor], pravastatin [Pravachol], etc.) was ineffective or contraindicated; **OR**
      2. The patient has not tolerated at least two statin medications as defined by at least <u>one</u> of the following:
         i. CK exceeds 10 times the upper limit of normal

ii. LFTs exceed 3 times the upper limit of normal
iii. Severe rhabdomyolysis leading to hospitalization
iv. Severe muscle weakness inhibiting activities of daily living, employment, or leading to temporary disability; **AND**

F. A diagnosis of one of the following:
1. **Atherosclerotic cardiovascular disease (ASCVD); AND**
i. Member is 18 years of age or older; **AND**
ii. Treatment with ezetimibe (Zetia) has been ineffective, contraindicated, or not tolerated; **AND**
iii. Documentation of clinical atherosclerotic disease via invasive or non-invasive testing (e.g., stress test, imaging); **OR**
iv. Diagnosis of atherosclerotic disease and primary prevention failure (e.g., member has had a stroke, myocardial infarction); **OR**
2. **Heterozygous familial hypercholesterolemia**; **AND**
i. The member is 18 years of age or older; **AND**
ii. Diagnosis of heterozygous familial hypercholesterolemia is confirmed by <u>one</u> of the following
a. Genotyping or clinical criteria using either the Simon Broome diagnostic criteria (definite diagnosis classification) or Dutch Lipid Network criteria (score greater than 8)
b. Clinical documentation or a DNA mutation analysis supporting the diagnosis of heterozygous familial hypercholesterolemia; **OR**
3. **Homozygous familial hypercholesterolemia**; **AND**
i. If the request is for evolocumab (Repatha), the member is 13 years of age or older; **OR**
a. If the request is for alirocumab (Praluent), the member is 18 years of age or older; **AND**
ii. The member has a history of an untreated LDL-cholesterol level greater than 500 mg/dL with either evidence of heterozygous familial hypercholesterolemia in both parents or xanthoma before the age of 10; **OR**
a. DNA mutation analysis supporting the diagnosis of homozygous familial hypercholesterolemia (e.g, *LDLR, APOB, PSCK9, LDLRAP1*); **AND**
iii. Evolocumab (Repatha) or alirocumab (Praluent) will not be used in combination with lopitamide (Juxtapid)

II. Alirocumab (Praluent) or evolocumab (Repatha) are considered <u>not medically necessary</u> when used for all other conditions, including but <u>not limited to</u>:
A. Hypercholesterolemia non-familial cause

III. Alirocumab (Praluent) or evolocumab (Repatha) are considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
A. ASCVD primary prevention in non-familial hypercholesterolemia

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 experienced a decrease from baseline LDL-C while on therapy

Supporting Evidence

I. Alirocumab (Praluent) is FDA-approved to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease and as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) or homozygous familial hypercholesterolemia who reduce low-density lipoprotein cholesterol (LDL-C).
II. Evolocumab (Repatha) is FDA-approved to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease and as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) or homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
III. The 2017 American Association of Clinical Endocrinologists (AACE) guidelines state statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. Additionally, guidelines state PCSK9 inhibitors should be considered in individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals.
IV. Seventy to ninety percent of patients are able to tolerate an alternate long-term statin. In clinical practice, 10-25% of patients have musculoskeletal adverse events associated with statin use; however, several studies have determined that the majority of patients with statin-associated muscle symptoms are able to tolerate subsequent statin therapy with modified dosing regimens.
V. The 2011 National Lipid Association (NLA) familial hypercholesterolemia guidelines define ineffective therapy as inability to achieve a LDL-C of less than 70 mg/dL with treatment in atherosclerotic cardiovascular disease.
VI. **Atherosclerotic cardiovascular disease (ASCVD)**: The 2018 American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol Guidelines recommend patients with clinical ASCVD reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy. In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should

include maximally tolerated statin therapy and ezetimibe (very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions).

- The 2017 American College of Cardiology (ACC) Recommendations for Non-Statin Therapy recommends consideration of adding ezetimibe first in patients that are statin intolerant with clinical ASCVD and may consider a bile acid sequestrant as an alternative if ezetimibe intolerant and triglycerides <300 mg/dL.
- Per Schmidt et al. Cochrane Review, "in comparisons of PCSK9 inhibitors versus no PCSK9 inhibitors, current evidence suggests that PCSK9 inhibitors decrease CVD incidence without affecting the incidence of all-cause mortality. In comparisons of PCSK9 inhibitors versus alternative (more established) treatments such as statins or ezetimibe, high-quality evidence is lacking. Differences in risk between people treated with and without PCKS9 inhibitors suggest the absolute treatment benefit will likely be modest (e.g. < 1% change in risk)."

VII. 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.

VIII. **Heterozygous familial hypercholesterolemia**: The presence of tendon xanthoma is a genetically modulated clinical syndrome of familial hypercholesterolemia. In addition, DNA testing can be used to diagnose familial hypercholesterolemia functional mutations. In clinical trials, enrolled patients with heterozygous familial hypercholesterolemia were diagnosed either by genotyping or clinical criteria ("definite FH" using either the Simon Broome or Dutch Lipid Network).

Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia	
Criteria	**Description**
A	Total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in adults or a total cholesterol concentration above 6.7 mmol/liter (259 mg/dL) in children aged less than 16 years, or
	Low density lipoprotein cholesterol concentration above 4.9 mmol/liter (189 mg/dL) in adults or above 4.0 mmol/liter (155 mg/dL) in children
B	Tendinous xanthomata in the patient or a first-degree relative
C	DNA-based evidence of mutation in the *LDLR, PCSK9,* or *APOB* gene
D	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
E	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
A "definite" FH diagnosis requires either criteria a and b, or criterion c. A "probable" FH diagnosis requires either criteria a and d, or criteria a and e.	

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

- Using DNA testing, patients with familial hypercholesterolemia (FH) have been identified as generally having a functional mutation of one of three genes: *LDLR, PCSK9,* or *APOB* gene. Mutations in these three genes can be detected in about 80 percent of patients with the definite FH clinical syndrome.
- The 2017 AACE guidelines state PCSK9 inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH.

IX. **Homozygous familial hypercholesterolemia (HoFH):** Evolocumab (Repatha) and alirocumab (Praluent) are FDA-approved in the setting of HoFH and includes patients ages 13 and older (Repatha) or 18 and older (Praluent). Evolocumab (Repatha) was studied in one multi-center, double-blind, randomized, placebo-controlled trial (TESLA Part B) patients greater than, or equal to, 13 years of age with homozygous familial hypercholesterolemia. Patients in the clinical trial had familial hypercholesterolemia diagnosed either by genetic analysis or clinical criteria (history of an untreated LDL cholesterol concentration >13 mmol/L (500 mg/dL) plus either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents. Alirocumab (Praluent) was studied in one randomized, double-blind, placebo-controlled, parallel-group, phase 3 study (ODYSSEY HoFH) in patients 18 years of age or older

with homozygous familial hypercholesterolemia. Patients in the clinical trial had a diagnosis of familial hypercholesterolemia confirmed in the patient's medical history by clinical diagnosis or by genotyping. The genotyping results from this study found patients had mutations in the *LDLR, LDLRAP1, PCSKP,* or *APOB* genes.

- Use of evolocumab (Repatha) and alirocumab (Praluent) with mipomersen (Kynamro) or lopitamide (Juxtapid) has not been studied in a large population, and the efficacy and safety is unknown. Concurrent use is considered experimental and investigational.

Investigational or Not Medically Necessary Uses

I. Primary hypercholesterolemia
   A. The use of statins, including in patients considered to be high risk, is recommended as first line therapy by multiple guidelines.
   B. 2018 AHA/ACC guidelines state "at any given price, the economic value of PCSK9 inhibitors will be improved by restricting their use to patients at very high-risk of ASCVD events".

II. ASCVD primary prevention in non-familial hypercholesterolemia
   A. Trials in prevention of cardiovascular events have occurred in the established cardiovascular disease population (secondary prevention). PCSK9 inhibitors have not been adequately evaluated in primary prevention in patients without familial hypercholesterolemia. Applicability of results to primary prevention is limited.
   B. Per 2018 AHA/ACC guidelines, among patients with FH without evidence of clinical ASCVD taking maximally tolerated statin and ezetimibe therapy, PCSK9 inhibitors provide uncertain value at mid-2018 U.S. list prices. Economic models have not been produced for primary prevention in non-familial hypercholesterolemia.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added new FDA-approved indication of HoFH for Praluent. Updated diagnosis confirmation requirements for HeFH and HoFH to align with current guidelines. Removed statement around combination use with Kynamro as product has been discontinued. Update to supporting evidence.	04/2021
Review. Update to supporting evidence	12/2020
Updated to policy format. Added requirement of ezetimibe trial and failure in ASCVD.	06/2019
Removed alternate statin dosing strategies in patients who are statin intolerant. Decreased LDL cutoff to >70 for all indications. Increased initial authorization to 12 months. Removed requirement to try and fail statin plus Zetia combination therapy. Removed DNA mutation analysis confirming homozygous familial hypercholesterolemia diagnosis. Required trial and failure of high intensity statin for a minimum of 8 week duration. Updated renewal criteria to assess overall reduction in LDL rather than specific percent reduction.	06/2018
Addition of Repatha 420mg/3.5mL pushtronex system to the approval language.	11/2018
Removed triple step therapy with an additional LDL lowering agent. Increased initial authorization to 6 months.	02/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP002

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

Description

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

Length of Authorization

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

Quantity limits

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

Initial Evaluation

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

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

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

Renewal Evaluation

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

Supporting Evidence

I. There is currently no evidence for safety and efficacy of any of these agents in combination with another ALK inhibitor, or in combination with any other therapies for the treatment of non-small-cell lung cancer (NSCLC). Any open prior authorizations for other ALK-inhibitors will be closed if coverage is approved for an agent in this policy. These agents have only been studied in the metastatic and adult populations with NSCLC in clinical trials.
II. Alectinib (Alecensa) has been evaluated in the first-line setting for metastatic ALK+ NSCLC, or after progression on crizotinib (Xalkori). A class review was done in 2018 which revealed advantages with alectinib (Alecensa) including superior head-to-head progression-free survival (PFS), intracranial response compared to crizotinib, and a more favorable safety profile via indirect comparison. As of 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.

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.

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

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Policy Implementation/Update:

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

Policy Type: PA/SP Pharmacy Coverage Policy: 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

Product Name	Dosage Form	Indication	Quantity Limit
grass pollen-timothy, standard (Grastek)	2800 BAU sublingual tablet	Allergic rhinitis due to Timothy grass pollen	30 tablets/30 days
mite,d.farinae-d.pteronyssinus (Odactra)	12 SQ-HDM sublingual tablet	Allergic rhinitis due to dust mite	30 tablets/30 days
		Allergy to *Dermatophagoides farinae* and *D pteronyssinus*	
gr pol-orc/sw ver/rye/kent/tim (Oralair)	100 IR Sublingual tablet	Allergic rhinitis due to one of 5 pollen extracts	30 tablets/30 days
	100 – 300 IR sublingual tablet		
	300 IR sublingual tablet		
weed pollen-short ragweed (Ragwitek)	12 Amb a 1-U sublingual tablet	Allergic rhinitis due to ragweed	30 tablets/30 days

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**

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**
      iv. Request is for Odactra; **OR**
   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 Grastek, 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

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated Ragwitek approval through age 5. Updated supporting evidence section.	5/2021
Updated to policy format. Combined existing criteria into one policy, added age requirements to match FDA-indications.	01/2020
Edit to Allergen Immunotherapy Criteria; add Odactra information and related mapping; general edits to format and criteria to accommodate Odactra.	02/2018
Combine existing criteria to create Allergen Immunotherapy Criteria	02/2018
Effective and created date of Grastek, Oralair, and Ragwitek criteria	09/2014

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

Product Name	Dosage Form	Indication	Quantity Limit	DDID
alpelisib (Piqray)	150 mg tablets (2 x 150 = 300 mg daily dose pack)	PIK3CA mutation, HR+, HER2-, advanced or metastatic breast cancer	56 tablets/28 days	206827
	200 mg tablets (200 mg daily dose pack)		28 tablets/28 days	206829
	200 mg and 50 mg tablets (200 + 50 = 250 mg daily dose pack)		56 tablets/28 days	206828

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.*

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Policy Implementation/Update:

Date Created	July 2019
Date Effective	August 2019
Last Updated	September 2020
Last Reviewed	September 2020

Action and Summary of Changes	Date
Updated supporting evidence section to include data from BYLieve clinical trial	09/2020
Policy created	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP004

Description

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

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
amifampridine (Firdapse)	10 mg tablets	LEMS	240 tablets/30 days	194155
amifampridine (Ruzurgi)	10 mg tablets	LEMS	240 tablets/30 days	206714

Initial Evaluation

I. Amifampridine (Firdapse, Ruzurgi) may be considered medically necessary when the following criteria are met:
   A. 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 antibody test;

   AND
   B. Prescribed by or in consultation with a neurologist; **AND**
   C. Documentation of an adequate trial and failure or intolerance to one of the following, or contraindication to both of the following:
      1. Pyridostigmine or IVIG; **AND**
   D. If the request is for Firdapse, documentation of an adequate trial and failure or intolerance to Ruzurgi.

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. Provider attestation of clinical improvement of symptoms.

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.
   - Incidence of LEMS is estimated to be approximately 156 to 244 new cases per year in the United States, with a total prevalence of 2.3 to five cases per million people.

II. Amifampridine (3,4-diaminopyridine) results in an increased release of acetylcholine via potassium channel blockade. Guanidine is approved for the treatment of LEMS, however, is associated with a high-level of toxicity and adverse effects. Pyridostigmine is known to be less toxic overall and is sometimes taken as monotherapy or in conjunction with guanidine. Use of pyridostigmine overall is generally accepted if amifampridine is not accessible, though its use is not supported by high-quality data.

III. 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.

IV. 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 antibody test.
   - 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. In LMS-002 or LMS-003 (Firdapse), subjects without any prior history of systemic treatment for LEMS, a QMG score of $\geq$ 5 was required.

VI. Trial patients were required to meet inclusion criteria, not limited to, the following (LMS-002, LMS-003):
   - No history of other or current respiratory disease and receiving amifampridine.
   - Normal swallowing function.
   - Completion of cancer treatment at least three months prior to initiation of therapy.

VII. Trial subjects were excluded if the any of the following criteria were met (LMS-002, LMS-003):
   - History of epilepsy of seizure.
   - Concurrent use of dalfampridine or any form of 3,4-diaminopyridine.

- A forced vital capacity at <1500 mL.
- Use of IVIG within 90 days; use of guanidine within seven days; or use of rituximab within 12 months prior.
- Use of medications that lower seizure threshold or inhibit neuromuscular function.

VIII. Use of amifampridine (Ruzurgi) in the pediatric population is supported by 24 submitted cases and reviewed by the FDA. Additionally, autoimmune LEMS was largely represented in most subjects among all studies. This renders the collected data particularly applicable to the pediatric population as autoimmune LEMS predominates in this population.

IX. The long-term efficacy and safety of amifampridine (Firdapse) was not thoroughly assessed in LMS-002 and LMS-003. Due to the small size of the study population and short duration of exposure and observation, it was likely adverse effects or toxicities resulting from long-term exposure were yet to be identified. Thirty-five adverse events have been reported to the FDA Adverse Event Reporting System since August of 2013. Amifampridine (Firdapse) received FDA approval in November of 2018. Twenty-one events have been reported since FDA-approval as of July 2019.

X. Safety and efficacy of amifampridine (Ruzurgi) is supported by a history of data collected from 247 patients using amifampridine through expanded access, compassionate use program through the FDA, with an average use of five years, range up to 27 years of use. A total of 630 patients have received 3,4-DAP (Ruzurgi) through 230 INDs prior to FDA approval.

XI. There is a lack of strong scientific evidence to support the safety and efficacy for an increased dosing frequency or doses above the recommended. Trials were too small to indicate a dose-related trend of improvement or indicate a variation in effectiveness among subgroup populations.

Investigational or Not Medically Necessary Uses

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

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Policy Implementation/Update:

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

Action and Summary of Changes	**Date**
Addition of Ruzurgi to policy	July 2019

amikacin liposomal (ARIKAYCE®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP005

Description

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

Length of Authorization

- Initial: Six months
- Renewal: Twelve months

Quantity limits

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

Initial Evaluation

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

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

Renewal Evaluation

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

IV. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. Amikacin liposomal (Arikayce)is FDA-approved as part of a combination regimen for the treatment of treatment of MAC lung disease in adults who do not achieve negative sputum cultures after 6 months of a multidrug background regimen therapy.

II. As per the package insert: Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Clinical benefit has not yet been established due to uncertainties with sputum culture conversion predicting clinical benefit in this patient population. As only limited clinical safety and effectiveness data for Arikayce is currently available, use should be reserved to adults who have limited or no alternative treatment options.

III. In the pivotal trial leading to approval, patients with a diagnosis of cystic fibrosis or HIV were excluded. The study met the primary efficacy outcome of culture conversion (three consecutive monthly negative sputum cultures) by month six.

IV. Per ATS/ISDA guidelines, the goals of therapy include symptomatic, radiographic, and microbiologic improvement. The primary microbiologic goal of therapy is 12 months of negative sputum cultures while on therapy; therefore, sputum must be collected from patients throughout treatment. Patients should show clinical improvement within 3 to 6 months and should convert their sputum to negative within 12 months on macrolide-containing regimens. Failure to respond in these time periods should prompt investigation for possible noncompliance (perhaps due to drug intolerance) or macrolide resistance or the presence of anatomic limitations to successful therapy (e.g., focal cystic or cavitary disease).

V. Recent genotyping studies support 12 months of culture-negative sputum as a reasonable treatment endpoint because new positive sputum cultures for MAC after initial sputum conversion and culture negativity for 10 to 12 months are usually due to reinfection (new MAC genotype) rather than disease relapse.

VI. The ATS/IDSA guidelines state that patients should continue to be treated until they have negative cultures for one year. Patients that have had negative cultures for 1 year will not be approved for continued treatment.

VII. Treatment beyond the first renewal approval (after 18 months) will not be approved as amikacin liposomal (Arikayce) has not been studied beyond 18 moths nor in the reinfection or disease relapse setting.

Investigational or Not Medically Necessary Uses

I. Cystic fibrosis patients with *Pseudomonas aeruginosa*

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

II. Non-refractory MAC lung disease

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

III. Use of amikacin liposomal (Arikayce) alone

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

References

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2. Insmed Announces FDA Approval of ARIKAYCE® (amikacin liposome inhalation suspension), the First and Only Therapy Specifically Indicated for the Treatment of Mycobacterium Avium Complex (MAC) Lung Disease in Adult Patients with Limited or No Alternative Treatment Options [press release]. Available at: http://investor.insmed.com/news-releases/news-release-details/insmed-announces-fda-approval-arikaycer-amikacin-liposome.
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Policy Implementation/Update:

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

Action and Summary of Changes	Date

Policy Type: PA Pharmacy Coverage Policy: UMP109

Description

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

Length of Authorization

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

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

Quantity Limits

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

Initial Evaluation

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

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

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

II. **Generic oxandrolone** may be considered medically necessary when the following criteria below are met:

A. Medication will be used as adjunctive therapy to promote weight gain; **AND**
   1. Weight loss is due to one of the following conditions:
      i. Extensive surgery; **OR**
      ii. Chronic infections; **OR**
      iii. Severe trauma; **OR**
      iv. Member fails to gain or maintain normal weight without definite pathophysiological reasons; **OR**

B. Medication will be used to offset the protein catabolism associated with prolonged administration of corticosteroids; **OR**

C. Medication will be used for the treatment of bone pain associated with osteoporosis; **OR**

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

E. Member has a diagnosis of Turner Syndrome

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

Renewal Evaluation

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

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

Supporting Evidence

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

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

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

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

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

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

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

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

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

Investigational or Not Medically Necessary Uses

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

References

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2. Anadrol-50 prescribing information. Unimed Pharma, Inc. October 2012
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Policy Implementation/Update:

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

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

Policy Type: PA/SP Pharmacy Coverage Policy: UMP087

Description

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

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

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

Initial Evaluation

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

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

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

Renewal Evaluation

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

Supporting Evidence

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

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

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

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

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

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

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

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

Investigational or Not Medically Necessary Uses

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

References

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Policy Implementation/Update:

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

Policy Type: PA Pharmacy Coverage Policy: UMP006

Description

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

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

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

*See appendix A for dose recommendations

Initial Evaluation

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

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

Renewal Evaluation

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

Supporting Evidence

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

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

Investigational or Not Medically Necessary Uses

I. Adult-onset HPP
   A. Asfotase alfa (Strensiq) is FDA-indicated for the treatment of members with perinatal/infantile- and juvenile-onset HPP; these populations are known to have the most severe disease and the benefit of enzyme replacement therapy is supported by data.
   B. There are limited to no research studies to support the efficacy of asfotase alfa (Strensiq) in the setting of adult-onset HPP <u>without</u> 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** <u>three times per week</u>

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

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

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

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

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Policy Implementation/Update:

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

Policy Type: PA/SP Pharmacy Coverage Policy: UMP181

Split Fill Management*

Description

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

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
avapritinib (Ayvakit)	300 mg tablets	Unresectable or metastatic Gastrointestinal Stromal Tumor with a PDGFRA exon 18 mutation	30 tablets/30 days
	200 mg tablets		
	100 mg tablets		

Initial Evaluation

I. Avapritinib (Ayvakit) is considered investigational when used for all conditions, **including** but not limited to gastrointestinal stromal tumor (GIST).

Renewal Evaluation

I. N/A

Supporting Evidence

I. 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 March 2020 were to treat patients with a PDGFRA mutation with avapritinib (Ayvakit) which is considered category 2A; however, is based on ongoing Phase I trial data.

II. 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.

III. 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.

IV. Avapritinib (Ayvakit) was FDA-approved off one on-going, 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 is overall response rate (ORR), which is 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).

V. 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.

VI. 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.

VII. Avapritinib (Ayvakit) showed a 49% dose reduction rate, a 57% dose interruption rate, and a 16% permanent discontinuation rate due to intolerable adverse events.

Investigational or Not Medically Necessary Uses

I. Avapritinib (Ayvakit) has not been FDA-approved, OR sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Gastrointestinal Stromal Tumor
      i. 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 medication has a significant safety profile. There is a lack of evidence indicated that avapritinib (Ayvakit) would provide a net health benefit for members. Trials evaluating for treatment of GIST were underway as of February 2020, further clinical evaluation of safety and efficacy are needed to confirm a net health benefit and place in therapy for this medication.
   B. Systemic mastocytosis (e.g. AdvSM, ASM, ISM, SSM)
   C. Mast cell leukemia (MCL)

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

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP169

Description

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

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

Length of Authorization

- Initial:
  - **Avatrombopag (Doptelet)**
    Thrombocytopenia associated with chronic liver disease, prior to planned procedure: one month
    Chronic immune thrombocytopenia (ITP): Three months
  - **Eltrombopag (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

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

lusutrombopag (Mulpleta)	3 mg tablet	Thrombocytopenia associated with chronic liver disease, prior to planned procedure	7 tablets/ 365 days
fostamatinib (Tavalisse)	100 mg tablets 150 mg tablets	Chronic Immune Thrombocytopenia	60 tablets/30 days

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 10^9/L; **AND**
         iii. Request is for *avatrombopag (Doptelet) OR lusutrombopag (Mulpleta);* **AND**
            a. Member is scheduled to undergo an invasive procedure that carries an intermediate-to-high risk of bleeding (e.g. spinal surgery, cardiac surgery, large polypectomy, or liver biopsy); **OR**
         iv. Member has a documented diagnosis of **chronic Hepatitis C** infection; **AND**
            a. Member is unable to initiate or maintain interferon-based treatment [eg. pegylated interferon (Pegasys®) and ribavirin]; **AND**
            b. Request is for *eltrombopag (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 10^9/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 anti-thymocyte 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 x 10^9/L to 450 x 10^9/L).

V. Avatrombopag (Doptelet) and lusutrombopag (Mulpleta) are indicated for the treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure that carries an intermediate-to-high risk of bleeding (e.g. spinal surgery, cardiac surgery, large polypectomy, liver biopsy). They should not be administered to patients with chronic liver disease, without associated thrombocytopenia or risk of surgical bleed, in an effort to normalize platelet counts (normal platelet count in adults ranges from 150 x 10^9/L to 450 x 10^9/L).

VI. Eltrombopag (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 x 10^9/L to 450 x 10^9/L).

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

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 x 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 x 10^9/L for at least six out of eight weeks, generally seen between weeks five and 12. Pediatric patients (75%) treated with eltrombopag (Promacta), compared with placebo (21%), saw an increased value with at least one platelet count greater than, or equal to, 50 x 10^9/L during the first 12 weeks of randomized treatment in absence of rescue therapy. Platelet response to eltrombopag (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 x 10^9/L to 450 x 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 × 10^3/µL above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks in those who were transfusion dependent on entry into the protocol); (2) erythroid response (when pretreatment hemoglobin was <9 g/dL, defined as an increase in hemoglobin by 1.5 g/dL or, in transfused patients, a reduction in the units of packed red blood cell transfusions by an absolute number of at least 4 transfusions for 8 consecutive weeks, compared with the pretreatment transfusion number in the previous 8 weeks); and (3) neutrophil response (when pretreatment absolute neutrophil count [ANC] of <0.5 × 10^3/µL as at least a 100% increase in ANC, or an ANC increase >0.5 × 10^3/µL, and the toxicity profile as measured using Common Terminology Criteria for Adverse Events).

Investigational or Not Medically Necessary Uses

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

II. Eltrombopag (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

ratio [OR] 0·20, 95% CI 0·05-0·87; p=0·032) although the difference between treatment groups was less than 30%. Serious adverse events were reported in 56 (58%) eltrombopag-treated patients and 32 (68%) placebo-treated patients. Seven eltrombopag recipients and two placebo recipients had serious adverse events that were suspected to be study drug-related (acute kidney injury, arterial thrombosis, bone pain, diarrhea, myocardial infarction, pyrexia, retinal vein occlusion, n=1 each; placebo: vomiting, white blood cell count increased, n=1 each). Two eltrombopag recipients had arterial thrombosis n=1 and myocardial infarction n=1. No placebo recipients experienced fatal or serious adverse events suspected to be study drug related.

3. Part 3 is an extension ongoing study.
4. Overall the clinical trial had a small patient population, showed limited efficacy and had questionable safety.

ii. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukemia was completed in a multicenter, randomized, placebo-controlled, double-blind, phase 1/2 trial.

1. Primary outcome was safety and tolerability parameters including non-hematological laboratory Grade 3/Grade 4 toxicities, change in bone marrow blast counts from baseline, and adverse events reporting. [Time Frame: Approximately 46 months].
2. Ninety-eight patients were randomized to receive either eltrombopag (n=64) or placebo (n=34). Sixty-three (98%) patients in the eltrombopag group and 32 (94%) patients in the placebo group had adverse events. The most common adverse events were pyrexia (27 [42%] vs 11 [32%]), nausea (20 [31%] vs 7 [21%]), diarrhea (19 [30%] vs 6 [18%]), fatigue (16 [25%] vs 6 [18%]), decreased appetite (15 [23%] vs 5 [15%]), and pneumonia (14 [22%] vs 8 [24%]). Drug-related adverse events of grade 3 or higher were reported in six (9%) patients in the eltrombopag group and four (12%) patients in the placebo group.
3. In this clinical trial efficacy was not assessed.

F. There is limited or no published clinical trial data to support the use of eltrombopag (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.
   ii. A Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of two dosing regimens of fostamatinib in patients with rheumatoid arthritis with an inadequate response to a tumor necrosis factor-α antagonist.
   - 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.
   - Due to efficacy and safety results from the clinical trial, the companies developing fostamatinib have decided not to study it further in RA at this time.

G. Renal Transplant Rejection (antibody mediated rejection)

i. Fostamatinib is being studied in a phase 2, single center, not randomized, open label, pilot study to assess the safety and efficacy of fostamatinib in the treatment of chronic active antibody mediated rejection in renal transplantation is still recruiting.

H. Chronic Graft vs. Host Disease

i. A phase I, open label, single group assignment trial of fostamatinib and chronic graft vs. host disease development after allogeneic stem cell transplantation with 18 participants is still recruiting.

I. There is limited or no published clinical trial data to support the use of fostamatinib (Tavalisse) in conditions other than chronic immune thrombocytopenia (ITP).

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Policy Implementation/Update:

Action and Summary of Changes	Date
• Added new strength of 25mg eltrombopag (Promacta) packet for oral suspension	05/2020
• Added investigational indications for avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) • Added age limits to eltrombopag (Promacta) for immunosuppressive naive Severe aplastic anemia at two years of age or older, and relapsed or refractory severe aplastic anemia at 18 years of age or older. • Added criteria for Severe aplastic anemia; [Member has to meet at least two of the following three criteria are met: 1) Absolute neutrophil count (ANC) less than 500/microL, or 2) Platelet count less than 20,000/microL, or 3) Absolute reticulocyte count (ARC) less than 60,000/microL • Added member is 18 years of age or older if request is for avatrombopag (Doptelet), fostamatinib (Tavalisse) and fostamatinib (Tavalisse) [for chronic ITP] • Added criteria if request is for eltrombopag (Promacta) packets, member has demonstrated inability to swallow tablets • Changed QL for eltrombopag (Promacta) packets • Changed QL for avatrombopag (Doptelet) for chronic immune thrombocytopenia (ITP) • Changed initial and renewal length of authorization for all agents	02/2020

• Combined as one policy: avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) with fostamatinib (Tavalisse)	
Previous reviews fostamatinib (Tavalisse)	06/2018, 11/2019,
Conversion to policy format fostamatinib (Tavalisse)	11/2019
Avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) combined as policy: TPO-Receptor Agonists	10/2019
Previous reviews avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)	10/2019,
Policy created avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)	10/2019
Policy created fostamatinib (Tavalisse)	06/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP007

Split Fill Management*

Description

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

Length of Authorization

- Initial: Three months
- Renewal: Six months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
axitinib (Inlyta)	1 mg tablets	Advance renal cell carcinoma	180 tablets/30 days	171511
	5 mg tablets		60 tablets/30 days	171512

Initial Evaluation

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

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

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

Renewal Evaluation

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

Supporting Evidence

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

Investigational or Not Medically Necessary Uses

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

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

References

1. Inlyta [Prescribing Information]. New York, NY: Pfizer, Inc. August 2018.
2. Keytruda [Prescribing Information]. White House Station, NJ: MERCK & CO, Inc. April 2019.
3. Bavencio [Prescribing Information]. Rockland, MA: EMD Serono, Inc. May 2019.
4. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. Lancet. 2011 Dec 3;378(9807):1931-9. Doi: 10.1016/S0140-6736(11)61613-9.
5. Motzer R, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019 Mar 380:1103-1115. Doi:10.1056/NEMJMoa1816047.
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Policy Implementation/Update:

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

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

azacitidine (Onureg®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

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

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

Initial Evaluation

I. **Azacitidine (Onureg)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. Medication will be used as monotherapy; **AND**
   D. A diagnosis of **acute myeloid leukemia (AML)** when the following are met:
      1. Provider attestation the member has intermediate <u>or</u> poor-risk disease; **AND**
      2. Member has achieved <u>first</u> complete remission (CR) after induction chemotherapy (e.g. cytarabine, idarubicin, daunorubicin, mitoxantrone); **AND**
      3. Member received at least <u>one</u> 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 <u>Not Medically Necessary</u> when used for:
   A. Treatment of Myelodysplastic syndrome (MDS)

III. Azacitidine (Onureg) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   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

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

1. Azacitidine (Onureg) prescribing information. Summit, NJ: Celgene Corporation; September 2020.
2. Estey, E H. Acute myeloid leukemia: 2019 update on risk-stratification and management. *Am J Hematol*. 2018;93(10):1267-1291.
3. Narayanan D, Weinberg OK. How I investigate acute myeloid leukemia. *Int J Lab Hematol.* 2020; 42:3-15.
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020; 70:7-30.
5. Garcia-Manero G, Savona MR, Gore SD, et al. CC-486 (oral azacitidine) in patients with hematological malignancies who had received prior treatment with injectable hypomethylating agents (HMAs): Results from phase 1/2 CC-486 studies. *Blood* (ASH Annual Meeting Abstracts) 2016b;128: Abstract 905.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP008

Description

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

Length of Authorization

- Initial: Six months
- Renewal: Twelve months

Quantity limits

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

* total of 7 fills in one year

Initial Evaluation

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

Renewal Evaluation

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

Supporting Evidence

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

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

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

References

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

Policy Implementation/Update:

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

Policy Type: PA/SP Pharmacy Coverage Policy: UMP112

Description

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

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

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

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)]; **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-creatine ratio (UPCR) >500 mg/g), unexplained decrease in glomerular filtration rate (GFR)) are candidates for kidney biopsy to confirm diagnosis/class of LN, which then guides treatment.

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

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.

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

Investigational or Not Medically Necessary Uses

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

References

1. Benlysta [Prescribing Information]. Rockville, MD: GlaxoSmithKline. December 2020.
2. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64(6):797-808.
3. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 Update of the EULAR Recommendation for The Management of Systemic Lupus Erethmatosus. Annals of the Rheumatic Diseases 2019;78:736-745. Available at: https://ard.bmj.com/content/78/6/736
4. Lam NC, Ghetu MV, and Bieniek M. Systemic Lupus Erythematosus: Primary Care Approach to Diagnosis and Management. Am Fam Physician. 2016 Aug 15;94(4):284-294. Available at: https://www.aafp.org/afp/2016/0815/p284.html
5. Furie R, Rovin BH, Houssiau F, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med. 2020;383(12):1117-1128.
6. Belimumab and Voclosporin for Lupus Nephritis: Effectiveness and Value. Draft Evidence Report. Institute for Clinical and Economic Review (ICER). January 2021. Available at: https://icer.org/wp-content/uploads/2020/11/ICER_Lupus-Nephritis_Draft-Evidence-Report_012221.pdf
7. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 update of the joint european league against rheumatism and european renal association-european dialysis and transplant association (Eular/era-edta) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020;79(6):713-723.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new indication of lupus nephritis and further specified specialist to include nephrologist. Removal of criteria excluding concomitant use of cyclophosphamide	02/2021
Criteria transitioned into policy with the following updates made: addition of supporting evidence and investigational section, removal of active infection question, removal of vaccine question, updated renewal question relating to symptom improvement into one question, and removing specific symptom improvement parameters to be consistent with the market.	11/2019
Previous review	11/2017
Criteria created	09/2017

Policy Type: PA Pharmacy Coverage Policy: UMP182

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

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

Quantity Limits

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

Initial Evaluation

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

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

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

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

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

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

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

Investigational or Not Medically Necessary Uses

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

References

1. Nexletol [Prescribing Information]. Esperion Therapeutics: Ann Arbor, MI. February 2020.
2. Nexletol/Nexlizet [E-Dossier]. Esperion Therapeutics: Ann Arbor, MI. May 2019.
3. Goldberg AC, Leiter LA, Stroes ESG, et al. Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-Density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial. JAMA. 2019;322(18):1780-1788.
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Policy Implementation/Update:

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

Policy Type: PA/SP Pharmacy Coverage Policy: UMP174

Description

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

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

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

Initial Evaluation

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

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

II. Benralizumab (Fasenra) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   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 <u>not</u> be used in combination with another monoclonal antibody (e.g., dupilumab, mepolizumab, omalizumab, reslizumab, etc.); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **AND**
V. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of benralizumab (Fasenra), unless contraindicated.

Supporting Evidence

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

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

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

Investigational or Not Medically Necessary Uses

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

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

References

1. Fasenra Pen [Prescribing Information]. Wilmington, DE: AstraZeneca LP. Updated October 2019. Accessed Feb 2021.
2. National Asthma Education and Prevention Program (NAEPP). Guidelines for the diagnosis and management of asthma. Expert Panel Report 3. Bethesda, MD: National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI); August 2007.
3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2020 Update. Available from: http://www.ginasthma.org. Accessed February 2021.
4. Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. J Asthma Allergy. 2014; 7: 53–65.
5. Goldman M, Hirsch I, Zangrilli JG, et al. The association between blood eosinophil count and benralizumab efficacy for patients with severe, uncontrolled asthma: subanalyses of the Phase III SIROCCO and CALIMA studies. Curr Med Res Opin. 2017 Sep;33(9):1605-1613. doi: 10.1080/03007995.2017.1347091. Epub 2017 Jul 19.

Policy Implementation/Update:

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

betaine anhydrous (Cystadane®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP113

Description

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

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

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

Initial Evaluation

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

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

Renewal Evaluation

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

Supporting Evidence

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

Investigational or Not Medically Necessary Uses

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

References

1. Cystadane [Prescribing Information]. Lebanon, NJ: Recordati Rare Diseases Inc. October 2018.
2. Kang SS. Treatment of hyperhomocyst(e)inemia: physiological basis. J Nutr. 1996;126(4 Suppl):1273S-5S.
3. Homocystinuria. Genetics Home Reference website. Available at: https://ghr.nlm.nih.gov/condition/homocystinuria. Updated November 12, 2019.
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8. Miglio F, Rovati LC, Santoro A, et al: Efficacy and safety of oral betaine glucuronate in non-alcoholic steatohepatitis. Arzneimittelforschung Drug Res 2000; 50(8):722-727.
9. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018;67(1):328-357.

Policy Implementation/Update:

Date Created	November 2019
Date Effective	December 2019
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date

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

Product Name	Dosage Form	Indication	Quantity Limit
betrixaban (Bevyxxa)	40 mg capsules	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	44 capsules/365 days
	80 mg capsules		44 capsules/365 days

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**

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

1. Bevyxxa [package insert].South San Francisco, CA: Portola Pharmaceuticals, Inc;2017.
2. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. The New England Journal of Medicine. May 2016; 375:534-544. doi: 10.1056/NEJMoa1601747.
3. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. "Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis". Chest. 2012 Feb; 141(2 Suppl): e195S–e226S. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278052/. Accessed September 20, 2017.

Policy Implementation/Update:

Date Created	September 2017
Date Effective	November 2017
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	**Date**
Criteria updated to new policy format. Specific changes include: member is 18 years of age or older was added.	11/2019
Criteria created	09/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP115

Split Fill Management*

Description

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

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

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

Initial Evaluation

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

iii. A body surface area that has been documented utilizing weight recorded in the past three months ; **AND**

iv. The dose prescribed does not exceed 300 mg/m2/day for at least eight weeks before dose escalation to a maximum of 400 mg/m2/day; **OR**

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

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

Supporting Evidence

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

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

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

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

V. The cost of one 60-gram tube of topical bexarotene (Targretin) is approximately $30,500; therefore, a quantity limit of one tube per 30-day supply is in place to ensure appropriate use without waste. Should a quantity exception be requested, clinical consideration will be taken to the amount of body surface area the medication is being applied, rate of application, and amount utilized with administration.

Investigational or Not Medically Necessary Uses

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

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

References

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

Policy Implementation/Update:

Date Created	August 2008
Date Effective	October 2008
Last Updated	November 2019
Last Reviewed	07/2012, 09/2012, 12/2012, 11/2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format, age edit added, updated specialist prescriber requirement to new format, removal of liver function test monitoring requirements. Addition of topical bexarotene (Targretin) to the policy. Initial approval criteria increased from six to 12 months.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP116

Split Fill Management*

Description

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

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

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

Initial Evaluation

I. Bosutinib (Bosulif) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. Medication will <u>not</u> 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 <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Glioblastoma
   B. Dementia
   C. Non-small cell lung cancer
   D. Mesothelioma
   E. Bladder cancer
   F. Ovarian, peritoneal, uterine cervical cancer
   G. Thymoma
   H. Thymus cancer

Renewal Evaluation

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

Supporting Evidence

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

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

VII. Intolerance is defined as progression while taking a TKI, and/or the inability to tolerate the current minimum recommended dose, or inability to dose-increase due to toxicity. Resistance and intolerance to both dasatinib (Sprycel) and nilotinib (Tasigna) are manifested similarly to that of imatinib (Gleevec).
VIII. Disease progression is defined as transformation to accelerated or blast phase, or loss of previously attained response. Treatment was continued until disease progression (transformation to accelerated or blast phase, or loss of previously attained response), unacceptable toxicity, or withdrawal of consent. Patients were removed from the study if they were unable to tolerate a bosutinib (Bosulif) dose of ≥ 300 mg/d.

Investigational or Not Medically Necessary Uses

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

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References

1. Bosulif [Prescribing Information]. New York, NY. Pfizer labs: October 2019.
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3. Cortes JE, Kantarjian HM, Brümmendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood. 2011;118(17):4567-76.
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Policy Implementation/Update:

Date Created	February 2013
Date Effective	February 2013
Last Updated	December 2019
Last Reviewed	01/2018, 12/2018

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format. Updated requirement of prior therapy to state prior tyrosine kinase inhibitor rather than stating imatinib. Extended renewal duration from four months to 12 months. Required agent be used as monotherapy and not in combination with other oncologic medications.	12/2019

Bypassing Agents – Hemophilia A&B

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP009

Description

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

Length of Authorization

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

Quantity limits

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

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

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

Initial Evaluation

Hemophilia A (congenital factor VIII deficiency)

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

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

Hemophilia B (congenital factor IX deficiency)

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

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

<u>Acquired Hemophilia</u>

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

<u>Congenital Factor VII Deficiency</u>

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

<u>Glanzmann's Thrombasthenia</u>

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

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

Renewal Evaluation

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

Supporting Evidence

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

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

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

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

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

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

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

Investigational or Not Medically Necessary Uses

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

References

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2. NovoSeven RT [prescribing information]. Bagsvaerd, Denmark; NovoNordisk. January 2019.
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Policy Implementation/Update:

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

Policy Type: PA/SP Pharmacy Coverage Policy: UMP010

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

cabozantinib (Cabometyx)	Indication	Quantity Limit	DDID
20 mg tablet	Renal cell carcinoma (RCC), advanced Liver carcinoma, in patients previously treatment with sorafenib	30 tablets/30 days	192650
40 mg tablet		30 tablets/30 days	192651
60 mg tablet		30 tablets/30 days	192652
cabozantinib (Cometriq)	**Indication**	**Quantity Limit**	**DDID**
60 mg per day blister cards	Medullary thyroid carcinoma, progressive, metastatic	84 capsules/28 days	177131
100 mg per day blister cards		56 capsules/28 days	177130
140 mg per day blister cards		112 capsules/28 days	177129

Initial Evaluation

I. Cabozantinib (Cabometyx or 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. Medication is used as monotherapy; **AND**
   D. A diagnosis of one of the following:
      1. **Medullary thyroid carcinoma**; **AND**
         i. Disease is progressive and metastatic (stage IV); **AND**
         ii. Member has RET M918T mutational status; **AND**
         iii. Cabozantinib (COMETRIQ) is prescribed; of note, cabozantinib (Cabometyx) shall not to be used for thyroid cancer; **OR**
      2. **Renal cell carcinoma**; **AND**

i. Disease is advanced or greater (stage III or IV); **AND**
ii. Cabozantinib (CABOMETYX) is prescribed; of note, cabozantinib (Cometriq) shall not be used for renal cell carcinoma

3. Hepatocellular (Liver) carcinoma

i. Disease is progressive and advanced stage or greater (stage III or IV); **AND**
ii. Member has been previously treated with sorafenib (Nexavar); **AND**
iii. Member has not received more than two previous systemic treatment for advanced or metastatic disease; **AND**
iv. Cabozantinib (CABOMETYX) is prescribed; of note, cabozantinib (COMETRIQ) shall not to be used for hepatocellular carcinoma

II. Cabozantinib (Cabometyx or Cometriq) is considered investigational when used for all other conditions, including but not limited to:

A. Adrenocortical carcinoma
B. Salivary gland cancer
C. Neurofibromas
D. Cholangiocarcinoma
E. Prostate cancer
F. Colorectal cancer
G. Phenochromocytomas and paraganglioma
H. Merkel cell carcinoma and skin cancer
I. Multiple myeloma, acute myeloid leukemia
J. Head and neck cancer
K. Breast cancer

Renewal Evaluation

I. Medication is used as monotherapy; **AND**
II. Medication is prescribed by or in consultation with an oncologist; **AND**
III. There is clinical documentation of response to treatment, such as stabilization of disease or decrease in tumor size or tumor spread; **AND**

A. **Medullary thyroid carcinoma**; **AND**
- Cabozantinib (COMETRIQ) is prescribed; **OR**

B. **Renal cell carcinoma; AND**
1. Cabozantinib (CABOMETYX) is prescribed; **OR**

C. **Hepatocellular (Liver) carcinoma; AND**
1. Cabozantinib (CABOMETYX) is prescribed

Supporting Evidence

I. Cabozantinib (COMETRIQ) is FDA-approved for the treatment of medullary thyroid carcinoma in the advance or greater setting. This medication was studied in patients with progressive disease in the phase III EXAM trial against placebo. The follow up analysis, published in 2017, indicated that cabozantinib did not show a statistically significant difference in overall survival compared to placebo for the overall group of 330 patients; however, in an exploratory assessment of overall survival, cabozantinib showed a statistically significant difference in overall survival for the RET M918T mutation population (44.3 months vs 18.9 months [HR 0.60; CI 0.38-.094;

p=0.03]). Cabozantinib (COMETRIQ) shall be used for this indication due to its specific formulary, dosing, and packaging differences compared to cabozantinib (Cabometyx)

II. Cabozantinib (Cabometyx) was evaluated in advance renal cell carcinoma against everolimus in an open-label trial. Cabozantinib (Cabometyx) showed a statistically significant improvement in progression-free survival, overall survival, and objective response rate compared to everolimus. Up to 80mg per day may be used in the setting of CYP3A4 interactions; however, 60mg per day is the usual dose.

III. Cabozantinib (Cabometyx) was evaluated in patients with advanced and progressing hepatocellular carcinoma against 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 (Cabmetyx) compared to placebo. (10.2 months vs. 8 months [HR 0.76; CI 0.63-0.92; p=0.005]). Up to 80mg per day may be used in the setting of CYP3A4 interactions; however, 60mg per day is the usual dose.

Investigational or Not Medically Necessary Uses

All indications listed below have not been sufficiently studied for safety and efficacy, or have insufficient or inconclusive evidence for use of cabozantinib (Cabometyx and/or Cometriq).

I. Non-small cell lung cancer
II. Adrenocortical carcinoma
III. Salivary gland cancer
IV. Neurofibromas
V. Cholangiocarcinoma
VI. Prostate cancer
VII. Colorectal cancer
VIII. Phenochromocytomas and paraganglioma
IX. Merkel cell carcinoma and skin cancer
X. Multiple myeloma, acute myeloid leukemia
XI. Head and neck cancer
XII. Breast cancer

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7. National Comprehensive Cancer Network. Thyroid Carcinoma Guidelines Version 3.2018. Available at https://www.nccn.org/professionals/physician_gls/default.aspx. [Accessed February 15, 2019].

8. National Comprehensive Cancer Network. Hepatobiliary Cancer Guidelines Version 1.2019. Available at https://www.nccn.org/professionals/physician_gls/default.aspx. [Accessed February 15, 2019].

Policy Implementation/Update:

Date Created	December 2012
Date Effective	December 2012
Last Updated	February 2019
Last Reviewed	01/2018, 02/2019

Action and Summary of Changes	**Date**
Transitioned criteria to policy format, added hepatocellular carcinoma indication, added age criteria and monotherapy criteria to all indications.	02/2019
Removed step therapy in RCC; Updated renewal language to assess response to therapy	01/2018

Policy Type: PA Pharmacy Coverage Policy: UMP088

Description

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

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

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

Initial Evaluation

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

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

Renewal Evaluation

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

Supporting Evidence

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

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

Investigational or Not Medically Necessary Uses

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

References

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Policy Implementation/Update:

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

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

Policy Type: PA/SP Pharmacy Coverage Policy: UMP025

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

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

Quantity limits

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

Initial Evaluation

Migraine

I. **Erenumab (Aimovig), galcanezumab (Emgality), and fremanezumab (Ajovy)** 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 of older; **AND**
   C. The medications in this policy will not be used in combination with each other (with the exception of rimegepant (Nurtec ODT) at a dose of 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 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. If the request is for galcanezumab (Emgality) or erenumab (Aimovig), 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; **AND**
    1. Member is 18 years of age or older; **AND**
    2. Treatment with at all of the following has been ineffective, contraindicated, or not tolerated:
        i. Two oral serotonin 5-HT1 receptor agonists (i.e., sumatriptan, naratriptan, rizatriptan); **AND**
        ii. One nasal (i.e., sumatriptan nasal spray) serotonin 5-HT1 receptor agonist; **AND**
        iii. One injectable (i.e., sumatriptan pen/vial/syringe) serotonin 5-HT1 receptor agonist; **OR**
B. The request is for 16 tablets per 30 days; **AND**
    1. Criteria I(A)-I(I) above are met; **AND**
    2. If requested for migraine prophylaxis: treatment with fremanezumab (Ajovy) has been ineffective, contraindicated, or not tolerated

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), and rimegepant (Nurtec ODT) 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), and fremanezumab (Ajovy); **AND**
         i. The medications in this policy will not be used in combination with each other (with the exception of rimegepant (Nurtec ODT) at a dose of 8 tablets per 30 days); **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**
            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 rimegepant (Nurtec ODT); **AND**
    i. The request is for less than or equal to 8 tablets per 30 days; **AND**
        a. Member is 18 years of age or older; **AND**
        b. Treatment with at all of the following has been ineffective, contraindicated, or not tolerated;
            i. Two oral serotonin 5-HT1 receptor agonists (i.e., sumatriptan, naratriptan, rizatriptan); **AND**
            ii. One nasal (i.e., sumatriptan nasal spray) serotonin 5-HT1 receptor agonist; **AND**
            iii. One injectable (i.e., sumatriptan pen/vial/syringe) serotonin 5-HT1 receptor agonist; **OR**
    ii. The request is for 16 tablets per 30 days; **AND**
        a. The medications in this policy will not be used in combination with each other; **AND**
        b. The provider has attested that the member has not received onabotulinum toxin (e.g., Botox, etc.) within the past three months; **AND**
        c. The member will not receive onabotulinum toxin (e.g., Botox, etc.) concurrently with any agent in this policy; **AND**
        d. 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**
            i. Upon subsequent renewals the member has maintained the initial response or gained further response to therapy; **AND**
        e. If requested for migraine prophylaxis: treatment with fremanezumab (Ajovy) has been ineffective, contraindicated, or not tolerated

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. An exception to use this in combination 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, nebivolol, pindolol, carbamazepine, Lisinopril, candesartan, calcium channel blockers, gabapentin, pregabalin, lamotrigine, oxcarbazepine, clomipramine, telmisartan, and benzodiazepines. Specifically, nortriptyline does not have the same level of efficacy supporting use for migraine prophylaxis as amitriptyline and should not be considered for adequate trials of prophylactic therapy.

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, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness, or agitation. Cluster periods range from two weeks and three months

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.

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

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

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

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.)
   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

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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of Nurtec ODT into policy (initial and renewal): reviewing coverage/setting of Nurtec via quantity requested; in migraine prophylaxis section aligned Nurtec ODT with non-preferred CGRP agents. Addition of standard language to renewal criteria addressing use of samples. Updates to supporting evidence.	04/2021
Update to require treatment of Ajovy prior to Aimovig or Emgality in the setting of migraines; effective 02/01/2021	01/2021
Added Ajovy autoinjector to policy	04/2020
Removed PFS and 2-pack of Aimovig from policy as it is no longer available one the market	02/2020
Criteria update: update to reflect preferred galcanezumab (Emgality)	11/2019
Criteria update: Transition from criteria to policy and compilation of all injectable CGRP therapies into one policy. Updated Aimovig quantity limit to 30 days vs 28 to align with other agents. Added comment that 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.	07/2019
No changes made	01/2019
Criteria update: Changed onabotulinum toxin requirement to three months versus previous four months of washout. Updated renewal questions to specify a reduction in monthly migraine days by two.	10/2018
Criteria created	10/2018

cannabidiol (Epidiolex®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP011

Description

Cannabidiol (Epidiolex) is an orally administered cannabinoid.

Length of Authorization

- Initial: Twelve months
- Renewal: Twelve months

Quantity limits

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

Initial Evaluation

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

II. Cannabidiol (Epidiolex) is considered investigational when used for all other conditions, including but not limited to the diagnosis of:

A. Infantile Spasms
B. Other non-FDA approve seizure disorder
C. Substance use disorder
D. Prader-Willi Syndrome
E. Gastrointestinal disorders
F. Parkinson's Disease/Essential tremors

Renewal Evaluation

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

Supporting Evidence

I. Cannabidiol (Epidiolex) (CBD) is indicated for the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS), Dravet syndrome (DS), or Tuberous Sclerosis Complex (TSC) in patients one year of age and older. It received initial approval for treatment of seizures associated with LGS and DS for patients two years of age and older. This approval was expanded in 2020 to include new indication of seizures associated with TSC in patients one year and older. Additionally, CBD also received approval for expanded age range (one year and older) for patients with LGS and DS.
II. Differential diagnosis of LGS, DS, or TSC require detailed clinical examination in combination with advanced testing such as MRI, EEG, and genetic screening (SCN1A mutation for DS). Given the complexities of diagnosing and treating these conditions, supervision of treatment by a neurologist is required.
III. CBD was studied in four Phase 3, double blind, randomized placebo-controlled clinical trials in patients with baseline characteristics of history of use of two or more antiepileptic drugs (AED). Efficacy of CBD for LGS was studied in two randomized, double-blind, placebo-controlled trials in patients aged 2 to 55 years old. Study 1 (N=171) compared a dose of Epidiolex 20 mg/kg/day with placebo, while Study 2 (N=225) used 10 mg/kg/day and 20 mg/kg/day doses with a match

with placebo. In both studies, patients had a diagnosis of LGS and were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. The primary efficacy measure in both studies was the percent change from baseline in the frequency (per 28 days) of drop seizures (atonic, tonic, or tonic-clonic seizures) over the 14-week treatment period. At 14 weeks, the median percent change from baseline (reduction) in the frequency of drop seizures was significantly greater for both dosage groups of CBD versus placebo with an observed reduction in drop seizures frequency within 4 weeks of initiating treatment.

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

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

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

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

Investigational or Not Medically Necessary Uses

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

References

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Policy Implementation/Update:

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

Policy Type: PA/SP Pharmacy Coverage Policy: UMP012

Description

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

Length of Authorization

- Initial: 30 days
- Renewal: 28 days

Quantity limits

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

Initial Evaluation

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

c. High serum troponin levels

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

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

Renewal Evaluation

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

Supporting Evidence

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

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

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

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

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

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

Investigational or Not Medically Necessary Uses

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

References

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Policy Implementation/Update:

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

Action and Summary of Changes	**Date**

Policy Type: PA/SP Pharmacy Coverage Policy: UMP189

Split Fill Management*

Description

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

Length of Authorization

- N/A

Quantity Limits

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

Initial Evaluation

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

Renewal Evaluation

I. N/A

Supporting Evidence

I. Capmatinib (Tabrecta) is the first therapy FDA-approved for NSCLC with a mutation that leads to MET 14 exon 14 skipping. Other therapies that may be used in this setting include 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-naïve 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 a several trials underway for NSCLC and other cancer types.

IV. The safety of capmatinib (Tabrecta) is based on patients from all cohorts (n=334). 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.

Investigational or Not Medically Necessary Uses

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

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

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2020

carglumic acid (Carbaglu®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

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: 12 months
  - i. Acute hyperammonemia: 3 months
  - ii. Chronic hyperammonemia: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Carglumic acid (Carbaglu)	200 mg tablets	Adjunctive therapy for acute hyperammonemia due to NAGS deficiency	250 mg/kg/day
		Maintenance therapy for chronic hyperammonemia due to NAGS deficiency	100 mg/kg/day

Initial Evaluation

I. Carglumic acid (Carbaglu) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a metabolic disorder specialist; **AND**
   B. Documentation of member's weight within the past three months; **AND**
   C. A diagnosis of **hepatic enzyme N-acetylglutamate synthase (NAGS) deficiency** when the following are met:
      1. Diagnosis is confirmed by mutation of the *NAGS* gene via molecular genetic testing; **AND**
      2. Baseline ammonia levels indicating member has hyperammonemia (ammonia level is above the upper limit of normal based on member's age)

II. Carglumic acid (Carbaglu) is considered investigational when used for all other conditions, including but not limited to:
   A. Hyperammonemia **NOT** due to NAGS deficiency
   B. Methylmalonic Acidemia
   C. Propionic Acidemia
   D. Carbamoyl-Phosphate Synthase I Deficiency
   E. Ornithine Carbamoyltransferase Deficiency

F. Other Urea Cycle disorders

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 member's weight within the past three months; **AND**
IV. 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

Supporting Evidence

I. 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 deficiency 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. Out of the 23 patients who received carglumic acid (Carbaglu), a total of 13 patients had well documented ammonia levels prior to treatment initiation and after long-term treatment were included in the analysis.
II. All 13 patients had abnormally elevated ammonia levels at baseline; an overall mean baseline plasma ammonia level of 271 micromol/L was recorded for these patients. For acute treatment, patients received a total daily dose of 100 to 250mg/kg/day in two to four divided doses for the first few days of treatment and by day three, normal ammonia levels were attained. For maintenance treatment, the dosage was reduced over time based on biochemical and clinical response. 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.
III. NAGS deficiency is a rare autosomal recessive genetic disorder caused by mutations of the NAGS gene leading to complete or partial deficiency in the enzyme N-acetylglutamate synthetase (NAGS). The hepatic enzyme NAGS is necessary to break down nitrogen in the body. NAGS deficiency leads to accumulation of nitrogen in the form of ammonia in the blood (hyperammonemia). In most cases, onset of symptoms occurs at, or shortly following, birth (neonatal period); however, some individuals with NAGS deficiency may not exhibit symptoms until later during infancy, childhood, or even adulthood due to a partial deficiency of the NAGS enzyme. Symptoms of a 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.

IV. 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 and disease management should be by, or in consultation with, a physician who specializes in metabolic disorders.

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

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

VI. 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).

VII. Carglumic acid (Carbaglu) is available in 5 or 60-count bottles that expire one month after opening and are therefore dispensed as unbreakable packages. Each tablet should be dissolved in 2.5ml of water to make a suspension of 80mg/mL prior to administration.

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. Hyperammonemia **NOT** due to NAGS deficiency
   B. Methylmalonic Acidemia
   C. Propionic Acidemia
   D. Carbamoyl-Phosphate Synthase I Deficiency
   E. Ornithine Carbamoyltransferase Deficiency
   F. Other Urea Cycle disorders

References

1. Carglumic acid (Carbaglu) [Prescribing Information]. Lebanon, NJ: Recordati Rare Diseases Inc. December 2019.
2. Center for Drug Evaluation and Research. Application Number: 22-562. Summary Review. 30 July 2009. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022562s000sumr.pdf
3. Haberle et al. Suggested guidance for the diagnosis and management of urea cycle disorders. *Orphanet Journal of Rare Diseases*. 2012, 7:32.
4. National Organization for Rare Disorders (NORD). N-Acetylgluatmate Synthetase Deficiency. Rare Disease Database. Accessed 2 December 2020. Available at: https://rarediseases.org/rare-diseases/n-acetylglutamate-synthetase-deficiency/
5. Ammonia. URMC Health Encyclopedia. Accessed 2 December 2020. Available at: https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=167&ContentID=ammonia

Policy Implementation/Update:

Action and Summary of Changes	Date
Transitioned criteria to policy format; Added requirement for weight documentation and supporting evidence section.	12/2020
Criteria created	12/2015

cenegermin-bkbi (Oxervate®)

UMP POLICY

Uniform Medical Plan

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP013

Description

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

Length of Authorization

- Initial: Eight weeks
- Renewal: Not approvable

Quantity limits

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

Initial Evaluation

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

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

Renewal Evaluation

I. 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

1. Oxervate [Prescribing Information]. Boston, MA: Dompé US, Inc. October 2019.
2. Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neutrophic keratitis. *Opthalmology.* 2018;125(9):1332-1343.
3. Shaheen B, Bakir M, Jain S. Corneal nerves in health and disease. *Surv Opthalmol.* 2014;59(3):263-285.

4. Mantelli F, Nardella C, Tiberi E, et al. Congenital corneal anesthesia and neurotrophic keratitis: diagnosis and management. *Biomed Res Int.* 2015;2015:805876. Epub Sept. 16, 2015.
5. Semeraro F, Forbice E, Romano V, et al. Neurotrophic keratitis. *Opthalmologica*. 2014;231(4):191-197.
6. Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Opthalmol.* 2014;8:571-579.
7. An Evidence based Approach to the Diagnosis and Treatment of Neurotrophic Keratopathy. CME monograph. Johns Hopkins School of Medicine. March 2020. Available at: https://hopkinscme.cloud-cme.com/assets/hopkinscme/Presentations/28879/28879.pdf

Policy Implementation/Update:

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

chenodiol (Chenodal®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP200

Description

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

Length of Authorization

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

Quantity Limits

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

Initial Evaluation

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

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

Renewal Evaluation

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

Supporting Evidence

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

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

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

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

Investigational or Not Medically Necessary Uses

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

References

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

Policy Implementation/Update:

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

cholic acid (Cholbam®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP089

Description

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

Length of Authorization

- Initial: three months
- Renewal: 12 months

Quantity limits

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

Initial Evaluation

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

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

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

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

i. Member has ONE of the following peroxisomal disorders:

a. Neonatal Adrenoleukodystropyhy
b. Generalized Peroxisomal Disorder
c. Refsum Disease
d. Zellweger Syndrome
e. Peroxisomal Disorder, Type Unknown; **AND**

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

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

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

A. Extrahepatic manifestation of bile acid synthesis disorders due to SEDs or PDs
B. Familial hypertriglyceridemia without the diagnosis of SEDs or PDs

Renewal Evaluation

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

Supporting Evidence

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

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

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

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

Investigational or Not Medically Necessary Uses

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

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

References

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

Policy Implementation/Update:

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

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

Chronic Inflammatory Disease

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP014

Description

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

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Medications Included in this Policy

Medication	Indications
abatacept (Orencia®)	• Polyarticular Juvenile Idiopathic Arthritis • Psoriatic Arthritis • Rheumatoid Arthritis
adalimumab (Humira®)	• Ankylosing Spondylitis • Crohn's Disease • Hidradenitis Suppurativa • Polyarticular Juvenile Idiopathic Arthritis • Pediatric Crohn's Disease • Plaque Psoriasis • Psoriatic Arthritis • Ulcerative Colitis • Pediatric Ulcerative Colitis • Rheumatoid Arthritis • Uveitis/Panuveitis
anakinra (Kineret®)	• Cryopyrin-Associated Periodic Syndromes (CAPS) (including Chronic Infantile Neurological, Cutaneous and Articular Syndrome (CINCA) or Neonatal-Onset Multisystem Inflammatory Disease (NOMID)) • Rheumatoid Arthritis • Systemic Juvenile Idiopathic Arthritis (off-label)
apremilast (Otezla®)	• Plaque Psoriasis • Psoriatic Arthritis • Behcet Syndrome – ulcer of the mouth
baricitinib (Olumiant®)	• Rheumatoid Arthritis
brodalumab (Siliq®)	• Plaque Psoriasis
certolizumab (Cimzia®)	• Ankylosing Spondylitis • Crohn's Disease • Non-radiographic Axial Spondyloarthritis

	• Plaque Psoriasis • Psoriatic Arthritis • Rheumatoid Arthritis
etanercept (Enbrel®)	• Ankylosing Spondylitis • Plaque Psoriasis • Polyarticular Juvenile Idiopathic Arthritis • Psoriatic Arthritis • Rheumatoid Arthritis
golimumab (Simponi®/Simponi Aria®)	• Ankylosing Spondylitis • Psoriatic Arthritis • Rheumatoid Arthritis • Ulcerative Colitis
guselkumab (Tremfya®)	• Plaque Psoriasis • Psoriatic Arthritis
ixekizumab (Taltz®)	• Ankylosing Spondylitis • Non-radiographic Axial Spondyloarthritis • Adolescent Plaque Psoriasis • Plaque Psoriasis • Psoriatic Arthritis
rilonacept (Arcalyst®)	• Cryopyrin-Associated Periodic Syndromes (CAPS) (including Familial Cold Autoinflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS))
risandizumab (Skyrizi®)	• Plaque Psoriasis
sarilumab (Kevzara®)	• Rheumatoid Arthritis
secukinumab (Cosentyx®)	• Ankylosing Spondylitis • Non-radiographic Axial Spondyloarthritis • Plaque Psoriasis • Psoriatic Arthritis
upadacitinib (Rinvoq™)	• Rheumatoid Arthritis
ustekinumab (Stelara®)	• Crohn's Disease • Adolescent Plaque Psoriasis • Plaque Psoriasis • Psoriatic Arthritis • Ulcerative Colitis
tocilizumab (Actemra®)	• Giant Cell Arteritis • Polyarticular Juvenile Idiopathic Arthritis • Rheumatoid Arthritis • Systemic Juvenile Idiopathic Arthritis
tofacitinib (Xeljanz®)	• Psoriatic Arthritis • Rheumatoid Arthritis • Ulcerative Colitis • Polyarticular Juvenile Idiopathic Arthritis

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(D)(5) 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 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 labelings, 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 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 this 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 (Kevzara), tocilizumab (Actemra), tofacitinib (Xeljanz/Xeljanz XR), baricitinib (Olumiant), or upadacitinib (Rinvoq)** 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) AND etanercept (Enbrel) have been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

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

II. 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 list above are approved for adult patients in the treatment of rheumatoid arthritis in adult patients based on safety and efficacy data from randomized-controlled trials.

II. The 2015 ACR guidelines recommend the use of DMARD monotherapy (methotrexate preferred) in patients who are DMARD-naïve with early RA. Recommended DMARDs include methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. The guidelines state azathioprine, cyclosporine, minocycline, and gold were not included due to infrequent use and lack of new data since 2012. For patients with moderate to high disease activity despite adequate trial of DMARD monotherapy, combination DMARD or use of tumor necrosis factor (TNF) inhibitors or non-TNF inhibitor biologics with or without methotrexate is recommended. In patients who have failed both TNF inhibitor and non-TNF inhibitor biologics, or multiple TNF inhibitors, guidelines recommend the use of either another non-TNF biologic or a JAK inhibitor with or without methotrexate. The guidelines do not address the use of baricitinib (Olumiant) given that the medication was approved after the most recent publication. Baricitinib (Olumiant) has demonstrated similar ACR20 responses to tofacitinib (Xeljanz) in clinical trials.

III. The 2016 European League Against Rheumatism (EULAR) guidelines follow similar recommendations to the ACR guidelines, and state that patients who have failed one TNF inhibitor may receive a different TNF inhibitor, as studies have demonstrated primary TNF non-responders have responded to other agents of the same mechanism of action.

References:

1. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken).* 2016;68(1):1-25.
2. Humira [Prescribing Information]. AbbVie Inc.: North Chicago, IL. January 2019.
3. Berglin E, Dahlqvist SR. Comparison of the 1987 ACR and 2010 ACR/EULAR classification criteria for rheumatoid arthritis in clinical practice: a prospective cohort study. *Scand J Rheumatol*. 2013;42(5):362-368.
4. UpToDate, Inc. Diagnosis and differential diagnosis of rheumatoid arthritis. UpToDate [database online]. Waltham, MA. Last updated August 23, 2019. Available at: http://www.uptodate.com/home/index.html.
5. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76(6):960-977.
6. Strand V, Schiff M, Tundia N, et al. Patient reported outcomes of upadacitinib: results from biologic inadequate responders (SELECT-BEYOND Phase III trial). Presented at: European League Against Rheumatism (EULAR) – Annual European Congress of Rheumatology: June 13-16, 2018; Amsterdam, The Netherlands. Poster SAT0255.

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 **PJIA** when the following are met:
      1. Treatment with at least one oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective, contraindicated, or not tolerated. Guidelines direct to use of methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.

II. **Abatacept (Orencia), tocilizumab (Actemra), tofacitinib (Xeljanz)** 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) AND etanercept (Enbrel) has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Member has exhibited improvement or stability of disease symptoms; **AND**
II. Agent 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)

Supporting Evidence

I. The above agents are approved for pediatric patients greater than two years of age with polyarticular juvenile idiopathic arthritis based on safety and efficacy data from randomized-controlled trials.
II. The 2019 JIA guidelines published by the ACR strongly recommends initial therapy with a DMARD for all patients with JIA and active polyarthritis. For patients both with and without risk factors, 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.
III. 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.
IV. A phase 3 double-blind, randomized, placebo-controlled withdrawal study (PROPEL) evaluated the efficacy and safety of tofacitinib (Xeljanz) in patients age 2-17 years old with active Polyarticular Juvenile Idiopathic Arthritis and who had inadequate response to at least one disease modifying antirheumatic drug (DMARD or biologic DMARD). The primary endpoint evaluated the occurrence of disease flare at week 44 in polyarticular juvenile Idiopathic Arthritis patients. The occurrence of disease flare at week 44 was 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 patents currently on DMARD or oral glucocorticoid.

References

1. Ringold S, Angeles-han ST, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. Arthritis Care Res (Hoboken). 2019.
2. UpToDate, Inc. Polyarticular juvenile idiopathic arthritis: treatment. UpToDate [database online]. Waltham, MA. Last updated October 9, 2018. Available at: http://www.uptodate.com/home/index.html.
3. Brunner H, Ting T, el al. Tofacitinib in treatment of Polyarticular-course Juvenile idiopathic Arthritis: Results of a Phase 3 Randomized Double-blind Placebo withdrawal Study. ACR 2019. Abstract number: L22
4. Safety and Tolerability of Tofacitinib for Treatment of Polyarticular Course Juvenile Idiopathic Arthritis. 2020 [PROPEL Study] (NCT02592434)

Systemic Juvenile Idiopathic Arthritis (SJIA)

Initial Evaluation

I. **Anakinra (Kineret)** may be considered medically necessary when the following criteria below are met:
   A. Member is 2 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **active SJIA** when the following are met:
      1. Treatment with at least one NSAID (e.g. ibuprofen, naproxen, indomethacin, meloxicam, celecoxib, etc.) or glucocorticoid (i.e. prednisone, hydrocortisone, methylprednisolone, etc.) has been ineffective, contraindicated, or not tolerated; **OR**
      2. Patient has severe active disease as indicated by one of the following:
         i. Suspected early macrophage activating syndrome (MAS)
         ii. Disabling polyarthritis
         iii. Serositis

II. **Tocilizumab (Actemra)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with anakinra (Kineret) has been ineffective, contraindicated, or not tolerated.

III. **Abatacept (Orencia)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with anakinra (Kineret) and tocilizumab (Actemra) has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Member has exhibited improvement or stability of disease symptoms; **AND**
II. 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)

Supporting Evidence

I. Anakinra (Kineret) does not have FDA approval for SJIA but did gain approval recently by the European Medicines Agency for this indication in 2018. A prospective trial examined 42 children with new-onset disease after no response to a seven-day trial of NSAIDs. Rapid improvement was seen, with inactive disease noted in 55% and 71% of patients at one and three months, respectively. A similar rate of response was seen in a small RCT (ANAJIS) to that seen in the tocilizumab trial and is described below in terms of ACR30.

II. Tocilizumab is approved for treatment of active SJIA in patients two years and older. In a RCT of 112 children with SJIA for greater than six months, who had an inadequate response to NSAIDs and glucocorticoids, tocilizumab patients were more likely to achieve JIA ACR30 response by week 12 compared to placebo (85% vs 24%, $p<0.001$).

III. The SJIA guidelines updated in 2013 by the ACR note that NSAIDs are recommended as an initial treatment approach. However, based off expert opinion, monotherapy is inappropriate for patients with an MD global assessment score of 5 or greater (0-10 scale), indicating severe disease. Likewise, it is noted that macrophage activation syndrome (MAS) which occurs in approximately 10% of SJIA patients, is a severe, life-threatening condition and delay in IL-1 or IL-6 inhibitor therapy should not occur in this scenario. Anakinra (Kineret) is recommended as an initial treatment option in patients with severely active disease, as well as for patients with continued disease activity after treatment with glucocorticoid or NSAID monotherapy. For those patients who have tried both anakinra (Kineret) and tocilizumab (Actemra) sequentially, abatacept (Orencia) is recommended based off expert opinion. A subset of 37 children with systemic JIA was examined in comparison to placebo in a RCT. After four months of treatment in the initial lead-in period, 24 of 37 patients (65%) treated with abatacept had a ACR30 response, which was similar to response rates seen in patients included with other JIA subtypes.

IV. TNF inhibitors demonstrate greater efficacy in patients with nonsystemic JIA compared to SJIA. For instance, a study of 45 children who had systemic symptoms at the start of TNF inhibitor therapy noted lower rates of remission and a high frequency of disease flare (24% and 45%, respectively).

References

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7. Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet.* 2008;372(9636):383-391.

Psoriatic Arthritis

Initial Evaluation

I. **Adalimumab (Humira), etanercept (Enbrel), apremilast (Otezla), secukinumab (Cosentyx) or ustekinumab (Stelara)** 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 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), tofacitinib (Xeljanz/Xeljanz XR), 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) AND ustekinumab (Stelara) 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 exhibited improvement or stability of disease symptoms; **AND**
II. 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. The above agents are approved for adult patients in the treatment of psoriatic arthritis based on safety and efficacy data from randomized-controlled trials.

II. The 2018 ACR guidelines make a conditional recommendation for starting a TNF inhibitor over an OSM as a first-line option for patients who are treatment-naïve with active psoriatic arthritis. This recommendation is based on low- to very-low quality of evidence. Many of the studies in which greater benefit was seen in terms of disease severity or radiographic progression compared methotrexate to TNF inhibitors, however, most patients included in these groups were not truly treatment-naïve to OSM medications. Guidelines note that OSM can be used first-line in naïve patients who do not have severe PsA, severe PsO, prefers oral therapy, or has contraindications to TNF inhibitors. In patients who continue to have active disease despite OSM treatment, it is recommended to switch to a TNF inhibitor rather than trying a different OSM.

III. 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).

IV. The 2018 guidelines also conditionally recommend for use of a TNF inhibitor biologics over IL-17 inhibitors (ixekizumab, secukinumab) or IL-12/23 inhibitors (ustekinumab). As of August 2020, guidelines have not been updated with regard to place in therapy for guselkumab.

References:

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2. Kingsley GH, Scott DL. Assessing the effectiveness of synthetic and biologic disease-modifying antirheumatic drugs in psoriatic arthritis - a systematic review. Psoriasis (Auckl). 2015;5:71-81.
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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) AND secukinumab (Cosentyx) has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Member has exhibited improvement or stability of disease symptoms; **AND**
II. 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. 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 off controlled trials demonstrating minimal to no benefit with agents such as sulfasalazine, methotrexate, and

leflunomide. Some benefit has been seen in patients with peripheral arthritis, and thus these agents may be considered for patients with ankylosing spondylitis with predominantly peripheral arthritis symptoms.

References:

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Non-radiographic Axial Spondyloarthritis

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 **non-radiographic axial spondyloarthritis** when the following are met:
      1. High disease activity as indicated by BASDAI score of at least 4 or ASDAS score of at least 2.1; **AND**
      2. Treatment with at least two different NSAIDs (e.g. indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated; **AND**
      3. Disease manifested as axial disease; **OR**
      4. Disease manifested as peripheral arthritis.

II. **Certolizumab (Cimzia) 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 exhibited improvement or stability of disease symptoms; **AND**
II. 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. 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 regards 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-naïve patients on secukinumab 150 mg with loading dose compared to placebo and ASAS40 response at week 52 in TNFi-naïve patients on secukinumab 150 mg without loading dose compared to placebo were achieved (week 16: 41.5% vs 29.2%, $p=0.0197$, and week 52: 39.8% vs 19.9%, $p<0.0021$). Improvement was seen in secondary outcomes at week 16 for Ankylosing Spondylitis Disease Activity Score (ASDAS) and quality of life.

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:

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Plaque Psoriasis

Initial Evaluation

I. **Adalimumab (Humira), etanercept (Enbrel), secukinumab (Cosentyx), apremilast (Otezla), or ustekinumab (Stelara)** 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), secukinumab (Cosentyx), or apremilast (Otezla); **OR**
      1. Member is 4 years of age or older if prescribed etanercept (Enbrel); **OR**
      2. Member is 6 years of age or older if prescribed ustekinumab (Stelara); **AND**
   B. Member is being managed by, or in consultation with, a dermatologist; **AND**
   C. A diagnosis of **moderate to severe plaque psoriasis** when the following are met:
      1. 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**
      2. Treatment with the following has been ineffective or not tolerated, or all are contraindicated:
         i. Phototherapy (UVB or PUVA); **OR**
         ii. At least one non-biologic, non-specialty DMARD (e.g. methotrexate, cyclosporine, acitretin, azathioprine, etc.)

II. **Brodalumab (Siliq), certolizumab (Cimzia), guselkumab (Tremfya), ixekizumab (Taltz), or risankizumab (Skyrizi) 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) AND ustekinumab (Stelara) have been ineffective, contraindicated, or not tolerated; **AND**
C. The member is 18 years of age or older if prescribed brodalumab (Siliq), certolizumab (Cimzia), guselkumab (Tremfya), or risankizumab (Skyrizi); **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 exhibited improvement or stability of disease symptoms; **AND**
II. 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).

Supporting Evidence

I. The above agents are approved in the treatment of moderate to severe plaque psoriasis in adult patients. As of March 2021, only etanercept (Enbrel), ixekizumab (Taltz), and ustekinumab (Stelara) have been studied and approved for use in pediatric patients. Etanercept (Enbrel) is indicated in patients at least four years of age; ixekizumab (Taltz) and ustekinumab (Stelara) 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.
   - <u>Induction and maintenance</u>:
     i. 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.
   - <u>Induction</u>:
     i. The following agents statistically significantly improve PASI by at least 90% compared to adalimumab (Humira) with moderate certainty: guselkumab (Tremfya) and risankizumab (Skyrizi).
     ii. The following agents statistically and significantly improve PASI by at least 90% compared to etanercept (Enbrel) with moderate certainty: certolizumab (Cimzia), ixekizumab (Taltz), and ustekinumab (Stelara).
     iii. Ixekizumab (Taltz) statistically significantly improves PASI by at least 90% compared to ustekinumab (Stelara) with moderate certainty.

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

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

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 mediations or phototherapy."
- Guidelines define moderate psoriasis by ≥3% of the total body surface area involved and severe psoriasis by ≥10%, with severity extending to the hands, feet, scalp, face, genital area, or 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 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.

References:

1. Adalimumab (Humira) [Prescribing Information]. North Chicago, IL; AbbVie. Updated March 2020.
2. Apremilast (Otezla) [Prescribing Information]. Thousand Oaks, CA; Amgen. Updated June 2020.
3. Brodalumab (Siliq) [Prescribing Information]. Bridgewater, NJ; Bausch Health. Updated April 2020.

4. Certolizumab pegol (Cimzia) [Prescribing Information]. Smyrna, GA; UCB. Updated September 2019.
5. Etanercept (Enbrel) [Prescribing Information]. Thousand Oaks, CA; Amgen. Updated August 2020.
6. Ixekizumab (Taltz) [Prescribing Information]. Indianapolis, IN; Eli Lilly. Updated May 2020.
7. Guselkumab (Tremfya) [Prescribing Information]. Horsham, PA; Janssen. Updated July 2020.
8. Risankizumab (Skyrizi) [Prescribing Information]. North Chicago, IL; AbbVie. Updated March 2020.
9. Secukinumab (Cosentyx) [Prescribing Information]. East Hanover, NJ; Novartis. Updated June 2020.
10. Ustekinumab (Stelara) [Prescribing Information]. Horsham, PA; Janssen. Updated July 2020.
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12. Menter A, Gelfand JM, Connor C et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. J Amer Academy of Dermol 2020;82:1445-86.
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15. Sawyer LM, Cornic L, Levin LA et al. Long-term efficacy of novel therapies in moderate-to-severe plaque psoriasis: a systematic review and network meta-analysis of PASI response. *J Eur Acad Dermatol Venereol* 2019;33(2):355-366.
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17. Reich K, Armstrong AW, Langley RG et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): results from a phase 3, randomised controlled trial. *Lancet* 2019;394(10201):831-839.

Crohn's Disease

Initial Evaluation

I. **Adalimumab (Humira) or ustekinumab (Stelara)** may be considered medically necessary when the following criteria below are met:
   A. Member is 6 years of age or older if prescribed adalimumab (Humira); **OR**
      1. Member is 18 years of age or older if prescribed ustekinumab (Stelara); **AND**
   B. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   C. A diagnosis of **moderate to severe Crohn's disease** when the following are met:
      1. Presence of at least one of the following:
         i. Crohn's Disease Activity Index (CDAI) score ≥ 220
         ii. Prominent symptoms (fever, weight loss, abdominal pain/tenderness, intermittent nausea/vomiting, weight loss, and/or significant anemia)
         iii. Mucosal disease evident on endoscopy; **AND**
      2. Treatment with oral corticosteroids (i.e. prednisone, hydrocortisone, methylprednisolone, etc.) used short-term to induce remission or alleviate signs/symptoms of disease flare has been ineffective, contraindicated, or not tolerated; **AND**
      3. Treatment with at least one immunomodulatory agents (e.g. methotrexate, azathioprine, 6-mercaptopurine) over an eight week period to maintain remission has been ineffective, contraindicated, or not tolerated; **OR**
   D. A diagnosis of **severe/fulminant Crohn's disease** when the following are met:
      1. Presence of at least one of the following:
         i. CDAI score > 450

ii. Prominent symptoms (persistent vomiting, involuntary guarding/rebound tenderness, and/or cachexia)
iii. Evidence of abscess or intestinal obstruction
iv. Severe mucosal disease evident on endoscopy; **AND**

2. Treatment with IV corticosteroids (i.e. methylprednisolone) has been ineffective, contraindicated, or not tolerated.

E. A diagnosis of **Crohn's disease with surgical resection completed or planned** when the following are met:

1. Presence of at least one of the following:
   i. Current smoker
   ii. Penetrating disease (i.e. fistulas, abscess, and/or intestinal perforation) with no history of previous surgical resection
   iii. Two or more previous surgeries or prior surgical resection in the past ten years.

II. **Certolizumab pegol (Cimzia)** may be considered medically necessary when the following criteria below are met:

A. Criteria I(B)-I(E) above are met*; **AND**
B. Member is 18 years of age or older; **AND**
C. Treatment with adalimumab (Humira) AND ustekinumab (stelara) have been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Member has exhibited improvement or stability of disease symptoms; **AND**
II. 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. The above agents are approved in the treatment of moderate to severe Crohn's disease based on safety and efficacy data from randomized-controlled trials. Per package labeling, adalimumab (Humira) is FDA-approved for use in pediatrics. Certolizumab pegol (Cimzia) and ustekinumab (Stelara) are approved in adults only.
II. The American College of Gastroenterology (ACG) guidelines on the management of Crohn's disease in adults was published in 2018. In patients with moderately to severely active disease as ACG describes above, a strong recommendation if made for the use of TNF inhibitors in patients who are resistant to treatment with corticosteroids and when refractory to thiopurines or methotrexate when used for maintaining remission.
III. The ACG states that ustekinumab (Stelara) should be given for moderate to severe disease in patients who failed previous treatment with corticosteroids, thiopurines, methotrexate, or TNF inhibitors. To date, no head-to-head trials are available comparing ustekinumab to TNF inhibitors or anti-integrin therapies (natalizumab and vedolizumab). A study is currently recruiting to compare the efficacy of ustekinumab to adalimumab in patients with Crohn's disease.

IV. ACG guidelines note that TNF inhibitors such as infliximab, adalimumab, and certolizumab pegol can be considered to treat severely active/fulminant Crohn's disease. This recommendation stems from clinical expertise, as patients with CDAI scores greater than 450 indicating severe disease were excluded from clinical trials.

V. Guidelines also describe the recommendations for patients in the postoperative setting to prevent recurrence of disease flare. It is noted that in high-risk patients as indicated by the risk factors described above, TNF inhibitors should be started within 4 weeks of surgery to prevent postoperative recurrence. Meta-analyses of the use of thiopurines in this setting have provided varying results, and therefore these agents may be more appropriate in low-risk surgical patients. Meta-analyses have demonstrated consistent results with the TNF inhibitors in preventing recurrence in postoperative patients.

References:

1. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. 2018;113(4):481-517.
2. UpToDate, Inc. Overview of the management of Crohn disease in children and adolescents. UpToDate [database online]. Waltham, MA. Last updated April 18, 2019. Available at: http://www.uptodate.com/home/index.html.

Ulcerative Colitis

Initial Evaluation

I. **Adalimumab (Humira)** may be considered medically necessary when the following criteria below are met:
   A. Member is 5-17 years of age; **AND**
      1. Documentation of member's current weight is provided; **OR**
   B. Member is 18 years of age or older; **AND**
   C. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
   D. 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. **Tofacitinib (Xeljanz/Xeljanz XR) or ustekinumab (Stelara)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Criteria I(C)-I(D) above are met; **AND**
   C. The request is for tofacitinib (Xeljanz/Xeljanz XR); **AND**
      1. Member has had an inadequate response or intolerance to tumor necrosis factor (TNF) blockers (e.g., Humira); **OR**
   D. The request is or ustekinumab (Stelara); **AND**
      1. Documentation of the member's current weight is provided

III. **Golimumab (Simponi) or ozanimod (Zeposia)** may be considered medically necessary when the following criteria below are met:
   A. Criteria II(A)-II(B) above are met; **AND**
   B. Treatment with adalimumab (Humira), tofacitinib (Xeljanz/Xeljanz XR), AND ustekinumab (Stelara) 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)

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), and ozanimod (Zeposia) 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.
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).

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:

1. Adalimumab (Humira) [Prescribing Information]. North Chicago, IL; AbbVie. Updated December 2020.
2. Ustekinumab (Stelara) [Prescribing Information]. Horsham, PA; Janssen. Updated December 2020.

3. Golimumab (Simponi) [Prescribing Information] Raritan, NJ; Janssen Biotech, Inc. Updated September 2019.
4. Infliximab (Remicade) [Prescribing Information] Raritan, NJ; Janssen Biotech, Inc. Updated May 2020.
5. Vedolizumab (Entyvio) [Prescribing Information] Chuo-ku, Tokyo, Japan; Takeda Inc., Updated March 2020.
6. Ozanimod (Zeposia) [Prescribing Information] New York, NY; Bristol Myers Squibb Inc., Updated May 2021.
7. Tofacitinib (Xeljanz) [Prescribing Information] New York, NY; Pfizer Inc., Updated September 2020.
8. Rubin DT, Ananthakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG Clinical Guideline: Ulcerative Colitis in Adults. *Am J Gastroenterol.* 2019;114(3):384-413.
9. Sands BE, Peyrin-Biroulet L, Loftus EV Jr, et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med. 2019 Sep 26;381(13):1215-1226. doi:10.1056/NEJMoa1905725. PMID: 31553834.
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14. Zeposia (ozanimod) Clinical Summary: TRUENORTH phase 3 trial for Ulcerative Colitis. Bristol Myers Squibb. December 2020.
15. Turner et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care—An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition, Journal of Pediatric Gastroenterology and Nutrition: August 2018.

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 treatment this condition (e.g., rheumatologist, dermatologist, ophthalmologist, etc.); **AND (one of the following)**
      1. A diagnosis of recurrent **Behcet's Disease manifesting as oral ulcers of the mouth**; **AND**
         i. All of the following have been ineffective, not tolerated, or are contraindicated:
            a. Topical corticosteroids (e.g., triamcinolone) OR sucralfate mouthwash; **AND**
            b. Oral corticosteroids; **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 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**

II. 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).

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 etancercept compared to placebo. Results indicated efficacy of etanercept on oral ulcers, nodular lesions, papulopustular lesions, and had an increased probability of being ulcer and nodular lesion free compared to the placebo group. Although a small trial, the rarity of Behcet's Disease shall be taken into account.
   - A multicenter study of refractory Behcet's Disease treated with and-TNF alpha treatments was conducted: The trial included infliximab and adalimumab. These therapies resulted in an overall 90.4% response rate for all clinical manifestations, and specifically an 88% response rate for mucocutaneous manifestations and 96.3% for severe and/or refractory ocular disease. The incidence of flares was reduced during anti-TNF alpha treatment.
   - An analysis of published data in 369 patients using anti-TNF alpha agents for Behcet's Disease: This included peer-reviewed articles on Medline/PubMed, and evaluated patients that were uncontrolled with or intolerant to other immunosuppressives. A rate of 90% clinical response was seen for the mucocutaneous manifestations of Behcet's disease, and a rate of 89% for ocular disease.

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

III. For oral manifestations first line treatment is triamcinolone acetonide cream 0.1% in orabase, applied three to four times daily. High potency 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.

IV. 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.

V. 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 regards 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.

VI. 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:

1. Mahr A., Takeno M., Kim DY. Efficacy of apremilast for oral ulcers associated with active Behcet's Syndrome in a phase III study: a prespecified analysis by baseline patient demographics and disease characteristics. ARHP Annual Meeting. 2018; abstract 1791.
2. Yazici H, Pazarli H, Barnes CG, et al. A controlled trial of azathioprine in Behçet's syndrome. N Engl J Med. 1990;322(5):281-5.
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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 exhibited improvement or stability of disease symptoms; **AND**

II. 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:

1. Kimball AB, Okun MM, Williams DA, et al. Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. *N Engl J Med*. 2016;375(5):422-434.
2. Ingram JR, Collier F, Brown D, et al. British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. *Br J Dermatol.* 2019;180(5):1009-1017.
3. UpToDate, Inc. Hidradenitis suppurativa: treatment. UpToDate [database online]. Waltham, MA. Last updated April 18, 2019. Available at: http://www.uptodate.com/home/index.html.
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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 exhibited improvement or stability of disease symptoms; **AND**
II. 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:

1. Nguyen QD, Merrill PT, Jaffe GJ, et al. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (VISUAL II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet.* 2016;388(10050):1183-1192.
2. Jaffe GJ, Dick AD, Brézin AP, et al. Adalimumab in Patients with Active Noninfectious Uveitis. *N Engl J Med*. 2016;375(10):932-943.
3. Dick AD, Rosenbaum JT, Al-dhibi HA, et al. Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative. *Ophthalmology*. 2018;125(5):757-773.
4. Ming S, Xie K, He H, Li Y, Lei B. Efficacy and safety of adalimumab in the treatment of non-infectious uveitis: a meta-analysis and systematic review. *Drug Des Devel Ther.* 2018;12:2005-2016.

Giant Cell Arteritis

Initial Evaluation

I. **Tocilizumab (Actemra)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by, or in consultation with, a rheumatologist; **AND**
   C. A diagnosis of **giant cell arteritis** when the following are met:
      1. Presence of at least three of the following:
         i. Age at disease onset of at least 50 years
         ii. New onset headache at time of diagnosis
         iii. Temporary artery abnormality (tenderness to palpation or decreased pulsation)

iv. Elevated ESR
v. Abnormal artery biopsy; **AND**

2. Previous treatment with at least one glucocorticoids (i.e. prednisone, hydrocortisone, methylprednisolone, etc.) and attempted dose reduction/taper has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Member has exhibited improvement or stability of disease symptoms; **AND**
II. 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 has 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 has 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:

1. Stone JH, Tuckwell K, Dimonaco S, et al. Trial of Tocilizumab in Giant-Cell Arteritis. *N Engl J Med*. 2017;377(4):317-328.
2. Buttgereit F, Dejaco C, Matteson EL, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. *JAMA*. 2016;315(22):2442-2258.
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4. UpToDate, Inc. Treatment of giant cell arteritis. UpToDate [database online]. Waltham, MA. Last updated April 18, 2019. Available at: http://www.uptodate.com/home/index.html.
5. Nesher G, Breuer GS. Giant Cell Arteritis and Polymyalgia Rheumatica: 2016 Update. Rambam Maimonides Med J. 2016;7(4)

6. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33(8):1122-1128.

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 exhibited improvement or stability of disease symptoms; **AND**
II. 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:

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Recurrent pericarditis

Initial Evaluation

I. **Rilonacept (Arcalyst)** may be considered medically necessary when the following criteria below are met:
   A. Member is 12 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist; **AND**
   C. Member has a history of three or more episodes of pericarditis; **AND**
   D. Documentation that ALL of the following were ineffective, or all are contraindicated:
      1. NSAID
      2. colchicine
      3. corticosteroids

Renewal Evaluation

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

II. 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 a Journal of American College of Cardiology (JACC) review on the management of acute and recurrent pericarditis, in acute pericarditis, the injury to the pericardium leads to a cascade of inflammatory process where IL-1 receptor (IL-1R) occupies a central role. In this process, IL-1α functions as an alarmin that is released during tissue injury and IL-1β gets released leading to amplification of the process. The rationale for the evaluation of rilonacept (Arcalyst) for recurrent pericarditis notes that this process is thought to stimulate the production of additional IL-1α and IL-1β which induces a self-perpetuating cycle of pericardial inflammation.

V. Both the 2015 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of pericardial diseases, and the 2020 American College of Cardiology review on the management of acute and recurrent pericarditis list treatment with NSAIDs/aspirin with colchicine for both acute pericarditis and recurrent pericarditis. According to ACC, anti-inflammatory therapy is the cornerstone of acute pericarditis. NSAIDs are recommended during an acute episode. Colchicine, which has a known anti-inflammatory effect, is recommended in patients with acute pericarditis in addition to aspirin or another NSAIDs. The benefit of colchicine is well established in both acute and recurrent pericarditis through various trials

including, but not limited to, the CORE trial (2005), COPE trial (2005), and ICAP (2013). The ACC also notes that the efficacy of colchicine in recurrence has been shown in various studies. Key opinion leader input also supports the use of NSAIDs/aspirin and colchicine for both acute and recurrent pericarditis and that trial of these prior to rilonacept (Arcalyst) is clinically appropriate and aligns with evidence. Currently a 3-month course of colchicine is recommended for acute pericarditis; whereas, for recurrent pericarditis, a treatment course of at least 6 months is recommended.

VI. According to available information or guidelines for recurrent pericarditis, key opinion leader input and available data for the use of rilonacept (Arcalyst) in recurrent pericarditis, NSAIDs and colchicine (≥ 6 months) remain the standard of care for the treatment for initial recurrence of pericarditis. Low-dose corticosteroids are also often used in the treatment of recurrent pericarditis and are associated with a high treatment success rate per ACC. Currently, the place in therapy for rilonacept (Arcalyst) can be considered for patients with multiple recurrence of pericarditis, and/or for patients where further use of NSAIDs, colchicine, and a low-dose corticosteroid are not clinically appropriate.

References:

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Investigational or Not Medically Necessary Uses

I. Atopic Dermatitis
   A. Early report from the BREEZE-AD1 and BREEZE-AD2 studies have indicated that baricitinib may be beneficial in patients with atopic dermatitis. The manufacturer reports a statistical improvement in Investigator's Global Assessment (IGA) scores at week 16 compared to placebo, though full trial data and outcomes has not been shared at this point in time. Three other studies are also planned which may provide data on safety and efficacy as well.

II. 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.

III. 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).

IV. 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.

V. 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.

VI. 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.

VII. 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.

VIII. 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.

IX. 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 baricitinib and ustekinumab are currently recruiting in patients with SLE.

X. 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.

XI. Palmoplantaris Pustulosis

A. A small placebo-controlled (n =15) of etanercept in palmoplantaris pustolosis supported potential efficacy of TNF inhibitors. Observations have also occurred demonstrating worsening of this disease with use of TNF inhibitors. Other biologics, such as the use of IL-12/IL-23 inhibitor ustekinumab, did not demonstrate benefit in palmoplantaris pustolosis. A phase II study has analyzed guselkumab, and case reports of IL-1 inhibitors such as anakinra have been reported, though further study is needed to confirm the use of biologics in this population.

XII. 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.

XIII. 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.

XIV. 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.

XV. 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.

XVI. Sciatica

A. One small RCT has examined adalimumab in patients with acute/severe radicular leg pain and imagine-confirmed lumber disc herniation. Of the 61 patients, a statistically significant, though small effect, was seen at week 6 compared to placebo. At the 6 month follow up, the statistically significant difference was lost. While a difference in surgical discectomies was also seen,

XVII. 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).

XVIII. 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.

XIX. 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 month 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.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria for treatment of recurrent pericarditis with Arcalyst	06/2021
Updated criteria for ulcerative colitis to include FDA approval of ozanimod (Zeposia) for adults with moderate to severe ulcerative colitis. Modified the weight requirement for Humira to a specific age group. Added a requirement to try and fail TNF blockers before allowing treatment with tofacitinib (Xeljanz) as recommended by FDA labeling. Supporting evidence and references updated.	06/2021
Updated criteria for ulcerative colitis to include FDA approval of adalimumab (Humira) for pediatric patients five years and older. Added the requirement for the documentation of member's current weight. Updated	05/2021

the language in the criterion requiring use of thiopurines only if corticosteroids were used to induce remission. Supporting evidence and references updated.	
Updated criteria for ulcerative colitis to include FDA approval for pediatric patients five years and older. Added the requirement for the documentation of member's current weight. Updated the language in the criterion requiring use of thiopurines only if corticosteroids were used to induce remission. Supporting evidence and references updated	05/2021
Added DIRA indication as E/I for anakinra (Kineret); Updated the supporting evidence and references for plaque psoriasis.	04/2021
Updated PA policy to include FDA approvals for Xeljanz for PJIA. Updated supporting evidence section with clinical trial data	11/2020
Updated PA policy to include FDA approvals for Stelara and Taltz for plaque psoriasis in pediatric population. Updated supporting information section for plaque psoriasis to include clinical trial data supporting use of Stelara and Taltz in pediatric patients	09/2020
Updated the products for psoriatic arthritis to include guselkumab (Tremfya). Updated the supporting evidence section for psoriatic arthritis to reflect no changes in the guidelines with regard to guselkumab (Tremfya). Updated non-radiographic axial spondyloarthritis (nr-axSpA) criteria to include secukinumab (Cosentyx) and ixekizumab (Taltz). Updated nr-axSpA supporting evidence section to include trial information regarding new addition of secukinumab (Cosentyx) and ixekizumab (Taltz), as well as updated ACR guidelines.	08/2020
Removed Behçet syndrome from the E/I section	02/2020
Updated preferred products to also include Cosentyx, Stelara, and Otezla within their FDA label designation.	01/2020
Updated policy to add new indications for Stelara and Taltz. Included Familial Mediterranean Fever to experimental/investigational section.	11/2019
Criteria updated to new policy format. Specific changes include: <u>Rheumatoid Arthritis</u> • Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement • Removed requirements for diagnosis due to varying methods to diagnose and limited value of this question from health plan standpoint • Clarified use of oral DMARD requirement may be bypassed if all of them are contraindicated • Added newly approved upadacitinib (Rinvoq) as a non-preferred alternative <u>Polyarticular Juvenile Idiopathic Arthritis (PJIA)</u> • Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement • Added route to approval of Actemra as Actemra was previously in a separate policy <u>Systemic Juvenile Idiopathic Arthritis (SJIA)</u> • Separated SJIA from PJIA to have individual requirements • Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement • Updated route to approval to require trial of NSAIDs or indication member has severe active disease • Routed therapy through anakinra (Kineret) over tocilizumab (Actemra) and abatacept (Orencia); followed by tocilizumab (Actemra) over abatacept (Orencia) as per <u>Psoriatic Arthritis</u> • Added requirement of the presence of active severe disease and provided specific indicators of severe disease • Added clinical note: "If a patient has a diagnosis of both plaque psoriasis and psoriatic arthritis, approval of the requested medication can be made as long as the patient fulfills the criteria for at least one of the disease states and associated medication criteria."	08/2019

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
  o Addition of IV corticosteroids as appropriate for this level of severity
• Addition of breakdown to Crohn's disease with surgical resection completed or planned
  o 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
Hidradentitis 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"
  o 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	

Criteria update: Increased initial approval from 3 months to 6 months, updated initial QL to reflect 6 month approval duration. Added new Xeljanz IR 10mg tablet availability. Added baricitinib (Olumiant) as an option for the treatment of rheumatoid arthritis after trial and failure of a TNF antagonist.	07/2018
Criteria update: Added new Kevzara auto injector formulation, Xeljanz new indication in ulcerative colitis, added Cimzia new indication in plaque psoriasis, minor formatting edits.	06/2018
Criteria update: Align dosage and administration with quantity limit. Removal of the question pertaining to active infection.	02/2018

New Criteria Set – consolidated from all biologic agents along with Otezla and Xeljanz criteria sets. Within this new criteria set, here are the following updates: 1. 18 years of age requirement has been removed for Stelara as it has now been FDA approved for pediatric plaque psoriasis. 2. New FDA approved indication of psoriatic arthritis has been added for Xeljanz/Xeljanz XR and Taltz 3. The question regarding dual therapy has been refined to encompass the language of biologics and other non-biologics (e.g. Otezla and Xeljanz). 4. The question regarding DMARDs has been refined to only include agents that are administered non-biologic, non-specialty and that are administered orally. 5. For the indication of plaque psoriasis, the question addressing the trial of UVB has been combined with the trial of DMARDs.	01/2018

Policy Type: PA 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

Short Acting: Active ingredients containing* Combination products containing any of these listed ingredients are included in this policy			
morphine sulfate	codeine sulfate	hydromorphone	oxymorphone
hydrocodone	levorphanol	meperidine	oxycodone
pentazocine	tapentadol	tramadol	butorphanol

Long Acting: Active ingredients containing*‡ Combination products containing any of these listed ingredients are included in this policy			
morphine sulfate	codeine sulfate	hydromorphone	oxymorphone
oxycodone	fentanyl patches	tramadol	hydrocodone
tapentadaol			

*Please note – acetaminophen products are limited to 4000 mg per day

‡Includes Extended release (ER) formulations as well as short acting or immediate release (IR) formulation use beyond 6 weeks.

Initial Evaluation

I. Chronic opioid use 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/sites/default/files/ump/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

1. Washington State Agency Medical Directors Group. Interagency Guideline on Prescribing Opioids for Pain. 3rd Edition, June 2015. Available: www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Added APAP limit wording to QL box	03/2020
Creation of policy	02/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP090

Description

Coagulation Factor X, human is a plasma-derived human blood coagulation factor that works by temporarily replacing the missing Factor X needed for effective hemostasis.

Length of Authorization

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

Quantity limits

Product Name	Dosage Form	Indication/FDA Labeled Dosing	Quantity Limit
Coagulation Factor X, human (Coagadex)	250 IU/vial, 500 IU/vial	**Factor X deficiency:** **On-demand treatment** <12 years: 30 IU/kg/dose >12 years: 25 IU/kg/dose Repeat every 24 hours until bleeding stops. Max of 60 IU/kg/day **Routine prophylaxis** <12 years: 40 IU/kg IV twice weekly initially >12 years: 25 IU/kg IV twice weekly initially Max of 60 IU/kg/day **Perioperative management** Max of 60 IU/kg/day	**On-demand Treatment**: Amount requested OR a max of 60 IU/kg/day *(whichever value is lower)* and no more than 5 on-demand doses on hand **Routine Prophylaxis:** 480 IU/kg every 28 days **Perioperative Management:** Amount requested OR a max of 60 IU/kg/day *(whichever value is lower)* Up to the number of doses requested for 28 days

Initial Evaluation

I. Coagulation Factor X, human (Coagadex) may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by, or in consultation with a hematologist; **AND**
   B. A diagnosis of **hereditary Factor X deficiency** when the following are met:
      1. Used for on-demand treatment and control of bleeding episodes; **AND**
         i. Member does **NOT** have more than 5 on-demand doses on hand; **OR**
      2. Used for routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
         i. Member must have severe factor X deficiency (factor X level of <1%); **OR** ii. Member has at least two documented episodes of spontaneous bleeding into joints; **OR**

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

1. Coagadex [Prescribing Information]. Durham, NC: Bio Products Laboratory USA, Inc. September 2018.
2. Brown DL, Kouides PA. Diagnosis and treatment of inherited factor X deficiency. Hemophilia. 2008 Nov;14(6):1176-82.
3. National Hemophilia Foundation for all Bleeding Disorders. Factor X. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Other- Factor-Deficiencies/Factor-X.
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Policy Implementation/Update:

Date Created	January 2016
Date Effective	January 2016
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Removed age requirement as now also approved in patients less than 12 years of age. Addition of agent to be prescribed by hematologist, limited to only allow 5 doses on hand in on demand treatment setting, added requirement of severe factor X deficiency or at least two spontaneous bleeds into joints for prophylaxis use, limited perioperative use to mild or moderate deficiency as per label. Updated initial approval duration from one month to now six months. Addition of renewal criteria.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP070

Description

Cobimetinib (Cotellic) is an orally administered mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2 inhibitor. Vemurafenib (Zelboraf) is an orally administered BRAF kinase inhibitor. These agents are FDA-approved for combination use or single use.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
cobimetinib (Cotellic)	20 mg tablets	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation	63 tablets/28 days
vemurafenib (Zelboraf)	240 mg tablets	Unresectable or metastatic melanoma with a BRAF V600E mutation; Erdheim-Chester Disease with a BRAF V600E mutation	224 tablets/28 days

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. Cobimetinib (Cotellic) and vemurafenib (Zelboraf) will **not** be used in combination with any other oncology therapy unless outlined below; **AND**
   D. A diagnosis of one of the following:
      1. **Unresectable, locally advanced (Stage IIIC) or metastatic (Stage IV) melanoma; AND**
         i. Documented BRAF V600E or V600K mutation; **AND**
         ii. Provider attests to ALL the following:
            a. Member has not previously received systemic anti-cancer therapy for metastatic melanoma (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy); **AND**

b. Cobimetinib (Cotellic) will be used in combination with one of the following:
    i. Vemurafenib (Zelboraf) *only*; **OR**
    ii. Vemurafenib (Zelboraf) AND atezolizumab (Tecentriq) *only*; **OR**

2. **Erdheim-Chester disease; AND**
    i. The request is for vemurafenib (Zelboraf) *only*; **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
    D. Solid tumors
    E. Colorectal cancer
    F. Thyroid cancer (e.g. anaplastic thyroid carcinoma, advanced papillary thyroid cancers with BRAF v600 mutation)
    G. Non-small cell lung cancer (NSCLC) with BRAF V600E mutation
    H. Hairy cell leukemia

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. Will not be used in combination with any other oncology therapy unless outlined below; **AND**
V. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
    - For treatment of melanoma: cobimetinib (Cotellic) will be used in combination with one of the following:
        i. Vemurafenib (Zelboraf) *only*; **OR**
        ii. Vemurafenib (Zelboraf) AND atezolizumab (Tecentriq) *only*; **OR**
    - For treatment of Erdheim-Chester disease: the request is for vemurafenib (Zelboraf) *only*

Supporting Evidence

I. **Advanced or Metastatic Melanoma**

A. As of January 2021, 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, 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. There is limited treatment option for Erdheim-Chester Disease (ECD). The use of vemurafenib (Zelboraf) in ECD was studied in a single-arm, open-label, and multiple cohort basket trial. 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
D. Solid tumors

E. Colorectal cancer
F. Thyroid cancer (e.g. anaplastic thyroid carcinoma, advanced papillary thyroid cancers with BRAF v600 mutation)
G. Non-small cell lung cancer (NSCLC) with BRAF V600E mutation
H. Hairy cell leukemia

References

1. Cotellic [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated January 2018. Accessed January 2021.
2. Tecentriq [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated December 2020. Accessed January 2021.
3. Zelboraf [Prescribing Information]. Genentech, Inc. South San Francisco, CA. Updated May 2020. Accessed January 2021.
4. National Comprehensive Cancer Network NCCN Guidelines: Melanoma: Cutaneous v1.2021. November 25, 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Accessed January 2021.
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6. Ascierto PA, McArthur GA, Dreno B et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2016;17:1248-1260. Available at: https://pubmed.ncbi.nlm.nih.gov/27480103/
7. Gutzmer R, Stroyakovskiy D, Gogas H et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced BRAFV600 mutation positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2020;395:1835-1844. Available at: https://pubmed.ncbi.nlm.nih.gov/32534646/

Policy Implementation/Update:

Action and Summary of Changes	Date
Cobimetinib (Cotellic) criteria transitioned to policy format. Consolidated cobimetinib (Cotellic) and vemurafenib (Zelboraf) criteria. Addition of E/I and supporting evidence section. Updated length of initial approval from three to six months. Addition of the following to initial criteria: age requirement (18+yrs); not to be used in combination with any other oncology therapy unless outlined in criteria; disease is unresectable/locally advanced (Stage IIIC) or metastatic (Stage IV); provider attestation to all the following: member has not previously received systemic anti-cancer therapy for melanoma (e.g., chemotherapy, radiation therapy, immunotherapy, hormonal therapy, biologic therapy), or if previously received immunotherapy, treatment was for use in the adjuvant setting only; additional combination agent option (atezolizumab [Tecentriq] and vemurafenib [Zelboraf]). Addition of the following to renewal criteria: member has received a previous prior authorization approval for this agent through this health; not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; medication prescribed by, or in consultation with, an oncologist; not to be used in combination with any other oncology therapy unless outlined in criteria. In consolidation, removed verbiage requiring BRAF V600E mutation "by an FDA-approved test" from vemurafenib (Zelboraf) criteria. Updated QL for vemurafenib (Zelboraf) to align with cobimetinib (Cotellic), from 240 tablets per 30 days to 224 tablets per 28 days.	01/2021
Policy created	02/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP107

Description

Continuous Glucose Monitors (CGMs) are blood glucose monitoring system used to manage in patients with diabetes mellitus that are insulin dependent.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Dexcom G6	System meter	Diabetes Mellitus	1 meter per 365 days
	Transmitter		1 transmitter per 90 days
	Sensors		3 sensors (1 kit) per 30 days
Freestyle Libre or Freestyle Libre 2	Reader		1 reader per 365 days
	Sensor (14 day)		2 sensors per 28 days
Medtronic Guardian Connect	Transmitter		1 transmitter per 365 days
	Sensor 3		5 sensors per 35 days

Initial Evaluation

I. **Dexcom** and **Freestyle Libre CGM products** may be considered medically necessary when the following criteria are met:
   A. Member is less than 19 years of age; **OR**
   B. Member is 20 years of age or older with diagnosis of one of the following:
      1. **Type I Diabetes**; **OR**
      2. **Type II Diabetes; AND**
         i. Unable to achieve 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
      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, hyper or hypoglycemic episodes) after previous trial of diet and/or oral medication.

II. **Medtronic CGM products** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(B) are met; **AND**
   B. Member uses an insulin pump not compatible with preferred Dexcom or Freestyle Libre CGM products (e.g Medtronic MiniMed); **OR**
   C. Use of Dexcom AND Freestyle Libre products has been ineffective, not tolerated, or not indicated

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. Based on the deliberations of key health outcomes, the Health Technology Clinical Committee (HTCC) decided that it had the most complete information for review at this time, which includes, a comprehensive and current evidence report, public comments, and state agency utilization information. This information was used by the HTCC to decide that the current evidence on Continuous glucose monitoring (CGM) is sufficient to make a determination on this topic. The HTCC discussed and voted on the evidence for use of continuous glucose monitoring compared to self-monitoring with conventional meters and other study methods (i.e. sham CGM). The HTCC considered the evidence and gave greatest weight to the evidence it determined, based on objective factors, to be the most valid and reliable.
II. The HTCC policy established utilized by Washington State Health Care Authorities can be found at: https://www.hca.wa.gov/assets/program/cgm-final-findings-decision-20180318.pdf
III. According to Dexcom, the G6 system is compatible with the t:slim X2™ Insulin Pump and Omnipod®.
IV. 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

1. American Diabetes Association (ADA) Standards of Medical Care in Diabetes, (2017).
2. Joslin Diabetes Center and Joslin Clinic Clinical guideline for adults with diabetes (2015, revised 2017).
3. Endocrine Society Clinical Practice Guideline Diabetes Technology—Continuous Subcutaneous Insulin Infusion Therapy and Continuous Glucose Monitoring in Adults: An Endocrine Society Clinical Practice Guideline, (2016).

4. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan, (2015). WA - Health Technology Assessment January 19, 2018 FINAL Continuous glucose monitoring: findings and decision Page 3 of 3
5. Endocrine Society Clinical Practice Guideline Diabetes and pregnancy, (2013).
6. Endocrine Society Clinical Practice Guideline Continuous Glucose Monitoring, (2011).
7. NICE National Clinical Guideline Centre, Integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system), (2016).
8. NICE National Clinical Guideline Centre Type 1 diabetes in adults: diagnosis and management, (2015).
9. National Collaborating Centre for Women and Children's Health Diabetes (Type 1 and Type 2) in children and young people: diagnosis and management, (2015).
10. National Collaborating Centre for Women and Children's Health Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period, (2015).
11. Wright et al, A Practical Approach to the Management of Continuous Glucose Monitoring (CGM) / Real-Time Flash Glucose Scanning (FGS) in Type 1 Diabetes Mellitus in Children and Young People under 18 Years, (2017).
12. Choudhary et al, Evidence-Informed Clinical Practice Recommendations for Treatment of Type 1 Diabetes Complicated by Problematic Hypoglycemia (2015).
13. Working Group of the Clinical Practice Guidelines on Diabetes Mellitus Type I: Clinical practice guidelines for diabetes type 1, (2012).The committee's determination is consistent with these guidelines.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	01/2021

corticotropin (Acthar®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP117

Description

Corticotropin (Acthar) is an injectable adrenocorticotropic hormone (ACTH) analogue that stimulates the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and other weak androgenic substances.

Length of Authorization

- Initial: One month
- Renewal: One month

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
corticotropin (Acthar)	400 Units/5mL	Infantile Spasms	4 vials/28 days

Initial Evaluation

I. Corticotropin (Acthar) 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. A diagnosis of one of **Infantile Spasms (West Syndrome)** when the following are met::
      1. Member is under 2 years of age; **AND**
      2. Must be used as monotherapy; **AND**
      3. Documentation that patient does not have a suspected congenital infection.

II. Corticotropin (Acthar) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for the following disorders and diseases:
   A. Exacerbation of Multiple Sclerosis
   B. Rheumatic Disorder: psoriatic arthritis; rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis
   C. Collagen Disease: systemic lupus erythematosus, systemic dermatomyositis (polymyositis)
   D. Dermatologic Disease: severe erythema multiforme, Stevens-Johnson syndrome
   E. Allergic states: serum sickness
   F. Ophthalmic Disease: keratitis; iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, anterior segment inflammation
   G. Respiratory Disease: symptomatic sarcoidosis
   H. Edematous state: nephrotic syndrome

III. Corticotropin (Acthar) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:

A. Uveitis
B. Prophylaxis of MS exacerbation
C. Adrenal insufficiency diagnosis
D. Rheumatoid Arthritis
E. Sarcoidodsis

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., complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle); **AND**

Supporting Evidence

I. The safety and efficacy of corticotropin (Acthar) in the setting of infantile spasm was studied in a single blinded (video EEG interpreter blinded), randomized, active control trial where patients were randomized to receive a two week course of treatment with corticotropin (Acthar) or prednisone. The primary efficacy outcome was a comparison of the number of patients in each group who were treatment responders. Treatment response was defined as a patient having a complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video EEG performed at two weeks following the treatment initiation. In the trial, 13 of 15 patients (86.7%) responded to corticotropin (Acthar) as compared to 4 of 14 patients (28.6%) who received prednisone ($p<0.002$).
II. Treatment guidelines for the exacerbation of MS recommend corticosteroid as the first choice of therapy, with other treatment options including: corticotropin (Acthar) or plasmapheresis.

Investigational or Not Medically Necessary Uses

I. Although the listed disorders and diseases (exacerbation of multiple sclerosis, rheumatic, collagen, dermatologic, allergic states, ophthalmic, respiratory, and edematous state) are labeled indications, at this time, corticotropin (Acthar) has not been shown to be effective due to limited data or potential safety concerns.
II. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for:
    A. Uveitis
    B. Prophylaxis of MS exacerbation
    C. Adrenal insufficiency diagnosis
    D. Rheumatoid Arthritis
    E. Sarcoidodsis

References

1. Acthar [Prescribing Information]. Bedminster, NJ: Mallinckrodt ARD LLC. March 2019.
2. National Multiple Sclerosis Society. Managing Relapses. Available at: https://www.nationalmssociety.org/Treating-MS/Managing-Relapses#section-2
3. Multiple Sclerosis Association of America. Treating Multiple Sclerosis Relapse. October 2017. Available at: https://mymsaa.org/ms-information/treatments/relapses/

Policy Implementation/Update:

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

Action and Summary of Changes	Date

Policy Type: PA/SP Pharmacy Coverage Policy: UMP118

Description

Cysteamine bitartrate (Cystagon; Procysbi) is a cystine-depleting agent that lowers cystine levels within cells.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
cysteamine (Cystagon)	50 mg capsule	Nephropathic cystinosis	60 capsules/30 days
	150 mg capsule		1.95 g/m^2/day
cysteamine (Procysbi)	25 mg DR capsule		60 capsules/30 days
	75 mg DR capsule		1.95 g/m^2/day
	75 mg DR granule packet		1.95 g/m^2/day
	300 mg DR granule packet		1.95 g/m^2/day

Initial Evaluation

I. Cysteamine bitartrate (Cystagon; Procysbi) may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of **nephropathic cystinosis** when the following are met:
      1. Diagnosis has been confirmed with <u>ONE</u> 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. **<u>If Procysbi is requested</u>**, 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 m^2 per day

II. Cysteamine bitartrate (Cystagon, Procysbi) is considered <u>investigational</u> 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 m^2 per day

Supporting Evidence

I. Cystinosis is a rare, multisystem genetic disorder caused by mutations within the CTNS gene on chromosome 17p13, which is characterized by the accumulation of cystine in different organs and tissues, increasing the potential for severe organ dysfunction. It is further classified into three forms known as 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

1. Cystagon [Prescribing Information]. Morgantown, WV: Mylan Pharmaceuticals Inc.; June 2018.
2. Procysbi [Prescribing Information]. Novato, CA: Raptor Pharmaceuticals, Inc.; December 2017.
3. UpToDate, Inc. Cystinosis. UpToDate [database online]. Waltham, MA. Last updated February 27, 2019 Available at: http://www.uptodate.com/home/index.html.
4. National Organization for Rare Disorders. Cystinosis. Available at: https://rarediseases.org/rare-diseases/cystinosis/

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of Procysbi granule packets	04/2020
Policy created	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP119

Description

Cysteamine (Cystaran; Cystadrops) is a cystine depleting ophthalmic solution agent indicated for the treatment of corneal cystine crystal accumulation in patients with cystinosis.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
cysteamine (Cystaran)	0.44% ophthalmic solution	Corneal cystine crystals	60 mL (4 bottles)/28 days
cysteamine (Cystadrops)	0.37% ophthalmic solution		20 mL (4 bottles)/28 days

Initial Evaluation

I. Cysteamine (Cystaran; Cystadrops) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an ophthalmologist; **AND**
   B. A diagnosis of **cystinosis** when the following are met:
      1. Diagnosis has been confirmed with ONE of the following:
         i. Presence of corneal cysteine accumulation; **OR**
         ii. CTNS gene analysis; **OR**
         iii. Elevated intracellular cystine levels (>1nmol cystine/mg protein)

II. Cysteamine (Cystaran; Cystadrops) is considered investigational when used for all other conditions.

Renewal Evaluation

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

Supporting Evidence

I. Cystinosis is a rare, multisystem genetic disorder characterized by the accumulation of cystine in various bodily organs and tissues leading to the potential for severe organ dysfunction. Cystinosis is further classified into three different forms, known as nephropathic cystinosis, intermediate cystinosis, and non-nephropathic (or ocular) cystinosis. Corneal cystine crystal accumulation may present in all three types.
II. Topical cysteamine is prescribed to prevent corneal deposits, as the oral formulation does not reach the cornea due to a lack of corneal vascularization.
III. The diagnosis of cystinosis is confirmed by elevated intraleukocyte cystine content, (i.e. measuring cystine levels in polymorphonuclear leukocytes), detection of CNTS gene mutation, or demonstration of cystine corneal crystals by the slit lamp examination.
IV. Per the package insert, each bottle of both Cystaran and Cystadrops lasts only 7 days after opening and the remaining contents should be discarded.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of cysteamine (Cystaran; Cystadrops) in any other condition.

References

1. Cystaran [Prescribing Information]. Gaithersburg, MD: Sigma Tau Pharmaceuticals; October 2012.
2. Cystadrops [Prescribing Information]. Lebanon, NJ: Recordati Rare Diseases Inc.; August 2020.
3. UpToDate, Inc. Cystinosis. UpToDate [database online]. Waltham, MA. Last updated February 27, 2019 Available at: http://www.uptodate.com/home/index.html.
4. National Organization for Rare Disorders. Cystinosis. Available at: https://rarediseases.org/rare-diseases/cystinosis/
5. Liang H, Labbé A, Le Mouhaër J, Plisson C, Baudouin C. A new viscous cysteamine eye drops treatment for ophthalmic cystinosis: an open-label randomized comparative phase iii pivotal study. Invest Ophthalmol Vis Sci. 2017;58(4):2275-2283.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new formulation, Cystadrops	01/2021
Policy created	11/2019

Cystic Fibrosis, CFTR Modulators

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP041

Description

Ivacaftor (Kalydeco) is an orally administered cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. Ivacaftor/lumacaftor (Orkambi) combines the potentiating mechanism of ivacaftor with lumacaftor which improves the conformational stability of F508del-CFTR. Ivacaftor/tezacaftor (Symdeko) includes tezacaftor, which is a CFTR modulator that acts as a CFTR corrector. Elexacaftor/tezacaftor/ivacaftor (Trikafta), adds an addition CFTR corrector with elexacaftor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

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

[a] Specific mutations listed below in policy criteria
[b] Based on clinical and/or *in vitro* assay data

Initial Evaluation

I. Agents listed in this policy may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   B. The medication is not used in combination with other agents in this policy (i.e., use of only one of the following at a given time: Kalydeco, Orkambi, Symdeko, Trikafta) (*please note: if a previous approval has been granted for one of these agents, and criteria is met for another, the previous PA approval will be discontinued)*; **AND**
   C. A diagnosis of **cystic fibrosis** when the following are met:
      1. For ivacaftor (Kalydeco):
         i. The member is 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: Ivacaftor PI
      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: Ivacaftor/Tezacaftor PI
      4. For elexacaftor/tezacaftor/ivacaftor (Trikafta):
         i. The member is 12 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: Elexacaftor/tezacaftor/Ivacaftor PI

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. 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.
VI. Ivacaftor (Kalydeco) has not been shown to have efficacy in those with the F508del mutation or any of the following: A46D, G85E, E92K, P205S, R334W, R347P, T338I, S492F, I507del, V520F, A559T, R560S, R560T, A561E, L927P, H1054D, G1061R, L1065P, R1066P, R1066C, R1066H, R1066M, L1077P, H1085R, M1101K, W1282X, N1303K.
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. The primary endpoint of change in FEV1 (4% vs 0% [3.1-4.8]; p<0.0001). Notable secondary outcomes included number of pulmonary exacerbations from baseline, absolute change in BMI from baseline, and change in CFQ-R Respiratory Domain Score from baseline. The change in number of pulmonary exacerbations was significantly reduced (0.65 [CI 0.48-0.88; p<0.0054).
- Trial 2 evaluated patients heterozygous for F508del and a second mutation predicted to be responsive to Ivacaftor/tezacaftor (Skydeko). Outcomes evaluated were similar to Trial 1. The change in FEV1 was 6.8 percentage point (CI 5.7-7.8; p<0.0001), while the change in CF-R Reparatory Domain Score was 11.1 points 9CI 8.7-13.6); p<0.0001).
- Trial 3 evaluated patients who were heterozygous for F508del mutation and a second mutation not predicted to be responsive to tezacaftor/Ivacaftor (Symdeko). The primary efficacy endpoint, a change in FEV1 compared to baseline, was 1.2 percentage points (CI -0.3-2.6), and was not significant. The study was terminated early.
- The efficacy of ivacaftor/tezacaftor (Symdeko) for patients 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 non responsive 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. 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.

XII. 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.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated *CFTR* gene mutation indications with new *in vitro data,* adding additional attestation and PI for verification to that mutation.	02/2021
Kalydeco age requirement updated to four months of age (previous six) based on updated FDA-approval.	10/2020
New FDA-approved therapy, Trikafta, added to the policy. Grammatical changes and formatting edits.	02/2020
Criteria combined, transitioned to policy format for all medications. Added new indication for Kalydeco for ages 6 months and older. Symdeko now approved down to six years of age.	06/2019
Criteria update: New indication for Orkambi, approved in CF patients two years of age and older. New approval in CF for patients between the ages of 12 and 24 months for Kalydeco, previously approved only for 24 months and older. Criteria added to not allow concomitant use.	09/2018
Updated criteria to new format, removed question assessing liver enzymes levels, added references, added question regarding combination therapy with other CFTR modulating medications. Symdeko criteria created.	05/2018
Criteria update: Excluded samples and updated renewal language to general improvement.	01/2016
Policy created	02/2012

dalfampridine ER (Ampyra®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP103

Description

Dalfampridine ER (Ampyra) is an orally administered broad-spectrum potassium channel blocker with an unknown mechanism of action for its therapeutic effect.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Dalfampridine ER (Ampyra)	10 mg tablets	Improve walking in patients with multiple sclerosis	60 tablets/30 days

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).

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

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Policy Implementation/Update:

Date Created	October 2011
Date Effective	October 2011
Last Updated	October 2019
Last Reviewed	05/2013, 01/2016, 11/2018, 10/2019

Action and Summary of Changes	**Date**
Transitioned criteria to policy	10/2019

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

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

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:
   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 brand abiraterone (Zytiga) plus prednisone OR brand abiraterone (Yonsa) plus methylprednisolone; **AND**
            a. The member has an intolerance or contraindication to generic abiraterone; **OR**
         iii. The request is for enzalutamide (Xtandi); **AND**
            a. The member has an intolerance or contraindication to generic abiraterone or 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; **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; **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;**
      i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
      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; **OR**
      iii. The request is for enzalutamide (Xtandi); **OR**
   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**

ii. The request is for enzalutamide (Xtandi) or apalutamide (Erleada); **OR**
iii. The request is for brand abiraterone (Zytiga); **AND**
    a. The member has had inadequate response, intolerance, or contraindication to generic abiraterone; **AND**
    b. Will be used in combination with prednisone

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).

VII. 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.

VIII. 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.*

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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of Grade Group referenced with Gleason Score	05/2021
Additional of newly approved enzalutamide (Xtandi) 40 mg and 80 mg tablets	11/2020
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	12/2019

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.	08/2019
Generic abiraterone requirement added prior to use of branded 250 mg.	12/2018
Enzalutamide new indication of non-metastatic resistant prostate cancer added. Clinical notes added and appropriate routing through criteria.	08/2018
Apalutamide (Erleada) criteria created	04/2018
Abiraterone new indication of metastatic, high-risk castration sensitive prostate cancer added. LATITUDE trial information incorporated as well.	02/2018
Enzalutamide (Xtandi) criteria created	02/2013
Abiraterone (Zytiga) criteria created	09/2011

Policy Type: PA/SP Pharmacy Coverage Policy: UMP016

Description

Dasatinib (Sprycel) is an orally administered tyrosine kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

dasatinib (Sprycel)	Indication	Quantity Limit	DDID
20 mg tablets	Philadelphia chromosome-positive (Ph+) Chronic myeloid leukemia (CML)/ Ph+ Acute lymphoblastic leukemia (ALL)	90 tablets/30 days	120505
50 mg tablets		30 tablets/30 days	120506
70 mg tablets		30 tablets/30 days	120504
80 mg tablets		30 tablets/30 days	163348
140 mg tablets		30 tablets/30 days	163349
100 mg tablets	Chronic phase CML	30 tablets/30 days	135944
70 mg tablets	Gastrointestinal Stromal Tumors (GIST)	60 tablets/30 days	120504

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 <u>pediatric</u> 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 historical control trial. Another TKI, Gleevec, was approved for this same patient population in 2013. There is no head to head study comparing Gleevec to Sprycel for Ph+ ALL in pediatric patients. NCCN guidelines recommend all tyrosine kinase inhibitors within the same 2a recommendation.

VI. Dasatinib (Sprycel) in the setting of newly diagnosed chronic phase CML in adults was approved based on the DASISION trial (NCT00481247) an open label, randomized trial comparing Sprycel to imatinib. The primary endpoint of rate of confirmed complete cytogenetic response (CCyR) within 12 months was achieved in 76.8% of Sprycel patients versus 66.2% of imatibib patients. After 60 months follow-up, median time to confirmed complete cytogenetic response was 3.1 months in 215 Sprycel responders and 5.8 months in 204 imatinib responders.

VII. Treatment of Ph+ CML in chronic phase in pediatric patients ≥1 year of age was evaluated in two pediatric studies: an open-label, non-randomized dose-ranging trial (NCT00306202) and an open label, non-randomized, single-arm trial (NCT00777036). With a median follow-up of 4.5 years in newly diagnosed patients, the median durations of CCyR, MCyR, and major molecular response (MMR) could not be estimated as more than half of the responding patients had not progressed at the time of data cut-off. With a median follow-up of 5.2 years in imatinib-resistant or -intolerant patients, the median durations of CCyR, MCyR, and MMR could not be estimated as more than half the responding patients had not progressed at the time of data cut-off.

VIII. In the setting of GIST, NCCN guidelines recommend following imatinib and sutinib, therapy with regorafenib (Cat 1). Regorafenib may then be followed by dasatinib (Sprycel) (Cat 2a). Dasatinib (Sprycel) is thus recommended as a fourth line agent in the setting of D842V mutation status.

Investigational or Not Medically Necessary Uses

I. Pancreatic Cancer Metastatic

   A. Sprycel is currently being evaluated for use in metastatic pancreatic cancer and is the subject of ongoing clinical trials. A phase 2 study of dasatinib (Sprycel) added to gemcitabine for subjects with locally-advanced pancreatic cancer (LAPC) was recently completed.

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Policy Implementation/Update:

Date Created	March 2017
Date Effective	March 2017
Last Updated	February 2019
Last Reviewed	01/2018, 02/2019

Action and Summary of Changes	Date
Updated to new format. Added new indication in pediatric patients with newly diagnosed Ph+ ALL. Added patient specific mutation assessment in the relapsed CML and ALL settings.	02/2019
Removed pregnancy question and adult only language as this is now approved for pediatric indications. Added regorafenib as an additional prior agent in GIST indication, as well as assessing patient specific mutation that received benefit in GIST in the salvage setting.	01/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP202

Description

Decitabine/cedazuridine (Inqovi) is an orally administered combination of DNA methylation inhibitor and cytidine deaminase inhibitor.

Length of Authorization

I. Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
decitabine/cedazuridine (Inqovi)	35/100 mg tablet	Myelodysplastic Syndrome (MDS); Chronic myelomonocytic leukemia (CMML)	5 tablets/28 days

Initial Evaluation

I. Decitabine/cedazuridine (Inqovi) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. Decitabine/cedazuridine (Inqovi) will be used as monotherapy; **AND**
   D. Provider attests that member's bone marrow blast count is less than (<) 20%; **AND**
   E. Member has a diagnosis of **Myelodysplastic syndrome (MDS)**; **AND**
      I. Member has one of the following French-American-British (FAB) subtypes of **myelodysplastic syndrome (MDS)**:
         a. Refractory anemia; **OR**
         b. Refractory anemia with ringed sideroblasts; **OR**
         c. Refractory anemia with excess blasts; **OR**
         d. Chronic myelomonocytic leukemia (CMML); **AND**
      II. Documentation of the members International Prognostic Score (IPSS) denoting whether the member has intermediate or high risk (e.g. IPSS Intermediate-1; Intermediate-2, or high risk); **AND**
      III. Treatment with IV azacitidine (Vidaza) OR IV decitabine (Dacogen) has been ineffective, contraindicated, or not tolerated

II. Decitabine/cedazuridine (Inqovi) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Acute myeloid leukemia (AML)

B. Lower risk myelodysplastic syndrome (e.g. IPSS low; IPSS-R Very low, low; WPSS very low, low)
C. Refractory anemia with del(5q) abnormality
D. Chronic myelogenous leukemia (CML)
E. Acute lymphoblastic leukemia (ALL)
F. Multiple myeloma (MM)
G. Ovarian cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited response to treatment defined by complete or partial response to treatment, disease stabilization, or achieving transfusion independence

Supporting Evidence

I. Decitabine/cedazuridine (Inqovi) is FDA-approved for use in patients aged 18 years and older. Decitabine/cedazuridine (Inqovi) is a combination of DNA methylation inhibitor and cytidine deaminase inhibitor, indicated for the treatment of MDS, including previously treated and untreated, de novo and secondary MDS, and CMML.
II. Myelodysplastic syndrome is a heterogeneous disease involving ineffective, dysplastic hematopoiesis leading to cytopenias, bleeding, infections, and in one-third of patients ultimately progressing to acute AML. CMML is a related hematopoietic condition involving peripheral blood monocytosis. MDS may be classified in to seven subtypes as per French-British-American (FAB) system. Decitabine/cedazuridine (Inqovi) received FDA-approved for four of the seven subtypes, namely: refractory anemia; refractory anemia with ringed sideroblasts; refractory anemia with excess blasts; and CMML**.** Additionally, approval of decitabine/cedazuridine (Inqovi) was limited to intermediate-1 (Int-1), Int-2, and high-risk MDS according to the IPSS classification.
III. Based on symptoms at presentation (fatigue, bone pain, frequent infections, and bleeding), MDS may be misdiagnosed as other conditions such as anemia, HIV infection, autoimmune disorder or osteomyelitis. Proper diagnosis and treatment of MDS requires histochemical and cytogenetic studies; therefore, decitabine/cedazuridine (Inqovi) must be prescribed by, or in consultation with an oncologist or hematologist.
IV. The only FDA-approved therapies for Int-1, Int-2, and high-risk MDS and CMML are IV administered hypomethylating agents (HMA): azacitidine (Vidaza) and decitabine (Dacogen). Lenalidomide (Revlimid) oral capsule also has FDA approval for treatment of MDS; however, use of this drug is limited to transfusion-dependent anemia in low-risk MDS with 5q deletion. Decitabine/cedazuridine (Inqovi) tablet is the first oral HMA and provides the advantage of self-

administration for patients. Decitabine/cedazuridine (Inqovi) may be considered an alternative first-line therapy option for MDS and CMML treatment.

V. Regimens involving combination of IV administered HMA (azacitidine and decitabine) with other agents such has ruxolitinib (Jakafi), and venetoclax (Venclexta) have been studied and recommended by NCCN guidelines in the settings of MDS, CMML, and AML. Limited low quality clinical data are also available with respect to combinations of IV HMA with lenalidomide (Revlimid), vorinostat (Zolinza), phenylbutyrate or valproic acid. However, efficacy and safety of decitabine/cedazuridine (Inqovi) in combination with other drugs for the treatment of MDS and CMML has not been studied and remains unknown. Additionally, decitabine/cedazuridine (Inqovi) has not received FDA-approval for any other indications (e.g. CLL, AML).

VI. Decitabine/cedazuridine (Inqovi) was studied in two (Phase 2 ASTX727-1-B trial, and Phase 3 ASCERTAIN), open-label, randomized, crossover trials in 222 patients with Int-1 or Int-2 or high risk MDS or CMML. Patients with de novo or secondary MDS or CMML were included. Additional inclusion criteria consisted of absence of secondary hematological malignancy and a bone marrow blast count of ≤ 20% (of note, a bone marrow blast count of >20% is a parameter used in differential diagnosis of AML versus MDS). One prior cycle of decitabine or azacitidine was allowed, but no other chemotherapy within two weeks before randomization was permitted.

VII. The primary efficacy outcome was pharmacokinetic (PK) measurement of five-day exposure of oral decitabine/cedazuridine (Inqovi) vs IV decitabine, using area under the curve (AUC) during first two cycles of treatment. Decitabine/cedazuridine (Inqovi) showed comparable PK data to that of IV decitabine during cycles one and two of the treatment. For Phase 3 (ASCERTAIN) study, five-day oral/IV decitabine exposure was 98.9% (90% CI; 92.7, 105.6). Additionally, overall response rates (ORR) were reported in 60% patients across all cohorts during Phase 2 trial, with 21% patients exhibiting complete response (CR) to decitabine/cedazuridine (Inqovi).

VIII. Safety data was pooled from both studies. Reported treatment emergent adverse events (TEAE) were similar between oral and IV decitabine patient populations with neutropenia, thrombocytopenia, leukopenia, anemia, pneumonia, and sepsis as the most common. Gastro-intestinal (GI) adverse reactions were comparable between oral and IV formulations of decitabine. Thirteen (6.1%) deaths were reported during treatment period, among which, 11 (5.2%) were associated to adverse events. Overall, 30-day mortality rate was 0.5%.

IX. Decitabine/cedazuridine (Inqovi) has not been compared with IV azacitidine (Vidaza) or IV decitabine (Dacogen) in head-to-head clinical trials. The majority of the safety and efficacy data for hypomethylating agents in the MDS treatment space are rooted in the trials for the IV therapies. Approval of decitabine/cedazuridine (Inqovi) was based off of comparative pharmacokinetic exposure to decitabine between oral and IV formulations. Although this trial showed comparable efficacy and safety, there is lack of data to show superiority of the oral decitabine/cedazuridine (Inqovi) over IV decitabine (Dacogen). Weighing the safety, efficacy, cost, and clinical experience, IV therapies are considered standard and appropriate high-value treatment options for MDS and CMML and are preferred over decitabine/cedazuridine (Inqovi).

Investigational or Not Medically Necessary Uses

I. Decitabine/cedazuridine (Inqovi) has not been sufficiently studied for safety and efficacy for any other condition to date.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP017

Description

Deferasirox (Exjade, Jadenu), and deferiprone (Ferriprox) are orally administered iron chelating agents.

Length of Authorization

- Initial: Three months
- Renewal: Six months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
deferasirox (generic Exjade)	125 mg tablet for suspension	Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome Hemosiderosis (chronic iron overload) – transfusion thalassemia	Non-transfusion thalassemia syndrome: Monthly quantity to allow for a maximum of 20 mg/kg per day Setting of transfusions: Monthly quantity to allow for a maximum of 40 mg/kg per day
	250 mg tablet for suspension		
	500 mg tablet for suspension		
deferasirox (Exjade)	125 mg tablet for suspension		
	250 mg tablet for suspension		
	500 mg tablet for suspension		
defirasirox (generic Jadenu)	90 mg tablet	Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome Hemosiderosis (chronic iron overload) – transfusion thalassemia	Non-transfusion thalassemia syndrome: Monthly quantity to allow for a maximum of 14 mg/kg per day Setting of transfusions: Monthly quantity to allow for a maximum of 28 mg/kg per day
	180 mg tablet		
	360 mg tablet		
deferasirox (Jadenu)	90 mg tablet		
	180 mg tablet		
	360 mg tablet		
	90 mg granule (sprinkle)		
	180 mg granule (sprinkle)		
	360 mg granule (sprinkle)		
deferiprone (Ferriprox)	100 mg/1 mL solution	Hemosiderosis (chronic iron overload) – transfusion thalassemia	Monthly quantity to allow for a maximum of 99 mg/kg per day
	500 mg tablet		
	1000 mg tablet		

Initial Evaluation

I. Deferasirox (Exjade, Jadenu), and deferiprone (Ferriprox) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in consultation with, a specialist (e.g., hematologist); **AND**
   B. Documentation of the members weight that has been measured in the past three months; **AND**
   C. A diagnosis of one of the following:
      1. **Chronic iron overload due to <u>non-transfusion</u> dependent thalassemia syndromes**; **AND**
         i. Member is ten years of age or older; **AND**
         ii. Documentation of a liver iron (Fe) concentration (LIC) of at least 5 mg per gram of dry weight; **AND**
         iii. Documentation serum ferritin levels are greater than 300 mcg/L; **AND**
         iv. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
            a. Brand Exjade or Jadenu is prescribed and **<u>both</u>** generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication) (deferiprone [Ferriprox] is not FDA-approved for this indication); **OR**
      2. **Chronic iron overload due to <u>blood transfusions</u>**; **AND**
         i. Member is two years of age or older if brand or generic deferasirox (Exjade) or deferasirox (Jadenu) are prescribed; **OR**
            a. Member is 18 years of age or older if deferiprone (Ferriprox) is prescribed; **AND**
         ii. Documentation is provided that the member has received transfusions that have resulted in consistent serum ferritin level greater than 1000 mcg/L; **AND**
         iii. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
            a. Brand Exjade, Jadenu, or deferiprone (Ferriprox) is prescribed and **<u>both</u>** generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication)

II. Deferasirox (Exjade), deferasirox (Jadenu) and deferiprone (Ferriprox) are considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. Plasmodium falciparum parasitemia

III. Deferasirox (Exjade), deferasirox (Jadenu) and deferiprone (Ferriprox) are considered investigational when used for all other conditions, including but not limited to:
   A. Hereditary hemochromatosis
   B. Porphyria cutanea tarda

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; 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 a specialist (e.g., hematologist); **AND**
IV. Documentation of the members weight that has been measured in the past three months; **AND**
   A. **Chronic iron overload due to non-transfusion dependent thalassemia syndromes**; **AND**
      1. Documentation of a serum ferritin levels are greater than 300 mcg/L; **AND**
      2. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed ; **OR**
         i. Brand Exjade or Jadenu is prescribed and **both** generic deferasirox (generic for Exjade) AND generic deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication) (deferiprone [Ferriprox] is not FDA-approved for this indication); **AND**
      3. A response to treatment, defined by a decline in serum ferritin level, has been documented; **OR**
   B. **Chronic iron overload due to blood transfusions**; **AND**
      a. Documentation that the member is continuing to receive transfusions resulting in serum ferritin levels consistently greater than 500 mcg/L; **AND**
      b. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
         i. Brand Exjade, Jadenu, or deferiprone (Ferriprox) is prescribed and **both** generic deferasirox (generic for Exjade) AND generic deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication); **AND**
      c. A response to treatment, defined by a decline in serum ferritin level, has been documented

Supporting Evidence

I. The agents listed in this policy are iron chelating agents indicated for chronic iron overload, but have not been shown to improve survival or disease-related symptoms. Of note, the products are not interchangeable on a dose basis. Deferiprone (Ferriprox) is an iron chelator indicated only for transfusional iron overload when other chelation therapy has been inadequate.
II. Per the package inserts for the medications listed in this policy, doses are based on weight. Safety and efficacy of the medications have been studied for FDA-approved weight based doses. Doses escalation beyond these limits has not been evaluated.

III. Clinical trials evaluated deferasirox (Exjade) and deferasirox (Jadenu) in patients 10 years of age or older for chronic iron overload due to non-transfusion dependent thalassemias, and for two years of age an older for iron overload due to blood transfusions. Deferiprone (Ferriprox) has not been evaluated for safety and efficacy in patients younger than 18 years of age.

IV. For iron overload not due to transfusion, deferasirox (Exjade) and deferasirox (Jadenu) were studied in patients with an LIC of at least 5 mg of iron per dry weight and a serum ferritin greater than 300 mcg/L. Levels of serum ferritin below 300 mcg/L are considered within normal range and would not meet medical necessity for dosing of iron overload treatment products.

V. For transfusion related iron overload, patient with a serum ferritin level greater than or equal to 1000 mcg/L will be considered for iron overload products. Upon renewal, patients with a serum ferritin level below 500 mcg/L will have therapy temporarily discontinued.

VI. As of December 2019, AB-rated generics for Exjade and Jadenu tablets were available on the market.

Investigational or Not Medically Necessary Uses

I. Plasmodium falciparum parasitemia
   A. In a prospective, double-blind, placebo-controlled trial, deferiprone was found to be clinically ineffective against plasmodium falciparum parasitemia.

II. Hereditary hemochromatosis and porphyria cutanea tarda
   A. Clinical trials are investigating iron overload agents in these settings.

References

1. Exjade [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May, 2018.
2. Jadenu [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May, 2018.
3. Ferriprox [Prescribing Information]. Toronto, Ontario, Canada. Apotex Inc. February, 2015.
4. Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in beta-thalassemia major. Blood. 2008;111(2):583-7.
5. Taher AT, Porter JB, Viprakasit V, et al. Deferasirox demonstrates a dose-dependent reduction in liver iron concentration and consistent efficacy across subgroups of non-transfusion-dependent thalassemia patients. Am J Hematol. 2013;88(6):503-6.
6. Vichinsky E, Onyekwere O, Porter J, et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. Br J Haematol. 2007;136(3):501-8.
7. Tricta F, Uetrecht J, Galanello R, et al. Deferiprone-induced agranulocytosis: 20 years of clinical observations. Am J Hematol. 2016;91(10):1026-31.

Policy Implementation/Update:

Date Created	May 2019
Date Effective	May 2019
Last Updated	December 2019
Last Reviewed	08/2013, 05/2019, 12/2019

Action and Summary of Changes	Date

Addition of generic Jadenu and new strength of deferiprone to the policy, with requirement to have trial and failure or contraindication, to both generic Exjade and Jadenu prior to payment consideration for brand products of this policy.	12/2019
Iron chelating agent policies combined, criteria added in regards to the following: weight documentation, ferritin level documentation, addition of a policy to Jadenu, specialist prescribing, additional of generic deferasirox (Exjade) tablet for oral suspension and step through this product. Transition to policy format.	05/2019

deflazacort (Emflaza™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP018

Description

Deflazacort (Emflaza) is an orally administered corticosteroid prodrug whose active metabolite exerts anti-inflammatory and immunosuppressive effects.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
deflazacort (Emflaza)	6 mg tablets	Duchenne Muscular Dystrophy	0.9 mg/kg/day (round to nearest tablet size)
	18 mg tablets		
	30 mg tablets		
	36 mg tablets		
	22.75 mg/mL oral suspension		

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 <u>investigational</u> when used for all other conditions, including, but <u>not limited to</u>:
   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

1. Emflaza [Prescribing Information]. Northbrook, IL: Marathon Pharmaceuticals. February 2017.
2. Gloss D, et al. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy. Neurology. 2016 Feb;86(5):465-72; DOI: 10.1212/WNL.0000000000002337
3. Griggs RC, et al. Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy. Neurology. 2016 Nov 15; 87(20): 2123-2131.
4. Matthews E, et al. Corticosteroids for the treatment of Duchenne muscular dystrophy. Cochrane Database Syst Rev. 2016 May 5;(5):CD003725.
5. Walter M, et al. Treatment of dysferlinopathy with deflazacort: a double-blind, placebo-controlled clinical trial. Ophanet Journal of Rare Diseases. 2013 Feb 14; 8(26):1750-1752.
6. Institute for Clinical and Economic Review. Draft Evidence Report – Deflazacort, Eteplirsen, and Golodirsen for DMD. July 2019; https://icer-review.org/topic/duchenne-muscular-dystrophy/
7. Darras B, Patterson MC, Firth HV, Dashe JF. Duchenne and Becker muscular dystrophy: Clinical features and diagnosis. Uptodate. https://www-uptodate-com. Updated February 13, 2020. Accessed May 5, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated initial approval duration to six months, and QLL box with weight-based dosing. Added requirement for neuromuscular specialist or neurologist. Included requirement for confirmation of diagnosis by genetic testing and addition of member weight to confirm dosing. Requires prednisone be tried and failed for six months to be deemed ineffective or have intolerance. Updated renewal criteria to include requirement for previous approval by Moda and not allowing establishing therapy with samples. Added examples of symptom improvement to renewal criteria.	05/2020

Revised to policy format, include use in pediatric patients down to two years of age.	07/2019
Update to criteria	01/2017
Criteria creation	05/2017

Diabetic Test Strips and Glucometer

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP165

Description

Test strips and glucometers are used to measure the concentration of glucose in the blood through a small blood draw sample from piercing the skin (typically on the finger).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Test Strips and Glucometers	Test Strips	Type 1 and type 2 diabetes mellitus	300 test strips/30 days
	Glucometers		One meter/365 days

Test Strips

Initial Evaluation

FreeStyle, FreeStyle Lite, FreeStyle InsuLinx, FreeStyle Precision Neo, Precision Xtra, Contour, and Contour Next are the preferred diabetic test strips.

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

I. **Non-preferred test strips** may be considered medically necessary when the following criteria below are met:
   A. Member is using one of the following quantity limits**:**
      1. 300 test strips per 30-day supply; **OR**
      2. Above 300 test strips per 30-day supply and there is documentation of medical necessity submitted for a quantity above 300 test strips per 30-day supply; **AND**
   B. Use of FreeStyle, FreeStyle Lite, FreeStyle InsuLinx, FreeStyle Precision Neo, Precision Xtra, Contour, and Contour Next has been ineffective, contraindicated, or not tolerated; **AND**
   C. There is documentation of medical necessity for a non-formulary glucometer and/or test strips that includes medical rationale and test strips previously tried
      Examples of medical necessity include:
      1. Member uses test strips with a glucometer built into, or communicates with, an insulin pump and preferred products cannot be utilized; **OR**
      2. Member uses a voice meter due to vision impairment

Glucometers

Initial Evaluation

FreeStyle Lite, FreeStyle Freedom Lite, Contour Next, Contour Next EZ, and Contour Next One are covered at zero cost share to the member only through the manufacturer's Free Meter Program. Members can access their free meter by using any of the options below:

- **By Pharmacy:**
  - Ascensia:
    BIN: 018844
    PCN: 3F
    Group: MGDCARE
    ID: CNMC7246982
  - Abbott:
    BIN: 610020
    PCN: PDMI
    GROUP: 99992432
    MedImpact ID: ERXMEDPERFORM
    Navitus 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: ContourNextFreeMeter.com, use offer code BDC-MOD
  - 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:

Action and Summary of Changes	Date
Separated out non-preferred glucometers and test strips criteria. Added in box regarding billing preferred glucometers. Updated Renewal language to run through initial each time.	01/2021
Updated requirements language to be more consistent with plan's standard language. Adjusted order of requirements to enhance clarity.	12/2020
Criteria transitioned into policy with medically not necessary and renewal evaluation sections added.	01/2020
Criteria created	01/2016

dichlorphenamide (Keveyis®)

UMP POLICY

Uniform Medical Plan

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

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 patients with periodic paralysis is unknown.

Length of Authorization

- Initial: Two months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
dichlorphenamide (Keveyis)	50 mg tablets	Primary periodic paralysis	120 tablets/30 days

Initial Evaluation

I. Dichlorphenamide (Keveyis) may be considered medically necessary when the following criteria below 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. A diagnosis of **periodic paralysis** when the following are met:
      1. Treatment with acetazolamide has been ineffective, contraindicated, or not tolerated.

II. Dichlorphenamide (Keveyis) is considered <u>investigational</u> 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 (e.g. reduced frequency or severity of paralytic attacks)

Supporting Evidence

I. Periodic paralysis is a rare neuromuscular disorder related to a defect in muscle ion channels. It is classified as hypokalemic when episodes occur with low potassium levels and hyperkalemic when occurring with high. It is characterized by episodes of painless muscle paralysis, which may be precipitated by heavy exercise, fasting, or high-carbohydrate meals. Attacks may last minutes, hours, or days causing increased morbidity and impaired quality of life. Primary periodic paralyses include hypokalemic paralysis (HypoPP), hyperkalemic paralysis (HyperPP), and Andersen-Tawil syndrome. To prevent attacks, various methods are used including dietary modification, avoidance of triggers, potassium supplementation, and using carbonic anhydrase inhibitors.

II. Keveyis is indicated for the treatment of primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants.

III. Carbonic anhydrase inhibitors, particularly acetazolamide and dichlorphenamide, have been used for almost 50 years as empiric treatment for both HypoPP and HyperPP. There are no comparative studies between acetazolamide and dichlorphenamide to suggest greater safety or efficacy in one agent over another.

IV. Per the package insert: Primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants are a heterogeneous group of conditions for which the response to KEVEYIS may vary. Therefore, prescribers should evaluate patient response to KEVEYIS after 2 months of treatment to determine whether KEVEYIS should be continued.

V. Withdrawal from the study due to the acute and severe worsening of symptoms, for example, an increase in attack frequency or severity, was also assessed as an endpoint in clinical studies. Acute, intolerable worsening of condition was observed in 2/42 patients on KEVEYIS.

Investigational or Not Medically Necessary Uses

I. Dichlorphenamide (Keveyis) has not been sufficiently evaluated outside of primary periodic paralysis.

References

1. Keveyis [Prescribing Information]. Hawthorne, NY: Taro Pharmaceuticals; November 2019.
2. UpToDate, Inc. Hypokalemic periodic paralysis. UpToDate [database online]. Waltham, MA. Last updated October 25, 2018 Available at: http://www.uptodate.com/home/index.html.
3. UpToDate, Inc. Hypokalemic periodic paralysis. UpToDate [database online]. Waltham, MA. Last updated March 08, 2019 Available at: http://www.uptodate.com/home/index.html.
4. Statland JM, Fontaine B, Hanna MG, et al. Review of the Diagnosis and Treatment of Periodic Paralysis. Muscle Nerve. 2018;57(4):522-530.

Policy Implementation/Update:

Date Created	September 2015
Date Effective	September 2015
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format. Updated initial and renewal durations as response should be seen within two months of therapy. Addition of specialist requirements. Addition of renewal criteria.	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP104

Description

Dornase alfa (Pulmozyme®) inhalation solution is highly purified solution of recombinant human deoxyribonuclease I (rhDNase), an enzyme which selectively cleaves DNA. In vitro, dornase alfa (Pulmozyme) hydrolyzes the DNA in sputum of cystic fibrosis (CF) patients and reduces sputum viscoelasticity.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
dornase alfa (Pulmozyme)	2.5 mg/2.5 mL single-use ampule	Cystic fibrosis	30 single-use ampule/ 30 days

Initial Evaluation

I. Dornase alfa (Pulmozyme) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by or in consultation with a pulmonologist; **AND**
   B. A diagnosis of **cystic fibrosis (CF); AND**
   C. Medication will be used in conjunction with standard CF therapy [e.g. tobramycin (Bethkis®; Kitabis Pak®; Tobi®; Tobi Podhaler®), azithromycin (Zithromax®), aztreonam (Cayston®), ivacaftor (Kalydeco®), lumacaftor/ivacaftor (Orkambi®), inhaled or oral N-acetylcysteine (Acetadote®, Acys-5®, Mucomyst®, Cetylev®)]

II. Dornase alfa (Pulmozyme) is considered <u>investigational</u> when used for all other conditions.

Renewal Evaluation

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

Supporting Evidence

I. Dornase alfa (Pulmozyme) has been evaluated in a randomized, placebo-controlled trial of clinically stable CF patients, five years of age and older and receiving standard therapies for CF. Patients were treated with placebo, 2.5 mg of dornase alfa (Pulmozyme) once a day, or 2.5 mg of dornase alfa (Pulmozyme) twice a day for six months.

II. Administration of dornase alfa (Pulmozyme) reduced the risk of all exacerbations of respiratory symptoms requiring parenteral antibiotic therapy and developing any respiratory tract infection by 27% and 29% for the 2.5 mg daily dose and the 2.5 mg twice daily dose. Data suggests that the effects on respiratory tract infections in older patients (> 21 years) may be lower than in younger patients, and that twice daily dosing may be required in the older patients.

III. While clinical trial data is limited in pediatric patients younger than five years of age, the use of dornase alfa (Pulmozyme) should be considered for pediatric CF patients who may experience potential benefit in pulmonary function or who may be at risk of respiratory tract infection.

IV. Dornase alfa (Pulmozyme) is used in treatment of CF; however, due to the complexity of the disease it should be prescribed by, or in consultation with, a pulmonologist experienced in the treatment of CF.

V. Several methods of newborn screening may be implemented to detect potential CF, such as the immunoreactivity trypsinogen test (IRT), double IRT testing, and pancreatitis-associated protein testing. A positive or equivocal screening test should be followed by CFTR genetic testing and the sweat chloride test.

VI. Dornase alfa (Pulmozyme) is indicated as an adjunct to standard CF therapies [e.g. tobramycin (Bethkis; Kitabis Pak; Tobi; Tobi Podhaler), azithromycin (Zithromax), aztreonam (Cayston), ivacaftor (Kalydeco), lumacaftor/ivacaftor (Orkambi), inhaled or oral N-acetylcysteine (Acetadote, Acys-5, Mucomyst, Cetylev), ipratropium Bromide (Atrovent HFA)].

VII. The recommended dosage is one 2.5 mg single-use ampule inhaled once daily using a recommended nebulizer. Some patients may benefit from twice daily administration. Maximum dose upon clinical review is 60 single-use ampule per 30 days.

Investigational or Not Medically Necessary Uses

There is limited or no evidence to support the use of dornase alfa (Pulmozyme) in conditions other than CF.

References

1. Pulmozyme [package insert]. Genetech, Inc. South San Francisco, CA. December 2014.
2. DeSimone, E. (2018, May 18). Cystic Fibrosis: Update on Treatment Guidelines and New Recommendations. Retrieved from https://www.uspharmacist.com/article/cystic-fibrosis-update-on-treatment-guidelines-and-new-recommendations
3. Fuchs, H. J., Borowitz, D. S., Christiansen, D. H., Morris, E. M., Nash, M. L., Ramsey, B. W., Wohl, M. E. (1994). Effect of Aerosolized Recombinant Human DNase on Exacerbations of Respiratory Symptoms and on Pulmonary Function in Patients with Cystic Fibrosis. New England Journal of Medicine, 331(10), 637–642. doi: 0.1056/nejm199409083311003
4. Mccoy, K., Hamilton, S., & Johnson, C. (1996). Effects of 12-Week Administration of Dornase Alfa in Patients with Advanced Cystic Fibrosis Lung Disease. Chest, 110(4), 889–895. doi: 10.1378/chest.110.4.889

Policy Implementation/Update:

Date Created	10/6/2017
Date Effective	10/6/2017
Last Updated	11/15/2019
Last Reviewed	11/15/2019

Action and Summary of Changes	**Date**
Updated criteria to policy format	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP122

Description

Droxidopa (Northera®) is an orally administered synthetic amino acid analog that is metabolized to a norepinephrine by the enzyme aromatic L-amino acid decarboxylase (dopa-decarboxylase). Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
droxidopa (Northera)	100 mg capsules	neurogenic orthostatic hypotension (nOH)	90 capsules /30 days
	200 mg capsules		180 capsules /30 days
	300 mg capsules		180 capsules/30 days

Initial Evaluation

Generic droxidopa is the preferred agent.
- There is no prior authorization required for generic droxidopa, unless requesting above the quantity limit noted above.

I. Brand droxidopa (Northera) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist or cardiologist; **AND**
   C. A diagnosis of **neurogenic orthostatic hypotension (nOH)** when the following are met:
      1. Member is experiencing one of the following symptoms:
         i. orthostatic dizziness
         ii. light-headedness
         iii. syncope; **AND**
      2. Member has an additional diagnosis of:
         i. Primary autonomic failure (Parkinson disease, multiple system atrophy, or pure autonomic failure); **OR**
         ii. Dopamine beta-hydroxylase deficiency; **OR**
         iii. Non-diabetic autonomic neuropathy; **AND**
      3. Member has attempted at least one non-pharmacologic intervention (e.g., use of compression stockings/abdominal binder, increasing salt and fluid intake, regular exercise, or discontinuation or reduction of antihypertensive medications); **AND**

4. Treatment with at least one standard therapy (e.g., dihydroergotamine, ephedrine, fludrocortisone, midodrine) for symptomatic nOH has been ineffective, contraindicated, or not tolerated; **AND**
5. Documentation of contraindication or intolerance to generic droxidopa oral capsule (e.g., allergy to an excipient).

II. Droxidopa (Northera) is considered investigational when used for all other conditions.

Renewal Evaluation

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

Supporting Evidence

I. There is a lack of scientific evidence from clinical trials to show safety and efficacy for the use of droxidopa (Northera) in pediatric patients.
II. Neurogenic orthostatic hypotension (nOH) is a fall in blood pressure upon standing as a result of reduced norepinephrine release from sympathetic nerve terminals. nOH is a feature of several neurological disorders that affect the autonomic nervous system, most notably in Parkinson's disease (PD), multiple system atrophy, pure autonomic failure, and other autonomic neuropathies. Droxidopa (Northera) is a prodrug, which is converted to norepinephrine, increases BP, and improves symptoms of nOH. Due to the complexity and association with progressive neurodegenerative disorders, droxidopa (Northera) needs to be prescribed by, or in consultation with, a neurologist or cardiologist.
III. Orthostatic hypotension (OH), a fall in blood pressure (BP) upon standing not due to reduced norepinephrine release, is a very common problem, particularly in the frail elderly. It is the result of a variety of medical conditions, such as intravascular volume depletion, severe anemia, use of antihypertensive therapies, and physical deconditioning. It usually resolves after the underlying cause is treated. nOH, in contrast, is a much less common and chronic condition. nOH is the result of a failure to increase sympathetic vasomotor nerve outflow and an inability to raise peripheral vascular resistance on standing. nOH is a feature of several neurological disorders that affect autonomic neurons. These include neurodegenerative diseases associated with the abnormal deposition of the protein α-synuclein (i.e., synucleinopathies such as Parkinson disease), other peripheral neuropathies, high spinal cord injury, and a handful of rare genetic diseases.
IV. Droxidopa (Northera) is indicated for the treatment of orthostatic dizziness, lightheadedness, or syncope in adult patients with symptomatic nOH caused by primary autonomic failure

(Parkinson's disease [PD], multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.

V. Consensus guidelines for the treatment of nOH are lacking, although there are expert reviews, there are currently no long-term studies showing the impact of treatment on survival, falls, or quality of life. Up to 70% patients with nOH also have supine hypertension, which poses a therapeutic challenge as increasing BP in the upright position can worsen hypertension when supine. Therefore, treatment of nOH requires careful consideration of the potential risks and benefits. The goal of treatment is to reduce symptom burden, prolong standing time, and improve physical capabilities. The steps in management include removing aggravating factors (drug-induced hypotension, anemia, dehydration, prolonged bed rest and physical deconditioning), implementing non-pharmacological measures (physical counter maneuvers, life-style changes, volume expansion, acute drinking of water, sleep with the head of the bed raised, compression stockings, small frequent meals), and pharmacological approaches; while the other methods are effective, many patients with nOH still require pharmacological treatment to raise BP. This is achieved with two strategies: Expanding intravascular volume and increasing peripheral vascular resistance. Medications used for the treatment of nOH consist of the following: dihydroergotamine, ephedrine, fludrocortisone, midodrine, erythropoietin, atomoxetine, pyridostigmine, and droxidopa (Northera).

VI. No sufficient evidence was found to show superiority of one agent over the other.

VII. Classic symptoms of nOH include lightheadedness, dizziness or feeling close to fainting, and when the fall in BP is severe enough: loss of consciousness. In contrast to vasovagal (neurally-mediated) syncope, syncope in nOH occurs without signs of autonomic activation such as sweating, tachycardia, nausea or abdominal discomfort. After syncope, patients with nOH recover quickly and may be unaware of the event. Patients report that symptom severity varies day-to-day and fluctuates throughout the day. Mornings tend to be most difficult as symptoms are aggravated by intravascular volume loss overnight. Meals, particularly carbohydrate-rich, produce splanchnic vasodilatation and post-prandial hypotension (i.e., fall in BP within 2 hours of eating). Physical inactivity and cardiovascular deconditioning are common in patients with nOH, and, as a result, worsens the symptom severity creating a vicious cycle.

Investigational or Not Medically Necessary Uses

There is limited or no evidence to support the use of droxidopa (Northera) in conditions other than nOH.

References

1. Northera (droxidopa) [prescribing information]. Lundbeck NA Ltd. Deerfield (IL). Updated July 2019. Accessed March 2021.
2. droxidopa. In: Lexi-Drugs Online. Hudson (OH):Lexi-Comp; 1978-2014 [cited 2014 October]. Available from http://online.lexi.com/ with subscription
3. Horacio Kaufmann, MD, Lucy Norcliffe-Kaufmann, PhD, and Jose-Alberto Palma, MD PhD (2015). Droxidopa in neurogenic orthostatic hypotension. Expert Review of Cardiovascular Therapy, 13(8), 875–891. Doi: 10.1586/14779072.2015.1057504. PMID: 26092297 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4509799/

4. Shibao C, Lipsitz LA, Biaggioni I. ASH position paper: evaluation and treatment of orthostatic hypotension. J. Clin. Hypertens. (Greenwich) 2013;15(3):147–153. PMID: 23458585

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated initial and renewal criteria to direct to generic	04/2021
Updated criteria to policy format; Added age limit, added attempted at least one non-pharmacologic intervention criteria	11/2019
Policy created	11/2014

Uniform Medical Plan

dupilumab (Dupixent®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

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: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
dupilimab (Dupixent)	200 mg/1.14mL prefilled syringe	Asthma (moderate to severe)	**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)	**Adult:** **First Month:** 4 (300mg) syringes/pens (8 mL)/28 days **Maintenance:** 2 (300mg) syringes/pens (4 mL)/28 days
			Pediatric: **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 • **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
	300 mg/2mL pen injector or prefilled syringe		
		Chronic rhinosinusitis with nasal polyposis	2 (300mg) syringes/pens (4 mL)/28 days

Initial Evaluation

I. Dupilumab (Dupixent) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); **AND**
   B. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, mepolizumab, omalizumab, reslizumab, etc.); **AND**
   C. A diagnosis of one of the following:
      1. **Atopic dermatitis (moderate to severe)**; **AND**
         i. Member is six years of age or older; **AND**
            a. Body surface area (BSA) involvement of at least 10%; **OR**
               i. Involves areas of the face, head, neck, hands, feet, groin, or intertriginous areas require documentation of severity; **AND**
         ii. Treatment with at least two of the following groups has been ineffective or not tolerated, unless ALL are contraindicated.
            a. Group 1: Topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
            b. Group 2: Topical calcineurin inhibitors (e.g. pimecrolimus cream, tacrolimus ointment)
            c. Group 3: Topical PDE-4 inhibitors (e.g. crisaborole [Eucrisa]); **OR**
      2. **Asthma (moderate to severe)**; **AND**
         i. Member is 12 years of age or older; **AND**
         ii. Member has **MODERATE** asthma as defined by one of the following:
            a. Daily symptoms
            b. Nighttime awakenings > 1x/week but not nightly
            c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs daily
            d. Some limitation to normal activities
            e. Lung function (percent predicted FEV1) >60%, but <80%
            f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to mild asthma; **OR**
         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**

c. Member has at least <u>one</u> of the following symptoms:

i. Nasal discharge

ii. Facial pain or pressure

iii. Reduction or loss of smell; **AND**

iii. Documentation of current persistent symptomatic nasal polyps despite maximal treatment with ALL of the following, unless ineffective, not tolerated, or contraindicated:

a. Intranasal corticosteroid; **AND**

b. Oral systemic corticosteroid therapy within the last 12 months; **AND**

iv. Background intranasal corticosteroid (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of Dupixent, unless contraindicated.

II. Dupilumab (Dupixent) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:

A. Pediatric (six to 11 years of age) asthma
B. Pediatric (six months to five years of age) atopic dermatitis
C. Eosinophilic esophagitis
D. Chronic obstructive pulmonary disease (COPD)
E. Food and environmental allergies

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**
      1. 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**
   C. **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.

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 years 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.

	Trial 1		Trial 2		Trial 3		Trial 4	
	DUPIXENT 300 mg Q2W N=224	PBO N=224	DUPIXENT 300 mg Q2W N=233	PBO N=236	DUPIXENT 300 mg Q2W + TCS N=106	PBO + TCS N=315	DUPIXENT 200 mg (<60 kg) or 300 mg (>60 kg) Q2W N=82	PBO N=85
% of patients with IGA 0 or 1	38%	10%	36%	9%	39%	12%	24%	2%
% of patients with EASI-75	51%	15%	44%	12%	69%	23%	42%	8%

- For patients aged 6 to 11 years, dupilumab (Dupixent) approval was based on the results from a 16-week, phase III, double-blind, placebo-controlled trial. Investigators enrolled pediatric patients who have had a previous inadequate response to a topical medication with a PGA score of four (scale of zero to four) and a minimum BSA involvement of ≥15%. Patients in both dupilumab arms achieved statistically significant improvements when compared to the placebo arm, see table below for details.

	<30 kg			≥30 kg		
	PBO + TCS n=61	Q4W + TCS n=61	Q2W + TCS n=63	PBO + TCS n=62	Q4W + TCS n=61	Q2W + TCS n=59
% of patients with IGA 0 or 1	13.1%	29.5% p<0.05	20.6%	9.7%	36.1% p<0.001	39% p<0.001
% of patients with EASI-75	27.9%	75.4% p<0.0001	60.3% p<0.001	25.8%	63.9% p<0.0001	74.6% p<0.0001

- 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, 300mg, or placebo, which were 25.9%, 25.8%, and 10.2%, respectively. Mean difference compared to placebo for the 200 mg and 300 mg were 0.26 (95% CI 0.11, 0.4) and 0.21 (95% CI 0.06, 0.36), respectively.

ii. Trial 2: Patients enrolled were at least 12 years of age with moderate to severe asthma on a medium to high-dose ICS and a minimum of one and up to two additional controller medications. Patients were randomized to receive either dupilumab (Dupixent) 200 mg or 300 mg every 2 weeks following initial dose of 400 mg, 600 mg, or placebo. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo-controlled period receiving 200 mg vs placebo or 300 mg vs placebo, which were RR 0.52 (95% CI 0.41, 0.66) and RR 0.54 (95% CI 0.43, 0.68), respectively, and change from baseline in FEV1 at Week 12 receiving 200 mg vs placebo or 300mg vs placebo, which were 29% vs 15.9% and 32.5% vs 14.4%. Mean difference compared to placebo for the 200 mg and 300 mg were 0.21 (95% CI 0.13, 0.29) and 0.24 (95% CI 0.16, 0.32), respectively.

iii. Trial 3: Patients enrolled were at least 12 years of age with asthma who required daily OCS in addition to regular use of high-dose ICS plus an additional controller. Patients were randomized to receive either dupilumab (Dupixent) 300 mg or placebo every 2 weeks for 24 weeks following an initial dose of 600 mg or placebo. Patients continued existing asthma therapy during the trial; OCS dose was reduced every 4 weeks during the OCS reduction phase (Weeks 4 to 20) as long as asthma control was maintained. The primary endpoint was the percent of reduction from baseline of the final oral corticosteroid dose at week 24 while maintaining asthma control in those receiving either 300 mg or placebo, which was 90% (95% CI 60%, 80%) vs 42% (95% CI 33%, 51%), respectively.

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

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 fuorate nasal spray (MFNS) and compared to placebo injection plus MFNS. In both trials, there were two co-primary endpoints, improvement in nasal congestion/obstruction severity and reduction in nasal polyps. At 24 weeks, patients in the dupilumab (Dupixent) arm achieved statistically significant improvements when compared to the placebo arm.
    i. Fifty-seven percent and 51% improvement in their nasal congestion/obstruction severity compared to a 19% and 15% improvement with placebo in SINUS-24 and SINUS-52, respectively.
    ii. Thirty-three percent and 27% reduction in their nasal polyps score compared to a 7% and 4% increase with placebo in SINUS-24 and SINUS-52, respectively.
- The American Academy of Allergy, Asthma, and Immunology (AAAAI), American College of Allergy, Asthma, and Immunology (ACAAI), and Joint Council of Allergy, Asthma, and Immunology (JCAAI) 2014 guidelines recommend short-term treatment with oral steroids in patients with CRSwNP "because it decreases nasal polyp size and symptoms". Additionally, guidelines recommend both intranasal corticosteroids and omalizumab for treatment of CRSwNP.

Investigational or Not Medically Necessary Uses

I. Dupilumab (Dupixent) is and has been studied in a variety of other conditions, there is currently insufficient evidence to support the use of dupilumab (Dupixent) outside of the FDA approved indications.

Appendix

I. Table 1: Topical Corticosteroid Potency Chart[12]

Potency Group	Corticosteroid	Vehicle type/form	Brand names	Available strength(s), percent (except as noted)
Super-high potency (Group 1)	Betamethasone dipropionate, augmented	Gel, lotion, ointment (optimized)	Diprolene	0.05
	Clobetasol propionate	Cream, gel, ointment, solution (scalp)	Temovate	0.05
		Cream, emollient base	Temovate E	0.05
		Lotion, shampoo, spray aerosol	Clobex	0.05
		Foam aerosol	Olux-E, Tovet	0.05
		Solution (scalp)	Cormax	0.05

	Fluocinonide	Cream	Vanos	0.1
	Flurandrenolide	Tape (roll)	Cordran	4 mcg/cm2
	Halobetasol propionate	Cream, lotion, ointment	Ultravate	0.05
High potency (Group 2)	Amcinonide	Ointment	Cyclocort¶, Amcort¶	0.1
	Betamethasone dipropionate	Ointment	Diprosone¶	0.05
		Cream, augmented formulation (AF)	Diprolene AF	0.05
	Clobetasol propionate	Cream	Impoyz	0.025
	Desoximetasone	Cream, ointment, spray	Topicort	0.25
		Gel	Topicort	0.05
	Diflorasone diacetate	Ointment	ApexiCon¶, Florone¶	0.05
		Cream, emollient	ApexiCon E	0.05
	Fluocinonide	Cream, gel, ointment, solution	Lidex¶	0.05
	Halcinonide	Cream, ointment, solution	Halog	0.1
	Halobetasol propionate	Lotion	Bryhali	0.01
High potency (Group 3)	Amcinonide	Cream	Cyclocort¶, Amcort¶	0.1
		Lotion	Amcort¶	0.1
	Betamethasone dipropionate	Cream, hydrophilic emollient	Diprosone¶	0.05
	Betamethasone valerate	Ointment	Valisone¶	0.1
		Foam	Luxiq	0.12
	Desoximetasone	Cream	Topicort LP¶	0.05
	Diflorasone diacetate	Cream	Florone¶	0.05
	Diflucortolone valerate (not available in United States)	Cream, oily cream, ointment	Nerisone (Canada, United Kingdom, others)	0.1
	Fluocinonide	Cream aqueous emollient	Lidex-E¶	0.05
	Fluticasone propionate	Ointment	Cutivate	0.005
	Mometasone furoate	Ointment	Elocon	0.1
	Triamcinolone acetonide	Cream, ointment	Aristocort HP¶, Kenalog¶, Triderm	0.5
Medium potency (Group 4)	Betamethasone dipropionate	Spray	Sernivo	0.05
	Clocortolone pivalate	Cream	Cloderm	0.1
	Fluocinolone acetonide	Ointment	Synalar¶	0.025
	Flurandrenolide	Ointment	Cordran	0.05
	Hydrocortisone valerate	Ointment	Westcort	0.2
	Mometasone furoate	Cream, lotion, ointment, solution	Elocon¶	0.1
	Triamcinolone acetonide	Cream	Kenalog¶, Triderm	0.1

		Ointment	Kenalog¶	0.1
		Ointment	Trianex	0.05
		Aerosol spray	Kenalog	0.2 mg per 2 second spray
		Dental paste	Oralone	0.1
Lower-mid potency (Group 5)	Betamethasone dipropionate	Lotion	Diprosone¶	0.05
	Betamethasone valerate	Cream	Beta-Val, Valisone¶	0.1
	Desonide	Ointment	DesOwen, Tridesilon¶	0.05
		Gel	Desonate	0.05
	Fluocinolone acetonide	Cream	Synalar¶	0.025
	Flurandrenolide	Cream, lotion	Cordran	0.05
	Fluticasone propionate	Cream, lotion	Cutivate	0.05
	Hydrocortisone butyrate	Cream, lotion, ointment, solution	Locoid, Locoid Lipocream	0.1
	Hydrocortisone probutate	Cream	Pandel	0.1
	Hydrocortisone valerate	Cream	Westcort¶	0.2
	Prednicarbate	Cream (emollient), ointment	Dermatop	0.1
	Triamcinolone acetonide	Lotion	Kenalog¶	0.1
		Ointment	Kenalog¶	0.025
Low potency (Group 6)	Alclometasone dipropionate	Cream, ointment	Aclovate	0.05
	Betamethasone valerate	Lotion	Beta-Val¶, Valisone¶	0.1
	Desonide	Cream	DesOwen, Tridesilon¶	0.05
		Lotion	DesOwen, LoKara	0.05
		Foam	Verdeso	0.05
	Fluocinolone acetonide	Cream, solution	Synalar¶	0.01
		Shampoo	Capex	0.01
		Oil (48% refined peanut oil)	Derma-Smoothe/FS Body, Derma-Smoothe/FS Scalp	0.01
	Triamcinolone acetonide	Cream, lotion	Kenalog¶, Aristocort¶	0.025
Least potent (Group 7)	Hydrocortisone (base, ≥2%)	Cream, ointment	Hytone, Nutracort¶	2.5
		Lotion	Hytone, Ala Scalp, Scalacort	2
		Solution	Texacort	2.5
	Hydrocortisone (base, <2%)	Ointment	Cortaid, Cortizone 10, Hytone, Nutracort	1
		Cream	Cortaid¶, Cortizone 10, Hytone, Synacort	1
		Gel	Cortizone 10	1
		Lotion	Aquanil HC, Sarnol-HC,	1

		Spray	Cortaid	1
		Solution	Cortaid, Noble, Scalp Relief	1
		Cream, ointment	Cortaid	0.5
	Hydrocortisone acetate	Cream	MiCort-HC	2.5
		Lotion	Nucort	2

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

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated Policy. Atopic dermatitis: combined pediatric and adolescent/adult criteria; updated BSA criterion and Group 1 corticosteroids. Asthma: updated criteria defining moderate or severe asthma; updated eosinophilic phenotype criterion; defined exacerbation criterion; revised maintenance treatment requirements; removed environmental trigger criterion. CRSwNP: revised diagnosis criteria to include provider attestation; updated treatment history to one intranasal corticosteroid and one OCS therapy. Renewal criteria: added standard renewal criteria documenting patient establishing treatment; added criterion excluding concomitant MCA use.	04/2021
Updated QL table to include pediatric dosing in AD	01/2021

Criteria update: updated age criteria to reflect newly FDA approved extended indication for atopic dermatitis use from 12 years of age to expanded use in pediatrics aged six to 11 years of age. Removal of PGA score as a requirement option with BSA in atopic dermatitis.	10/2020
Criteria was transitioned to policy format with the addition of supporting evidence and a section for investigation/not medically necessary usage. Addition of newly FDA approved age expansion for atopic dermatitis from 18 years of age to 12 years of age. Also, addition of newly FDA approved indication for chronic rhinosinusitis with nasal polyposis along with criteria for approval based on guidelines and clinical trials review. Lastly, the duration of initial approval has been increased form 3 months to 6 months based on evidence from ICER reports and the study design of the most recent FDA approved indication for chronic rhinosinusitis with nasal polyposis.	08/2019
Criteria update: Incorporated new diagnosis of moderate to severe asthma and appropriate criteria	12/2018
Updated format and added the renewal approval duration	01/2018
Criteria update: excluded samples and updated renewal language to general improvement	04/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP222

Split Fill Management*

Description

Duvelisib (Copiktra) is an orally administered inhibitor of phosphoinositide 3-kinase (PI3K) with inhibitory activity predominantly against PI3K-δ and PI3K-γ isoforms expressed in normal and malignant B-cells.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
duvelisib (Copiktra)	15 mg capsules	Relapsed/refractory chronic lymphocytic leukemia (CLL); Relapsed/refractory small lymphocytic lymphoma (SLL); Relapsed/refractory follicular lymphoma (FL)	56 capsules/28 days
	25 mg capsules		

Initial Evaluation

I. Duvelisib (Copiktra) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
   C. Member does not have a history of histological transformation (HT); **AND**
   D. Not used in combination with any other oncology therapy; **AND**
   E. Member has not progressed while on therapy with another PI3K inhibitor [e.g. copanlisib (Aliqopa), idelalisib (Zydelig)]; **AND**
   F. A diagnosis of **relapsed/refractory chronic lymphocytic leukemia (CLL) OR relapsed/refractory small lymphocytic lymphoma (SLL)** when the following are met:
      i. Treatment with one of the following has been ineffective or not tolerated or BOTH have been contraindicated:
         a. Bruton tyrosine kinase (BTK) inhibitor [e.g. ibrutinib (Imbruvica), acalabrutinib (Calquence)] **OR**
         b. BCL2 inhibitor [e.g. venetoclax (Venclexta)]; **AND**
      ii. Treatment with at least **ONE** of the following additional therapies has been ineffective, not tolerated, or ALL are contraindicated:

a. fludarabine/cyclophosphamide/rituximab (FCR)
b. alkylating agent (e.g., chlorambucil, bendamustine, cyclophosphamide)
c. monoclonal antibody (e.g., ofatumumab, rituximab, obinutuzumab)
d. purine analog (e.g., fludarabine, pentostatin, cladribine)

II. Duvelisib (Copiktra) is considered investigational when used for all other conditions, including but not limited to:
   A. Relapsed/refractory follicular lymphoma (FL)
   B. Head and Neck Cancer
   C. Stage IIB-IVB Mycosis Fungoides and Sezary Syndrome
   D. Moderate to Severe Rheumatoid Arthritis
   E. Coronavirus Infection (COVID-19)

Renewal Evaluation

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

Supporting Evidence

I. The safety and efficacy of duvelisib (Copiktra) for the treatment of relapsed and refractory CLL/SLL has been studied in a global, multicenter, randomized, open-label, Phase 3, superiority trial in 319 adult patients.
   - The two treatment arms included the duvelisib (Copiktra) and ofatumumab arm. Treatment groups were balanced, had a median number of prior therapies of two with approximately one-third having received three or more prior lines of therapy. Most patients had previously received an alkylating agent (chlorambucil, bendamustine, cyclophosphamide) 93% in the duvelisib (Copiktra) and 95% in the ofatumumab group, a monoclonal antibody (ofatumumab, rituximab, obinutuzumab) 78% in the duvelisib (Copiktra) and 83% in the ofatumumab group, and purine analog (60% duvelisib (Copiktra); 71% ofatumumab).
   - The primary endpoint of Progression-free Survival (PFS) was significantly longer for the duvelisib (Copiktra) arm compared with the ofatumumab arm (13.3 months vs 9.9 months, HR = 0.52, P < 0.0001).

- The key secondary endpoint of Overall Response Rate (ORR) was also significantly higher compared with ofatumumab (73.8% vs 45.3%; P < 0.0001), but the OS was not statistically different and the median overall survival (OS) was not reached on either treatment arm with a 12-month probability of survival of 86% (HR = 0.99; 95% CI, 0.65-1.50) for both treatments. This could be due to the availability of multiple CLL therapies to rescue patients on either arm following disease progression, including administration of duvelisib in a separate, optional extension study to 89 patients who had confirmed progressive disease on ofatumumab in the DUO study.
- Almost all patients in the study experienced an AE, 124 duvelisib (Copiktra)-treated patients had discontinued treatment, with the most common reasons being AEs (35%), disease progression (22%), subject withdrawal (8%), and death (8%).
- Fatal adverse reactions within 30 days of the last dose occurred in 36 patients (8%) treated with duvelisib (Copiktra) 25 mg twice daily. Serious adverse reactions were reported in 289 patients (65%). The most frequent serious adverse reactions that occurred were infection (31%), diarrhea or colitis (18%), pneumonia (17%), rash (5%), and pneumonitis (5%). Adverse reactions resulted in treatment discontinuation in 156 patients (35%), most often due to diarrhea or colitis, infection, and rash. Duvelisib (Copiktra) was dose reduced in 104 patients (24%) due to adverse reactions, most often due to diarrhea or colitis and transaminase elevation. The median time to first dose modification or discontinuation was 4 months (range: 0.1 to 27), with 75% of patients having their first dose modification or discontinuation within 7 months.

II. Histological transformation (HT) refers to the evolution of a clinically indolent disease (e.g. FL) to a clinically aggressive disease [e.g. diffuse large B-cell lymphoma (DLBCL)] defined as those lymphomas in which survival of the untreated patient is measured in months. The HT that occurs in patients with CLL/SLL has been termed Richter's transformation. When histological transformation is present, these patients are generally treated differently than their primary diagnosis. The goal of therapy for most patients is to eliminate the aggressive component of the disease (i.e. the histologically transformed cells) while minimizing toxicity. The most common treatment regimens for patients with HT include conventional chemotherapy with immunotherapy and high dose therapy followed by hematopoietic cell transplantation. There is no clinical trial data to support the use of duvelisib (Copiktra) in patients with HT.

III. Per the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, CLL/SLL, recognizes duvelisib (Copiktra) as a preferred regimen for r/r CLL/SLL (Category 2A recommendation). Ibrutinib (Imbruvica), acalabrutinib (Calquence), venetoclax (Venclexta) plus rituximab are Category 1 recommendation, based on the results of the Phase 3 randomized studies (ASCEND, RESONATE and MURANO, respectively). Idelalisib (Zydelig) plus rituximab and duvelisib (Copiktra) are also preferred regimens in these populations with a category 2A recommendation due to their toxicity profile (colitis, diarrhea, and increased risk of infections).

Investigational or Not Medically Necessary Uses

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

A. Relapsed/refractory follicular lymphoma (FL)

i. The safety and efficacy of duvelisib (Copiktra) for the treatment of relapsed and refractory FL has been studied in a single-arm, Phase 2, open-label study in 129 patients.

- Duvelisib (Copiktra) 25 mg twice daily was administered in patients with FL (N = 83) who were refractory to rituximab and to either chemotherapy or radioimmunotherapy. Patients were refractory to rituximab either alone or in combination (127 patients [98%]), 119 patients (92%) had disease refractory to an alkylating agent or purine analog, and 117 patients (91%) had disease refractory to combination therapy with rituximab and an alkylating agent.
- Patients had a median of three prior lines of therapy (range: 1 to 10), and 40% receiving four or more prior regiments, with 94% being refractory to their last therapy and 81% being refractory to 2 or more prior lines of therapy.
- The primary endpoint was met with Overall Response Rate (ORR) being 47% (95% CI, 38% to 56%). The key secondary endpoint of duration of response (DOR was 10 months (95% CI, 6.5 to 10.5 months)
- Due to treatment emergent adverse events (TEAE), forty patients (31%) discontinued duvelisib (Copiktra). In 85 (66%) of patients TEAEs were managed with dose interruption or reduction.
- The most frequent grade 3 or greater TEAEs were neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), and thrombocytopenia (11.6%). Seventeen deaths (13.2%) occurred on treatment

ii. Almost all patients in the study assessing the safety and efficacy of duvelisib (Copiktra) were refractory to rituximab (98.4%), alkylating agent/purine analog (92.2%) and alkylating agent (90.7%).

iii. The NCCN B-cell Lymphomas guideline set duvelisib (Copiktra) as a second-line therapy for FL that is relapsed or refractory to at least two prior therapies, a category 2A recommendation. Anti–CD20 antibody–based chemoimmunotherapy [e.g., obinutuzumab (Gazyva), ofatumumab (Arzerra)] is the standard initial treatment for newly diagnosed and relapsed/refractory FL. Options for treatment at first relapse include alternate non–cross-resistant chemoimmunotherapy regimens or combination lenalidomide + rituximab. Rituximab monotherapy may be appropriate for patients with late relapse as well, particularly if disease burden is low.

iv. Patients with Grade 3b FL were excluded from the clinical trial. Grade 3b FL is often referred to as follicular large cell lymphoma and patients commonly present with a more clinically aggressive course. It is commonly treated with regimens used for clinically aggressive lymphomas, such as a Diffuse Large B-Cell Lymphoma (DLBCL).

v. Although, the primary outcome of ORR was met, the quality of evidence is low considering the single arm, Phase 2, open-label trial design. Furthermore, patients included in this trial experienced significant TEAEs and limited efficacy. Given

these considerations treatment with duvelisib (Copiktra) in the setting of relapsed/refractory follicular lymphoma (FL) is considered experimental/investigational.

B. Head and Neck Cancer
   i. A Phase 1b/2, open label, non-randomized, single group study of duvelisib (Copiktra) in combination with pembrolizumab in subjects with recurrent or metastatic head and neck squamous cell cancer is still recruiting.

C. Stage IIB-IVB Mycosis Fungoides and Sezary Syndrome
   i. A Phase 1 open label, non-randomized, single group study with an expansion cohort of duvelisib (Copiktra) and nivolumab in Mycosis Fungoides (MF) and Sezary Syndrome (SS) is not yet recruiting.

D. Moderate to Severe Rheumatoid Arthritis
   i. A Phase 2, double blind, placebo-controlled, randomized study to evaluate multiple dose levels of duvelisib (Copiktra) with background methotrexate in subjects with active rheumatoid arthritis and an inadequate response to methotrexate alone was completed in 2018 but no results have been published.

E. Coronavirus Infection (COVID-19)
   ii. A Phase 2, double blind, placebo-controlled, randomized study to evaluate whether a two-week exposure to duvelisib (Copiktra), reduces inflammation in the lungs in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 who do not require mechanical ventilation at study initiation. The study is not yet recruiting.

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

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria: age requirement, requirement of monotherapy, requirement of non-progression on a different PI3K inhibitor, requirement of one or more prior therapy if diagnosed with CLL/SLL Removed criteria: requirement for pneumocystis jirovecii pneumonia (PCP) prophylaxis and no history of allogenic stem cell transplant Moved the follicular lymphoma indication to investigational uses Criteria updated to policy format	2/2021
Policy created	11/2018

Policy Type: PA 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

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

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/norethidone (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

1. Orilissa [Prescribing Information]. North Chicago, IL: AbbVie Inc.; July 2018.
2. Oriahnn [Prescribing Information]. North Chicago, IL: AbbVie Inc.; May 2020.
3. UpToDate, Inc. Endometriosis: Treatment of pelvic pain. UpToDate [database online]. Waltham, MA. Updated July 29, 2019.
4. UpToDate, Inc. Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women. UpToDate [database online]. Waltham, MA. Updated July 11, 2019.
5. Taylor HS, Giudice LC, Lessey BA et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med*. 2017;377:28-40. doi: 10.1056/NEJMoa1700089.
6. UpToDate, Inc. Overview of treatment of uterine leiomyomas (fibroids). UpToDate [database online]. Waltham, MA. Updated November 11, 2019.
7. Lupron Depot [Prescribing Information]. Abbvie Inc. Chicago, IL. January 2019.
8. Gillispie V, Muneyyirci-Delale O, Kim J, Liu R, et al. Up to 12 months of efficacy and safety of elagolix treatment in women with heavy menstrual bleeding associated with uterine fibroids. Presented at the American Association of Gynecologic Laparoscopists, November 9-13, 2019; Vancouver, Canada.
9. Schlaff W, Al-Hendy A, Barnhart K, et al. Elagolix Reduced Heavy Menstrual Bleeding with Uterine Fibroids: Primary, 6-month, Phase 3 Results. Presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists, May 3-6, 2019; Nashville, Tennessee, USA.
10. Bradley L, Feinberg E, Liu R, et al. Elagolix Treatment in Women with Uterine Fibroids: Secondary, 6-Month, Phase 3 Efficacy Results. Presented at the 2019 American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting, May 3-6, 2019; Nashville, Tennessee, USA.

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria updated to require specialist prescriber, removal of check on pregnancy status and menopausal status, and addition of assessment for prior use of GnRH antagonist relugolix. Supporting evidence updated, and format of policy updated to follow new standards. Experimental and investigational section added.	05/2021
Removed criteria: "Must be used in combination with a estradiol/norethindrone acetate product (Activella, Combipatch, Mimvey Lo, etc.)" from the indication heavy menstrual bleeding associated with uterine fibroids	12/2020
Added criteria for treatment of heavy menstrual bleeding associated with uterine fibroids, added requirements for premenopause and confirmation member is not pregnant. Also added NSAIDS as an option for trial and failure for pain associated with endometriosis.	12/2019
Transition from criteria to policy	09/2019
Criteria created	10/2018

eluxadoline (Viberzi®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP179

Description

Eluxadoline (Viberzi) is an orally administered mu-opioid receptor agonist that interacts with receptors in the stomach.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
eluxadoline (Viberzi)	75 mg tablets	Irritable bowel syndrome with diarrhea (IBS-D)	60 tablets/30 days
	100 mg tablets		

Initial Evaluation

I. Eluxadoline (Viberzi) may be considered medically necessary when the following criteria are met:
   A. A diagnosis of **Irritable Bowel Syndrome with Diarrhea (IBS-D)**; **AND**
      1. The member is 18 year of age or older; **AND**
      2. Prescribed by, or in consultation with, a gastroenterologist; **AND**
      3. Treatment with at least <u>three therapies from three different groups</u> 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 <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Diabetic diarrhea
   B. Diarrhea associated with fecal incontinence
   C. Pediatric IBS-D
   D. Mixed IBS or IBS with constipation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
IV. The member has demonstrated a beneficial response to therapy [e.g., symptomatic improvement, improvement in pain associated with IBS-D, a decrease in score for the Bristol Stool Scale (BSS) for stool consistency]

Supporting Evidence

I. The efficacy and safety of eluxadoline (Viberzi) for IBS-D was evaluated in two randomized, double-blind, placebo-controlled trials. Treatment arms were 75 mg, 100 mg or placebo, all administered twice daily. Patients were 18-80 years of age, and all met ROME III criteria for IBS-D. Patients, on average, had a pain score of 3 (0-10) in abdominal pain due to IBS-D, an average daily stool consistency of 5.5 or greater, and at least five days with a BSS score of 5 or greater (1-7). The BSS for stool consistency is rated on a scale of 1-7, with 1 being hard to pass or lumpy stool, and 7 being entirely liquid stool. Efficacy was assessed via a responder composite endpoint of simultaneous improvement in the daily worse abdominal pain score by 30% or greater compared to baseline AND a reduction in BSS to less than 5 for at least half of the days within a 12-week timeframe.
    - Study 1: A 26-week study of 1281 patients, with an additional 26 weeks for safety evaluation. Eluxadoline (Viberzi) showed a 23-29% response rate compared to 17% for placebo. Composite response rates were statistically significant at 12 weeks for both strengths, and the 26-week endpoint was statistically significant for the 100 mg.
    - Study 2: A 26-week study of 1145 patients. This study also included a 4-week withdrawal period upon completion of the 26-week phase. During the withdrawal period, patients were permitted to take rescue loperamide therapy for uncontrolled diarrhea. Eluxadoline (Viberzi) showed a 29-33% response rate compared to 16-20% for placebo. Composite response rates were statistically significant for both strengths at week 12 and 26.

II. Conventional treatment options for IBS-D include antidiarrheals, antibiotics, antispasmodics, antidepressants, and bile acid sequestrants; all of which, the American College of Gastroenterology gave moderate or weak recommendations because of poor quality of evidence and applicability to patient groups. However, due to insufficient comparative evidence for efficacy, conventional treatment options still provide a better value over eluxadoline (Viberzi). Notably, Of the antidepressants, tricyclic agents have been shown to slow intestinal transit; however, SSRI/SNRI agents have less published data and the data available is inconsistent in showing benefit in IBS.

Investigational or Not Medically Necessary Uses

I. Eluxadoline (Viberzi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Diabetic diarrhea
   B. Diarrhea associated with fecal incontinence
   C. Pediatric IBS-D
   D. Mixed IBS or IBS with constipation

References

1. Viberzi [Prescribing Information]. Madison, NJ: Allergan USA. April 2018.
2. U.S. National Library of Medicine. clinicaltrials.gov. https://clinicaltrials.gov/ct2/results?cond=eluxadoline&term=&cntry=&state=&city=&dist=. Accessed March 2020.
3. Lembo AJ, Lacy BE, Zuckerman MJ, et al. Eluxadoline for Irritable Bowel Syndrome with Diarrhea. N Engl J Med. 2016;374(3):242-53.
4. Weinberg DS, Smalley W, Heidelbaugh JJ, Sultan S; Amercian Gastroenterological Association. American Gastroenterological Association Institute Guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014 Nov;147(5):1146-8. doi: 10.1053/j.gastro.2014.09.001. Epub 2014 Sep 16.
5. Shah ED, Basseri RJ, Chong K, Pimentel M, Abnormal breath testing in IBS: a meta-analysis. Dig Dis Sci. 2010 Sep;55(9):2441-9. Epub 2010 May 14.
6. Clinical Guidelines (Sortable List. American College of Gastroenterology. http://gi.org/clinical-guidelines/clinical-guidelines-sortable-list/. Accessed March 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Update to three conventional therapies required prior to coverage. Update to require specialist prescriber.	04/2020
Policy Created	02/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP022

Description
Emicizumab-kxwh (Hemlibra) is a monoclonal antibody used for routine prophylaxis to prevent or decrease the frequency of bleeding episodes for patients with hemophilia A with or without inhibitors.

Length of Authorization
- Initial: 6 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*‡
Hemlibra, emicizumab-kxwh	30 mg	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A with or without factor VIII inhibitors	Up to 690 mg every 28 days
	60 mg		
	105 mg		
	150 mg		

* 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.

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
2. National Hemophilia Foundation. Hemophilia A. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed July 5, 2019.
3. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
4. Recommendation on the Use and Management of Emicizumab-kxwh (Hemlibra®) for Hemophilia A with and without Inhibitors. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations/Recommendation-on-the-Use-and-Management-of-Emicizumab-kxwh-Hemlibra-for-Hemophilia-A-with-and-without-Inhibitors Accessed August 19, 2019
5. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	**Date**
New policy created for emicizumab-kxwh (Hemlibra)	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP188

Description

Emtricitabine/tenofovir alafenamide (Descovy®) is a two-drug combination of emtricitabine (FTC) 200 mg and tenofovir alafenamide (TAF) 25 mg indicated for the treatment of HIV-1 infection and pre-exposure prophylaxis of HIV infection from sexual acquisition. 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

Product Name	Dosage Form	Indication	Quantity Limit
bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy)	50-200-25 mg tablets	Treatment of HIV-1	30 tablets/30 days
emtricitabine/tenofovir alafenamide (Descovy)	200-25 mg tablets	Pre-Exposure Prophylaxis (PrEP); Treatment of HIV-1	30 tablets/30 days

Initial Evaluation

I. **bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) and 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. For emtricitabine/tenofovir alafenamide (Descovy) member has a body weight greater than, or equal to, 35 kg (77lbs); **OR**
   C. For bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy):
      1. Member has a body weight greater than, or equal to, 25 kg (56 lbs); **AND**
      2. Documentation of Hepatitis B virus (HBV) screening prior to initiation; **AND**
      3. Member is treatment naïve; **OR**
      4. Member is virologically suppressed with HIV-1 RNA < 50 copies/mL; **AND**
         i. 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**
      5. bictegravir/emtricitabine/tenofovir alafenamide (Biktarvy) will **not** be co-administered with dofetilide or rifampin; **AND**
   D. 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**

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. Use is in adults and adolescents at risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex; **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

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; **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 one of the following:
   A. **HIV-1**; **AND**
      1. Member's condition has not worsened, while on therapy as evidenced by one of the following:
         i. A viral load less than 200 copies/mL; **OR**
         ii. An increasing CD4 cell count; **OR**
   B. Medication will be used in the setting of **Pre-Exposure Prophylaxis (PrEP); AND**
      a. Use is in adults and adolescents at risk of HIV-1 infection from sexual acquisition, excluding individuals at risk from receptive vaginal sex; **AND**
      b. Request is for emtricitabine/tenofovir alafenamide (Descovy); **AND**
      c. Member has a negative HIV-1 test

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 alafenamide (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. Emtricitabine/tenofovir alafenamide (Descovy) is not recommended in patients with estimated creatinine clearance below 30 mL per minute as data in this population is insufficient.

III. Emtricitabine/tenofovir alafenamide (Descovy) is not approved in the treatment of chronic HBV infection, as the safety and efficacy of emtricitabine/tenofovir alafenamide (Descovy) 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 tenofovir disoproxil fumarate (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 DESCOVY should be closely monitored with both clinical and laboratory follow-up.

IV. 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.

V. 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.

VI. Adverse Reactions in Clinical Trials of FTC+TAF with EVG+COBI in Treatment-Naïve Adults with HIV-1 Infection:

A. In pooled 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects the most common adverse reaction in those treated with FTC+TAF with EVG+COBI (N=866) (incidence greater than or equal to 10%, all grades) was nausea (10%). In this treatment group 0.9% of subjects discontinued FTC+TAF with EVG+COBI due to adverse events.

B. The safety profile of Antiretroviral treatment-naïve adult subjects treated with FTC+TAF with EVG+COBI was similar in virologically-suppressed adults with HIV-1 infection who were switched to FTC+TAF with EVG+COBI (N=799). Those who were antiretroviral treatment-naïve adult subjects treated with FTC+TAF with EVG+COBI experienced a mean increase of 30 mg/dL of total cholesterol, 15 mg/dL of LDL cholesterol, 7 mg/dL of HDL cholesterol, and 29 mg/dL of triglycerides after 48 weeks of use.

C. In two 48-week trials in antiretroviral treatment-naïve HIV-1 infected adults treated with FTC+TAF with EVG+COBI (N=866) with an average baseline eGFR of 115 mL per minute, the mean serum creatinine increased by 0.1 mg per dL from baseline to Week 48. The average urine protein-to-creatinine ratio (UPCR) was 44 mg per gram at baseline

and at Week 48. In a 48-week trial in virologically-suppressed TDF-treated adults who switched to FTC+TAF with EVG+COBI (N=959) with a mean baseline eGFR of 112 mL per minute, mean serum creatinine was similar to baseline, median UPCR was 61 mg per gram at baseline, and 46 mg per gram at week 48. In a 24-week trial in adults with renal impairment (baseline eGFR 30 to 69 mL per minute) who received FTC+TAF with EVG+COBI (N=248), mean serum creatinine was 1.5 mg per dL at both baseline and week 24, while median UPCR was 161 mg per gram at baseline and 93 mg per gram at Week 24.

D. In the pooled analysis of two 48-week trials of antiretroviral treatment-naïve HIV-1 infected adult subjects, bone mineral density (BMD) from baseline to Week 48 was assessed by a dual-energy X-ray absorptiometry (DXA). Mean BMD decreased from baseline to Week 48 (−1.30% with FTC+TAF with EVG+COBI at the lumbar spine and −0.66% at the total hip). Ten percent of FTC+TAF with EVG+COBI subjects experienced BMD declines of 5% or greater at the lumbar spine; while only 7% of the FTC+TAF with EVG+COBI subjects experienced BMD declines of 7% or greater at the femoral neck. The long-term clinical significance of these BMD changes is not known. Fractures (excluding fingers and toes) were reported in 7 (0.8%) subjects in the FTC+TAF with EVG+COBI group. In 799 virologically-suppressed TDF-treated adult subjects, who switched to FTC+TAF with EVG+COBI had, at Week 48, a mean BMD increase (1.86% lumbar spine, 1.95% total hip), 1% experienced a BMD decline of 5% or greater at the lumbar spine, and 1% experienced a BMD decline of 7% or greater at the femoral neck.

VII. Adverse Reactions in Clinical Trials in Pediatric Subjects with HIV-1 Infection

A. In a 24 week, open-label trial of 23 antiretroviral treatment-naïve HIV-1 infected pediatric subjects, aged 12 to 18 years old, weighing at least 35 kg, and who had received FTC+TAF with EVG+COBI, showed a similar safety profile to that that of adults. However, among these pediatric subjects, the mean BMD increased from baseline to Week 24, +1.7% at the lumbar spine and +0.8% for the total body less head. Mean changes from baseline BMD Z-scores were −0.10 for lumbar spine and −0.11 for total body less head at Week 24. Two subjects had significant (greater than 4%) lumbar spine BMD loss at Week 24.

VIII. The efficacy and safety of 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 and who had a body weight greater than, or equal to, 35 kg. Use of 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

IX. 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 less than 65 years of age.

X. Emtricitabine/tenofovir alafenamide (Descovy), even with a dosage adjustment, is not recommended in patients with severe renal impairment (estimated creatinine clearance below 30 mL per minute).

XI. 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).

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

1. Washington States Health Care Authority's "Antivirals : HIV – emtricitabine / tenofovir alafenamide (Descovy®)" policy (Medical policy no. 12.10.99.02). WA: WA HCA Apple Health, August 2020.
2. Washington States Health Care Authority's "Antivirals : HIV – Combinations" policy (Medical policy no. 12.10.99.02). WA: WA HCA Apple Health, August 2020
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5. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf [Prescribing Information]. Silver Spring, MD: U.S. Food and Drug Administration
6. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208215s000lbl.pdf [Prescribing Information]. Silver Spring, MD: U.S. Food and Drug Administration

Policy Implementation/Update:

Action and Summary of Changes	Date
Edits to wording of criteria C.2. for requirement of HBV screening prior to therapy initiation with Biktarvy; added supporting information to the supporting evidence section	01/2021
Instead of tenofovir disoproxil fumarate (Truvada) requiring step through generic tenofovir disoproxil fumarate	12/2020
Policy created	07/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP091

Description

Encorafenib (Braftovi) is a kinase inhibitor of in-vitro growth of tumor cell lines expressing BRAF V600 E, D, and K mutations. Binimetinib (Mektovi) is a reversible kinase inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activity. These agents are FDA-approved for combination use.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

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

Initial Evaluation

I. Encorafenib (Braftovi) and binimetinib (Mektovi) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medications are prescribed by, or in consultation with, an oncologist, dermatologist, or gastroenterologist; **AND**
   C. Encorafenib (Braftovi) and binimetinib (Mektovi) will **not** be used in combination with any other oncolytic agent unless specified below (e.g. encorafenib (Braftovi) and cetuximab (Erbitux) for the treatment of colorectal cancer); **AND**
   D. The member has **not** progressed on prior BRAF-inhibitor therapy (e.g., dabrafeinib, vemurafenib); **AND**

E. A diagnosis of one of the following:
   1. **Advanced (stage III) or metastatic (stage IV) cutaneous melanoma**; **AND**
      i. Encorafenib (Braftovi) and binimetinib (Mektovi) will be used in combination; **AND**
      ii. Mutation status of BRAF V600E or V600K; **OR**
   2. **Metastatic (stage IV) colorectal cancer (CRC)**; **AND**
      i. The request is for encorafenib (Braftovi) in combination with cetuximab (Erbitux); **AND**
      ii. Mutation status of BRAF V600E mutation; **AND**
      iii. The member has previously tried and failed at least one systemic therapy (e.g. FOLFIRI, irinotecan, oxaliplatin)

II. Encorafenib (Braftovi) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Colorectal cancer in combination with binimetinib (Mektovi) and cetuximab (Erbitux)

III. Encorafenib (Braftovi) and binimetinib (Mektovi) are considered investigational when used for all other conditions, including but not limited to:
   A. KRAS-mutated cancer
   B. Adolescents with BRAF-mutant melanoma
   C. Thyroid cancer
   D. Lung cancer (e.g., non-small cell lung cancer, non-squamous carcinoma of the lung)
   E. CNS cancers (e.g., glioma, neurofibromas)
   F. Gastrointestinal cancer (e.g., GIST)
   G. Pancreatic cancer
   H. Colorectal cancer in combination with panitumumab (Vectibix)

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
   A. For treatment of melanoma: encorafenib (Braftovi) and binimetinib (Mektovi) will be used in combination; **OR**
   B. For treatment of colorectal cancer: encorafenib (Braftovi) and cetuximab (Erbitux) will be used in combination

Supporting Evidence

I. Advanced or Metastatic Melanoma

- BRAF/MEK inhibitors have been studied in advanced and metastatic melanoma. Surgical resection remains the mainstay of therapy prior to stage III and have favorable outcomes for most patients. Patients at stage II have a high risk of progressing to advanced disease and have a high risk of recurrence; however, there is currently no evidence to support safety and efficacy in this population for any BRAF/MEK therapy combination.
- There is limited evidence regarding the safety and efficacy of BRAF/MEK inhibitor therapy in those that have progressed on a previous or alternative BRAF/MEK therapy combination. Results from a phase I/II study showed that those that had previous BRAF therapy, further treatment with dabrafenib (Tafinlar)/trametinib (Mekinist), had poor response rates, progression free survival (PFS), and overall survival (OS) compared to those that had not been previously treated with these specific mechanisms of action. Most notably, a subset analysis showed that patients who had rapidly progressed on BRAF therapy (less than six months to progression) derived no clinical benefit from second line/subsequent treatment.
- BRAF V600E and V600K mutations are the most common mutation of BRAF driver mutations; however, several other BRAF mutations exist. NCCN supports the use of BRAF/MEK inhibitors for any V600 mutation; however, there is currently no evidence for safety or efficacy to support the use of encorafenib (Braftovi) and binimetinib (Mektovi) in settings outside of V600E or V600K.
- Encorafenib (Braftovi), in combination with binimetinib (Mektovi), was evaluated in a randomized, active-controlled, open-label multicenter trial (n=577). Subjects had a BRAF V600E or K mutation-positive, unresectable or metastatic melanoma, and were permitted to have prior immunotherapy for advanced or metastatic disease. Prior use of BRAF therapy was not allowed.
    i. Subjects were randomized to receive encorafenib (Braftovi) in combination with binimetinib (Mektovi), encorafenib (Braftovi) monotherapy, or vemurafenib (Zelboraf) monotherapy. The primary outcome was PFS. Secondary outcomes included OS, objective response rate (ORR), and duration of response (DoR).
    ii. The combination of Braftovi and Mektovi showed a statistically significant improvement in PFS compared to vemurafenib (Zelboraf) (14.9 months vs 7.3 months, $p<0.0001$). There were statistically significant improvements in ORR and DoR. Overall survival data was published in 2018, with OS duration of 33.6 months for combination therapy compared to 16.9 months with vemurafenib monotherapy ($p<0.0001$).
    iii. The safety and efficacy of combination therapy with Braftovi and Mektovi was evaluated, compared to encorafenib (Braftovi) alone, and results were more favorable for combination therapy. The current FDA-approval is for dual therapy.

II. Metastatic Colorectal Cancer

- Encorafenib (Braftovi), in combination with cetuximab (Erbitux), was studied in one ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 trial with 645 patients with BRAF V600E mutation-positive metastatic CRC. The primary efficacy endpoint was OS. The median OS was 9 months for encorafenib

(Braftovi)/binimetinib/(Mektovi)/cetuximab (Erbitux) and 8.4 months for encorafenib (Braftovi)/cetuximab (Erbitux) compared to 5.4 months for irinotecan (Camptosar)/cetuximab (Erbitux) with a HR of 0.52 (95% CI 0.39, 0.70) and 0.60 (95% CI 0.45, 0.79), respectively. The median PFS was 4.3 months for encorafenib (Braftovi)/binimetinib/(Mektovi)/cetuximab (Erbitux) and 4.2 months for encorafenib (Braftovi)/cetuximab (Erbitux) compared to 1.5 months for irinotecan (Camptosar)/cetuximab (Erbitux) with a HR of 0.38 (95% CI 0.29, 0.49) and 0.40 (95% CI 0.31, 0.52), respectively. The estimated six-month survival was 71% in the triple therapy group and 65% in the dual therapy group with a HR of 0.79 (95% CI 0.59, 1.06).

- NCCN guidelines note that triple therapy with encorafenib (Braftovi)/binimetinib (Mektovi)/cetuximab (Erbitux) has evidence for use in metastatic colorectal cancer; however, when listing recommended therapy options, they only note encorafenib (Braftovi) in combination with cetuximab (Erbitux) or panitumumab (Vectibix). The recommendation for encorafenib (Braftovi) in combination with cetuximab (Erbitux) or panitumumab (Vectibix) is Category 2A.

Investigational or Not Medically Necessary Uses

I. Encorafenib (Braftovi) and binimetinib (Mektovi) have not been sufficiently studied for safety and/or efficacy in the following settings:
   A. KRAS-mutation cancer
   B. Adolescents with BRAF-mutant melanoma
   C. Thyroid cancer
   D. Lung cancer (e.g., non-small cell lung cancer, non-squamous carcinoma of the lung)
   E. CNS cancers (e.g., glioma, neurofibromas)
   F. Gastrointestinal cancer (e.g., GIST)
   G. Pancreatic cancer
   H. Colorectal cancer in combination with panitumumab (Vectibix)
      i. There have been no large, well-designed studies of encorafenib (Braftovi) or binimetinib (Mektovi) in combination with panitumumab (Vectibix).
   I. Encorafenib (Braftovi) in combination with binimetinib (Mektovi) and cetuximab (Erbitux) for colorectal cancer
      i. Encorafenib (Braftovi), in combination with binimetinib (Mektovi), and cetuximab (Erbitux) was studied in one ongoing, randomized, active-controlled, open-label, multicenter, Phase 3 trial with 645 patients with BRAF V600E mutation-positive metastatic colorectal cancer. The efficacy of triple therapy was not significantly superior to dual therapy.

References

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2. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615.
3. Braftovi [Prescribing Information]. Array BioPharma Inc. Boulder, CO. 2020.

4. Mektovi [Prescribing Information]. Array BioPharma Inc. Boulder, CO. 2018.
5. NCCN Clinical Practice Guidelines in Oncology, Cutaneous Melanoma. V 3.2019. National comprehensive Cancer Network. October 22, 2019. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#melanoma.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated with new indication for Braftovi for metastatic colorectal cancer in combination with cetuximab. Updated language to state not for combination use besides agents listed in the criteria. Removed exclusions for colorectal cancer and V600-mutated cancer besides melanoma.	06/2020
Prior authorization criteria transitioned to policy, updated criteria with the following: age edit, allowance of dermatologist prescribing, specialist requirement on renewal.	11/2019
Criteria created	07/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP082

Split Fill Management*

Description

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

Length of Authorization

- Initial: Three months, split fill
- Renewal: Six months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
entrectinib (Rozlyrek)	100 mg capsules	Neurotrophic receptor tyrosine kinase gene fusion positive solid tumors	30 capsules/30 days	207677
	200 mg capsules	Non-small cell lung cancer, metastatic, ROS1-positive	90 capsules/30 days	207687

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).

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

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Policy Implementation/Update:

Date Created	September 2019
Date Effective	November 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

Policy Type: PA/SP Pharmacy Coverage Policy: UMP023

Split Fill Management* (applies to dacomitinib [Vizimpro] and erlotinib [Tarceva] only)

Description

Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), afatinib (Gilotrif), and gefitinib (Iressa) are orally administered epidermal growth factor receptor (EGFR) and tyrosine kinase inhibitors (TKIs).

Length of Authorization

- Initial: Three months; split fill applies to dacomitinib (Vizimpro) and erlotinib (Tarceva) only
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
osimertinib (Tagrisso)	40 mg tablets	NSCLC	30 tablets/30 days
	80 mg tablets		
dacomitinib (Vizimpro)	15 mg tablets	NSCLC	30 tablets/30 days
	30 mg tablets		
	45 mg tablets		
erlotinib (Tarceva)	25 mg tablets	NSCLC; Pancreatic cancer	90 tablets/30 days
	100 mg tablets		30 tablets/30 days
	150 mg tablets	NSCLC	30 tablets/30 days
afatinib (Gilotrif)	20 mg tablets	NSCLC	30 tablets/30 days
	30 mg tablets		
	40 mg tablets		
gefitinib (Iressa)	250 mg tablets	NSCLC	30 tablets/30 days

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;

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.

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

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy updated to include osimertinib (Tagrisso) indication of early stage, adjuvant treatment to surgical resection in NSCLC.	01/2021

Criteria update and policy creation: All EGFR TKI agents combined into one policy, streamline quantity limits, renewal criteria, duration or approval upon initial and renewal request. Update Tagrisso criteria to allow for use in the first line setting. Addition of age requirement and prescriber requirement for all agents.	07/2019
Gilotrif criteria update: updated criteria to include L861Q, G719X, or S768I mutations and metastatic, squamous NSCLC that has progressed after treatment with platinum-based chemotherapy. Due to the statement that afatinib is not recommended as second-line therapy for squamous cell carcinoma from National Comprehensive Cancer Network (NCCN), a clinical note has been added to address the request for afatinib in members who are diagnosed with squamous NSCLC that has progressed on platinum-based chemotherapy. Tagrisso criteria update: Include clinical note regarding the Flaura trial and recent NCCN NSCLC Guidelines. Also, a route for approval if patient has a contraindication to erlotinib, afatinib and gefitinib.	03/2018
Gilotrif criteria update: updated criteria to new format, deleted renal and hepatic function questions, and deleted female contraception questions as this is properly managed by providers	01/2018
Previous reviews	12/2015, 01/2015, 09/2013, 05/2013, 11/2012, 03/2012, 03/2012, 10/2008, 04/2007
Criteria created	09/2005

Policy Type: PA/SP Pharmacy Coverage Policy: UMP024

Split Fill Management*

Description

Erdafitinib (Balversa) is an oral kinase inhibitor that inhibits enzymatic activity of FGFR 1-4.

Length of Authorization

- Initial: Three months, split fill
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*	DDID
erdafitinib (Balversa)	3 mg tablets	Advanced or metastatic urothelial carcinoma FGFR3 or FGFR2 genetic alteration, second-line after platinum therapy progression	**Maintenance**: 90 tablets/30 days	206400
	4 mg tablets		**Initial**: 28 tablets per 14-day supply for one fill **Maintenance**: 60 tablets/30 days	206401
	5 mg tablets		**Maintenance**: 30 tablets/30 days	206402

*Total daily dose should not exceed 9 mg per day. This may be achieved by 5 mg plus 4 mg, or by three 3mg tablets.

Initial Evaluation

I. Erdafitinib (Balversa) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. The medication is prescribed by or in consultation with an oncologist or urologist; **AND**
   C. Not to be used in combination with other oncolytic medications (i.e., must be used as a monotherapy for the conditions listed below); **AND**
   D. The provider attests that the member will be treated with a maximum of 8 mg per day for at least two weeks to assess for tolerability before considering a total daily dose of 9 mg per day; **AND**
   E. A diagnosis of urothelial carcinoma when the following are met:
      1. Disease is considered advanced or metastatic; **AND**
      2. Genetic alteration is FGFR**3** point mutation or fusion as detected by an FDA-approved test; **AND (one of i or ii)**
         i. The member has previously progressed during or following at least one line of prior platinum-containing chemotherapy (e.g., cisplatin, carboplatin); **OR**

ii. The member previously progressed during or following neoadjuvant or adjuvant platinum-containing chemotherapy (e.g., cisplatin, carboplatin); **AND**
    a. The platinum-containing chemotherapy was administered within the last 12 months

II. Erdafitinib (Balversa) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
    A. Urothelial carcinoma that has FGFR**2** genetic alteration (e.g., fusion or point mutation)

III. Erdafitinib (Balversa) is considered <u>investigational</u> when used for all other conditions, including, but <u>not limited to</u>:
    A. Urothelial carcinoma prior to the advanced or metastatic setting
    B. Urothelial carcinoma without FGFR mutation, or without previous treatment with platinum-based chemotherapy
    C. For urothelial carcinoma, or otherwise, treatment with a dose greater than 9 mg per day
    D. Conditions outside of urothelial carcinoma (e.g., Non-Hodgkin Lymphoma, gliomas, osteosarcoma, histiocytosis, soft tissue sarcoma, etc.)

Renewal Evaluation

I. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
II. The medication is not used in combination with other oncolytic medications (i.e., erdafitinib [Balversa] is used as monotherapy); **AND**
III. Tumor response is documented with stabilization of disease or decrease in size of tumor or tumor spread; **AND**
IV. The member has an absence of unacceptable toxicity from the drug (e.g., ophthalmic disturbances, hyperphosphatemia).

Supporting Evidence

I. Erdafitinib (Balversa) was evaluated in one, single-arm, open-label trial. Eighty-seven subjects (n=87) had advanced or metastatic urothelial carcinoma with FGFR**2** or FGFR**3** genetic alterations. Additionally, subjects must have progressed on or after at least one line of prior platinum-containing chemotherapy. This included those that had received neoadjuvant or adjuvant platinum-containing chemotherapy in the past 12 months.
II. No pediatric patients were included in the trial. Subjects assessed were between the ages of 36 and 87. Ninety-seven percent of subjects had received prior cisplatin or carboplatin, and 10% had received both. Twenty-four percent of subjects had received prior anti-PD-L1/PD-1 therapy (immunotherapy). No concomitant oncolytic medications were allowed during the trial.
III. The study assessed for objective response rate (ORR), including both partial and complete response (PR and CR), and duration of response (DoR). Thirty-two percent of subjects met the ORR (2 patients showed CR), and the median duration of response was 5.4 months.
IV. High rates of dose-reduction and dose-interruption were observed, at 53% and 68% respectively. Serious adverse events including, but not limited to, ophthalmic disturbances, hyperphosphatemia, and fatal myocardial infarction, occurred during the trial (1-20%).

Investigational or Not Medically Necessary Uses

I. The pivotal trial evaluated for the FDA-approved indication of urothelial carcinoma included six patients with a FGFR**2** fusion genetic alteration, and no patients that had FGFR**2** point mutation. None of these six patients showed an ORR on or after treatment with erdafitinib (Balversa). As of April 2019, there is no evidence that this population has responded to therapy.
II. Currently, the available outcomes data for erdafitinib (Balversa) was based on a maximum dose of 9 mg per day. No subjects were on concurrent oncolytic therapies. All subjects were verified to be with FGFR-mutation, and with advanced or metastatic urothelial carcinoma. Safety and efficacy outcomes in patients not previously progressed on or after platinum-containing chemotherapy is unknown at the time of this writing.
III. Erdafitinib (Balversa) is currently in clinical trials for a variety of other conditions (e.g, Non-Hodgkin Lymphoma, gliomas, osteosarcoma, histiocytosis, soft tissue sarcoma, etc.).

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

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Policy Implementation/Update:

Date Created	April 2019
Date Effective	August 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

Policy Type: PA/SP Pharmacy Coverage Policy: UMP124

Description

Epoetin alfa (Retacrit, Procrit, Epogen) is a glycoprotein that stimulates red blood cell production; whereas, darbepoetin alfa (Aranesp) stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

Length of Authorization

Initial and Renewal:

Epoetin alfa (Procrit, Epogen):

- Chronic kidney disease with or without dialysis – Three months
- Cancer chemotherapy – 12 months
- Anemia due to zidovudine therapy – 12 months
- Allogeneic blood transfusion in surgery patients – 14-days

Darbepoetin alfa (Aranesp):

- Chronic kidney disease with or without dialysis – Three months
- Cancer chemotherapy – 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
darbepoetin alfa (Aranesp)	25 mcg/mL vial	Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy	4 vials/syringes per 30 days
	40 mcg/mL vial		
	60 mcg/mL vial		
	100 mcg/mL vial		
	150 mcg/mL vial		
	200 mcg/0.75 mL vial		
	300 mcg/mL vial		
	10 mcg/0.4 mL syringe		
	25 mcg/0.42 mL syringe		
	40 mcg/0.4 mL syringe		
	60 mcg/0.3 mL syringe		
	100 mcg/0.5 syringe		
	150 mcg/0.3 syringe		
	200 mcg/0.4 mL syringe		
	300 mcg/0.6 mL syringe		
	500 mcg/mL syringe		
epoetin alfa (Retacrit)	2000 units/mL vial	Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy; Anemia due to	**2,000U, 3,000U, 4,000U and 10,000U vials**: 12 vials per 30 days
	3000 units/mL vial		
	4000 units/mL vial		
	10000 units/mL vial		

	40000 units/mL vial	zidovudine therapy; Allogeneic blood transfusion	**20,000U and 40,000U vials:** 4 vials per 30 days
epoetin alfa (Procrit)	2000 units/mL vial	Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy; Anemia due to zidovudine therapy; Allogeneic blood transfusion	**2,000U, 3,000U, 4,000U and 10,000U vials**: 12 vials per 30 days **20,000U and 40,000U vials:** 4 vials per 30 days
	3000 units/mL vial		
	4000 units/mL vial		
	10000 units/mL vial		
	20000 units/mL vial		
	20000 units/2 mL vial		
	40000 units/mL vial		
epoetin alfa (Epogen)	2000 units/mL vial	Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy; Anemia due to zidovudine therapy; Allogeneic blood transfusion	**2,000U, 3,000U, 4,000U and 10,000U vials**: 12 vials per 30 days **20,000U and 40,000U vials:** 4 vials per 30 days
	3000 units/mL vial		
	4000 units/mL vial		
	10000 units/mL vial		
	20000 units/mL vial		
	20000 units/2 mL vial		

Initial Evaluation

Epoetin alfa (Retacrit) is the preferred short-acting erythropoiesis stimulating agent (ESA) product.

- **Members must have failed, have a contraindication to, or intolerance to Retacrit prior to the consideration of epoetin alfa (Procrit or Epogen).**
- There is no prior authorization required for epoetin alfa (Retacrit) unless requesting above the quantity limit noted above.

I. **Darbepoetin alfa (Aranesp), 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. If the request is for epoetin alfa (Procrit or Epogen), member must have failed, have a contraindication to, or intolerance to Retacrit; **AND**
   E. A diagnosis of one of the following when the request is for **darbepoetin alfa (Aranesp) or 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); **OR**

2. **Anemia secondary to Myeloproliferative Neoplasms (MPN) – Myelofibrosis; AND**
   i. Member has an endogenous serum erythropoietin level of < 500 mUnits/mL; **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; **OR**
4. **Anemia secondary to chronic kidney disease; AND**
   i. Member is at least one month of age or older; **OR**

F. A diagnosis of one of the following when the request is for **epoetin alfa (Procrit, Epogen)**:
1. **Anemia secondary to rheumatoid arthritis; OR**
2. **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; **OR**
3. **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

II. Darbepoetin alfa (Aranesp), epoetin alfa (Procrit, Epogen) are considered investigational when used for all other conditions.

Renewal Evaluation

I. Lab values are obtained within 30 days of the date of administration (unless otherwise indicated); **AND**

II. Adequate iron stores as demonstrated by serum ferritin ≥ 100 ng/mL (mcg/L) and transferrin saturation (TSAT) ≥ 20% measured within the previous 3 months; **AND**

III. Documentation of continued need for therapy indicated by Hemoglobin (Hb) and/or Hematocrit (Hct) as follows:

Indication	Hb and/or Hct Response
Anemia secondary to myelodysplastic syndrome (MDS)	Hemoglobin (Hb) <12 g/dL and/or Hematocrit (Hct) <36%
Anemia secondary to myeloproliferative neoplasms (MF, post-PV myelofibrosis, post-ET myelofibrosis)	Hemoglobin (Hb) <10 g/dL and/or Hematocrit (Hct) <30%
Reduction of allogeneic blood transfusions in elective, non-cardiac, non-vascular surgery	Hemoglobin(Hb) between 10 g/dL and 13 g/dL and/or Hematocrit(Hct) between 30% and 39%
Anemia secondary to chemotherapy treatment	Hemoglobin (Hb) <10 g/dL and/or Hematocrit (Hct) < 30%
Anemia secondary to zidovudine treated, HIV-infected patients	Hemoglobin (Hb)< 12 g/dL and/or Hematocrit (Hct) < 36%;
Anemia secondary to chronic kidney disease	*Pediatric patients*: Hemoglobin (Hb) < 12 g/dL and/or Hematocrit (Hct) < 36% *Adults*: Hemoglobin (Hb) < 11 g/dL and/or Hematocrit (Hct) < 33%
All other indications	Hemoglobin (Hb) < 11 g/dL and/or Hematocrit (Hct) < 33%

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated renewal section criteria point III to read as "Documentation of continued need for therapy indicated by Hemoglobin (Hb) and/or Hematocrit (Hct) as follows:".	04/2020
• Transitioned to policy format • Added language regarding preferred product, Retacrit and removal of PA requirement • Aligned criteria with medical benefit for consistency across benefits, which included clarifying initial requirements (e.g. labs obtained within 30 days, adequate iron stores, Hg/Hct levels) • Added coverage criteria for anemia associated with rheumatoid arthritis, anemia secondary to MDS, and anemia secondary to myelofibrosis • Added specific renewal criteria	12/2019
Previous reviews	10/2018, 11/2012, 08/2012
Policy created	06/2011

esketamine (Spravato™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

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

Product Name	Dosage Form	Indication	Quantity Limit
esketamine (Spravato)	56 mg dose kit	Treatment resistant depression (TRD) in conjunction with an oral antidepressant	**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*:** - 6 devices per 28 days (to allow for 56mg or 84mg at bi-weekly dosing)
	84 mg dose kit		
	56 mg dose kit	Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior in conjunction with an oral antidepressant	24 devices per 28 days
	84 mg dose kit		

‡Second dose for week one accounted for in PA#2
*If determined to be medically necessary, more frequent dosing (i.e. once weekly) may be considered appropriate

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 different classes (i.e. SSRI, SNRI, TCA, MAO) at an optimized dose for at least 8 weeks; **AND**
         iii. Augmentation with an additional antidepressant from a different class; **AND**
         iv. Augmentation with an 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. The dosing request is for one every other week; **OR**
   i. Documentation of medical necessity for once weekly dosing.

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), it 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 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 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 guidelines specific to TRD. In the 2010 American Psychiatric Association (APA) guidelines, initial treatment of MDD was recommended to include an oral antidepressant in combination with psychotherapy.

- Recommended psychotherapies include:
  - 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.
- 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. 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.

XI. 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.

XII. 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, predose) 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.

XIII. 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.

XIV. 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.

XV. 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.

XVI. 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.

XVII. 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.

XVIII. 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.

XIX. 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%.

XX. 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.

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)

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

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

Week	Cumulative Spravato Doses/Devices
Day 1	84mg (3 devices)
Week 1 (twice weekly)	56mg (5 devices) or 84mg (6 devices)
Week 2-4 (twice weekly)	56mg (12 devices) or 84mg (18 devices)

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Policy Implementation/Update:

Action and Summary of Changes	Date
• Added new indication of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior and appropriate criteria • Updated criteria for TRD to reflect that prior treatment failures must be associated with the current depressive episode and changed the number of prior antidepressants to four from two different classes ○	10/2020
• Added major depressive disorder (MDD) symptoms, including suicidal ideation in patients who are at imminent risk for suicide as an investigational indication • Added criteria: ○ 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,); ○ The member does not have a contraindication to and has not previously failed ketamine ○ 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 ○ 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) ○ 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 ○ Medication is prescribed by, or in consultation with a psychiatrist • Updated quantity limit to better align with dosing regimen	03/2020
• Policy effective	05/2019
• Policy created	03/2019

estradiol/progesterone (Bijuva™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: Step Pharmacy Coverage Policy: UMP027

Description

Estradiol and progesterone (Bijuva) is an orally administered estrogen/progestin hormone replacement combination.

Length of Authorization

- Initial/Renewal: 12 months

Coverage Criteria

I. Estradiol and progesterone (Bijuva) may be considered medically necessary when the following criteria below are met:
   A. Treatment with two of the following: Amabelz, estradiol/norrthindone acet, Fyavolv, Jinteli, Lopreeza, Mimvey, Mimivey Lo, or norethindrone ac-eth estradiol has been ineffective, contraindicated, or not tolerated.

Policy Type: PA/SP Pharmacy Coverage Policy: UMP125

Split Fill Management*

Description

Everolimus (Afinitor, Afinitor Disperz) is an orally administered mammalian target of rapamycin (mTOR) inhibitor to reduce cell proliferation, angiogenesis, and glucose uptake.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

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

Initial Evaluation

I. Everolimus (Afinitor, Afinitor Disperz) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **OR**
      1. Everolimus (Afinitor Disperz) is requested; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist, hematologist, or neurologist; **AND**
   C. **Not** used in combination with any other oncolytic medication unless outlined below (e.g., exemestane in breast cancer); **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**
            a. The request is for everolimus (Afinitor) 10 mg; **OR**
            b. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
            c. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
               i. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**
      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 or everolimus (Afinitor) will be used in combination with exemestane (Aromasin); **AND**
            a. The request is for everolimus (Afinitor) 10 mg; **OR**
            b. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
            c. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
               i. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**
      3. Neuroendocrine tumor; AND
         i. 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; **AND**
               i. The request is for everolimus (Afinitor) 10 mg; **OR**
               ii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**

iii. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
    a. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **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 (Afinitor) will be used as monotherapy; **OR** in combination with lenvatinib (Lenvima); **AND**
    - a. The request is for everolimus (Afinitor) 10 mg; **OR**
    - b. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
    - c. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
        1. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**

5. Subependymal giant cell astrocytoma; AND
- i. The request is for everolimus (Afinitor) 10 mg; **OR**
- ii. The request is for everolimus (Afinitor Disperz); **OR**
- iii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
- iv. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg is requested; **AND**
    - a. The member has a contraindication to generic everolimus; **OR**

6. Partial seizure, associated with tuberous sclerosis syndrome; AND
- i. The member is refractory to at least two other antiepileptic therapies (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine); **AND**
- ii. The member will continue therapy with at least one other antiepileptic medication (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine); **AND**
- iii. Everolimus (Afinitor Disperz) is requested [Note: everolimus (Afinitor) is not FDA-approved in this setting]

II. Everolimus (Afinitor) is considered not medically necessary when criteria above are not met and/or when used for:
- A. Carcinoid tumor

III. 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. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Everolimus (Afinitor, Afinitor Disperz) is prescribed by, or in consultation with, an oncologist, hematologist, or neurologist; **AND**
IV. Member has exhibited a positive response to therapy, such as improvement or stability in disease or symptoms; **AND**
V. **Not** used in combination with any other oncolytic medication unless outlined below (e.g., exemestane in breast cancer); **AND**
VI. A diagnosis of one of the following:
- **Angiomyolipoma of the kidney, associated with tuberous sclerosis; AND**
  i. The request is for everolimus (Afinitor) 10 mg; **OR**
  ii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
  iii. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
    1. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**
- **Breast cancer; AND**
  i. Everolimus (Afinitor) will be used in combination with exemestane (Aromasin); **AND**
  ii. The request is for everolimus (Afinitor) 10 mg; **OR**
  iii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
  iv. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
    1. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**
- **Neuroendocrine tumor; AND**
  i. The request is for everolimus (Afinitor) 10 mg; **OR**
  ii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
  iii. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
    1. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**
- **Renal cell carcinoma; AND**

i. Everolimus (Afinitor) will be used as monotherapy; **OR** in combination with lenvatinib (Lenvima); **AND**
ii. The request is for everolimus (Afinitor) 10 mg; **OR**
iii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
iv. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg; **AND**
    1. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **OR**

- **Subependymal giant cell astrocytoma; AND**
    i. The request is for everolimus (Afinitor) 10 mg; **OR**
    ii. The request is for everolimus (Afinitor Disperz); **OR**
    iii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; **OR**
    iv. The request is for brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mgd; **AND**
    1. The member has a contraindication to generic everolimus; **OR**
- **Partial seizure, tuberous sclerosis syndrome associated; AND**
    i. The member will continue therapy with at least one other antiepileptic medication (e.g., carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine); **AND**
    ii. Everolimus (Afinitor Disperz) is requested [Note: everolimus (Afinitor) is not FDA-approved in this setting]

Supporting Evidence

I. Everolimus (Afinitor, Afinitor Disperz) has been evaluated in many clinical studies for various indications; however, they were focused on oncological indications (and not for transplantation management and rejection prophylaxis). Of note, everolimus (Zortress) does not have a prior authorization and is indicated for transplantation management and rejection prophylaxis. Everolimus products (Afinitor, Afinitor Disperz, Zortress) are not interchangeable, and it is recommended that utilization stay within the products' FDA-approved indication(s). Given the much lower cost as well as timely need for transplant medication access, prior authorization for everolimus (Zortress) is not commonly utilized.

II. Everolimus (Afinitor Disperz) received FDA-approval for subependymal giant cell astrocytoma related to tuberous sclerosis complex (TSC), and TSC associated partial onset seizures for adult as well as pediatric patients. On the contrary, everolimus (Afinitor) has FDA-approval only for adult patients (18 years and older) for all approved indications.

III. Everolimus (Afinitor) has been evaluated in combination with exemestane for HR+, HER2-, advanced or metastatic breast cancer. In clinical trials, subjects had previously progressed on or after an aromatase inhibitor, such as, anastrozole or letrozole. Additionally, subjects may have received one or more previous lines of chemotherapy. The major efficacy outcome was progression-free survival (PFS) which was statistically significant versus placebo; however, an overall survival (OS) benefit was not shown.

IV. Everolimus (Afinitor) was evaluated for safety and efficacy in neuroendocrine tumors, including those of pancreatic, lung, and gastrointestinal origin. Subjects were allowed previous somatostatin analog use, and the major efficacy outcome, PFS, was statistically significant regardless of previous somatostatin use in comparison to placebo. Overall survival was not statistically different between the treatment arms.

V. Everolimus (Afinitor) has been evaluated for safety and efficacy in renal cell carcinoma in patients who have previously received sunitinib (Sutent), sorafenib (Nexavar), or both sequentially. Subjects may also have had bevacizumab (Avastin), interleukin 2, or interferon alpha. Progression-free survival was shown to be statistically significant in favor of everolimus (Afinitor); however, OS was not statistically different compared to placebo. Results may have been confounded by high rates of crossover from placebo to active therapy (80%).

VI. A phase two, randomized trial to study efficacy and safety of lenvatinib (Lenvima) in renal cell carcinoma included everolimus (Afinitor) as active comparator. Lenvatinib (Lenvima) was administered in combination with everolimus (Afinitor) to the participants in treatment arm. Subjects in treatment arm had progressed on previous anti-angiogenesis therapy (VEGF-targeted therapy) such as pazopanib [Votrient], bevacizumab [Avastin], sunitinib [Sutent], or axitinib [Inlyta]. Primary outcome of progression-free survival (PFS) was shown to be statistically significant in favor of combination of lenvatinib (Lenvima) with everolimus (Afinitor) as compared to everolimus (Afinitor) monotherapy comparator. NCCN guidelines recommend everolimus (Afinitor) in combination with lenvatinib (Lenvima) and everolimus (Afinitor) monotherapy as category 1 and category 2A recommendations, respectively.

VII. Everolimus (Afinitor) was evaluated for safety and efficacy in tuberous sclerosis complex associated renal angiomyolipomas. Response rate was statistically significant in favor of everolimus (Afinitor), as well as the time to progression compared to placebo.

VIII. Everolimus (Afinitor, Afinitor Disperz) was evaluated in tuberous sclerosis completed-associated subependymal giant cell astrocytomas. Subjects included were of pediatric and adult populations. The primary outcome was SEGA response rate, which was statistically significant in favor of everolimus (Afinitor, Afinitor Disperz).

IX. Everolimus (Afinitor Disperz) was evaluated as an adjunct therapy for partial onset seizures associate with tuberous sclerosis complex (TSC). Subjects included were refractory to at least two conventional antiepileptic medications.

X. Everolimus is the AB-rated generic of everolimus (Afinitor) and as of October 2020, the 2.5 mg, 5 mg, and 7.5 mg strengths have generic availability. Medical necessity for brand Afinitor will be indicated by a contraindication to generic as intolerance to the generic is an indicator of intolerance to brand, given their therapeutic equivalence. Everolimus (Afinitor Disperz) is only available as brand (2 mg, 3 mg, and 5 mg).

Investigational or Not Medically Necessary Uses

I. Carcinoid tumor
   A. Everolimus (Afinitor) was evaluated in a clinical trial for safety and efficacy for carcinoid tumor. The primary efficacy outcome was not reached, and overall survival outcomes favored placebo. At this time efficacy of everolimus (Afinitor) in this setting is not known to be clinically beneficial.

II. Everolimus (Afinitor, Afintor Disperz) has not been sufficiently evaluated for safety and/or efficacy, and/or is in clinical trials for the following indications:
   A. Graft-versus-host disease
   B. Ependymoma
   C. Hodgkin Lymphoma or Non-Hodgkin Lymphoma

D. Central nervous system cancers
E. Kaposi's sarcoma
F. Thymoma and thymic carcinoma
G. Endometrial, ovarian, uterine cancers
H. Prostate cancer
I. Gastroesophageal carcinomas
J. Waldenstrom macroglbulinemia

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

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10. NCCN guidelines for kidney cancer, version 01.2021; 07/15/2020. Accessed 10/08/2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy for renal cell carcinoma to allow after trial and failure of one prior anti-angiogenic therapy rather than only sorafenib (Nexavar) or sunitinib (Sutent); and combination of everolimus (Afinitor) with lenvatinib (Lenvima); Updated supporting evidence to include clinical data; Added supporting evidence for FDA-approvals based on age for everolimus (Afinitor) and everolimus (Afinitor Disperz)	10/2020
Generic everolimus 2.5 mg, 5 mg, and 7.5 mg added to the policy, with brand coverage only if medical necessity established for brand over generic.	01/2020
Prior authorization criteria transitioned to policy format, specialist providers updated to include neurologist, Addition of trial of conventional antiepileptic therapies prior to payment consideration for everolimus (Afinitor Disperz), addition of age requirement for everolimus (Afinitor), updated QLL for everolimus (Afinitor Disperz) to be calculated upon clinical review.	12/2019

Afinitor Disperz with indications added to criteria, formatting update and quantity limits changed to mirror available package sizes.	05/2018
Criteria created	05/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP028

Description

Alprolix, Idelvion, and Rebinyn are extended half-life factor IX products for the treatment and prevention of bleeding in patients with hemophilia B.

Length of Authorization

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

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
Alprolix, coagulation factor IX (recombinant, Fc fusion protein	250, 500, 1000, 2000, 3000, 4000 IU	**On-demand Treatment**δ**:** Up to 100 IU/dL for the first dose, then again every 6 to 10 hours for another dose. Dosing is then every 24 hours for three days, then every 48 hours until healing is achieved **Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg once weekly or 100 IU/kg once every ten days • <12 years: Up to 60 IU/kg once weekly. More frequent or higher doses may be required **Perioperative Management**δ**:** • *Minor surgery*: Up to 80 IU/dL as a single infusion, then every 24 to 48 hours if needed until bleeding stops • *Major surgery*: Up to 100 IU/dL as the initial dose, then repeat dose after 6 to 10 hours and then every 24 hours for the first three days. After day three, the dosing may be extended to every 48 hours until healing is achieved	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 315 IU/kg every 28 days • <12 years: Up to 255 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Idelvion, coagulation factor IX (recombinant, albumin fusion protein	250, 500, 1000, 2000, 3500 IU	**On-demand Treatment*:** Up to 100 IU/dL every 48-72 hours for seven to 14 days until bleeding stops **Routine Prophylaxis:** • ≥12 years: Up to 40 IU/kg once weekly. Patients who are well controlled may be changed to 50-75 IU/kg every 14 days • <12 years: Up to 55 IU/kg every seven days **Perioperative Management*:** • *Minor*: Up to 80 IU/dL every 48 to 72 hours for at least one day until healing is achieved • *Major*: Up to 100 IU/dL every 48 to 72 hours for 7 to 14 days, or until bleeding stops and healing is achieved	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 170 IU/kg every 28 days • <12 years: Up to 230 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Rebinyn, coagulation factor IX (recombinant, GlycoPEGylated	500, 1000, 2000 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

‡Allows for +5% to account for assay and vial availability

δ One unit per kilogram body weight increases the circulating Factor IX level by 1% (IU/dL). Estimate the required dose or the expected in vivo peak increase in Factor IX level expressed as IU/dL (or % of normal) using the following: IU/dL (or % of normal) = [Total dose (IU)/Body Weight (kg)] x Recovery (IU/dL per IU/kg)

* One IU of Idelvion per kg body weight is expected to increase the circulating activity of factor IX as follows: adolescents and adults: 1.3 IU/dL per IU/kg; pediatrics (<12 years): 1 IU/dL per IU/kg. Determine the initial dose using the following: Required dose (IU) = body weight (kg) x desired factor IX rise (%of normal or IU/dL) x (reciprocal of recovery (IU/kg per IU/dL))

Initial Evaluation

I. Extended half-life factor IX products may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **hemophilia B (congenital factor IX deficiency)** and the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Use of extended half-life factor IX is planned for one of the following indications:
         i. On-demand treatment and control of bleeding episodes **AND** the number of factor IX units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
         ii. Perioperative management of bleeding; **OR**
         iii. ***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 trails. 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
3. Rebinyn® [Prescribing Information]. Plainsboro, NJ: Novo Nordisk; May 2017
4. National Hemophilia Foundation. Hemophilia B. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-B. Accessed July 8, 2019.
5. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
6. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	Date
New policy created for 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

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
Adynovate, antihemophilic factor (recombinant), PEGylated	250, 500, 750, 1000, 1500, 2000, 3000 IU	**On-demand Treatment:** Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg two times per week • <12 years: 55 IU/kg two times per week with a maximum of 70 IU/kg **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 50 IU/kg within one hour before surgery; Repeat after 24 hours as needed until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 60 IU/kg within one hour before operation; Repeat every 8-24 hours (6 to 24 hours for patients <12 years of age) until adequate round healing	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 420 IU/kg every 28 days • <12 years: Up to 590 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Eloctate, antihemophilic factor (recombinant), Fc fusion protein	250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000, 6000 IU	**On-demand Treatment:** Up to 50 IU/kg every 12 to 24 hours (every 8 to 24 hours in patients <6 years of age) until bleeding is resolved **Routine Prophylaxis:** • ≥6 years: Up to 65 IU/kg every three to five days • <6 years: Up to 65 IU/kg every three to five days. More frequent or higher doses (up to 80 IU/kg) may be required **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 40 IU/kg every 24 hours (every 12-24 hours for patients <6 years of age) for at least 1 day until healing is achieved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Preoperative dose of up to 60 IU/kg followed by a repeat dose of up to 50 IU/kg after 8-24 hours (6-24 for patients <6 years of age) and then every 24 hours until adequate wound healing (at least 7 days)	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥6 years: Up to 820 IU/kg every 28 days • <6 years: Up to 1,010 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Esperoct, antihemophilic factor (recombinant), glycopegylated	500, 1000, 1500, 2000, 3000 IU	**On-demand Treatment:** • ≥12 years: Up to 50 IU/kg per dose • <12 years: Up to 65 IU/kg per dose **Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg every four days • <12 years: Up to 65 IU/kg twice weekly **Perioperative Management:** *Minor and Major surgery:* Up to 50 IU/kg for those ≥12 years of age and up to 65IU/kg for those < 12 years of age	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 368 IU/kg every 28 days • <12 years: Up to 546 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days

Jivi, antihemophilic factor (recombinant), PEGylated	500, 1000, 2000, 3000 IU	**On-demand Treatment:** Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:** • ≥12 years: Up to 40 IU/kg two times per week • <12 years: Not FDA approved **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 30 IU/kg within every 24 hours for at least 1 day until healing as achieved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 50 IU/kg every 12-24 hours until adequate wound healing is complete, then continue therapy for at least another 7 days	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 340 IU/kg every 28 days • <12 years: Not FDA approved **Perioperative Management:** Up to the number of doses requested for 28 days

‡Allows for +5% to account for assay and vial availability

Initial Evaluation

I. Extended half-life factor VIII products may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **hemophilia A (congenital factor VIII deficiency)** and the following are met:
      1. Treatment is prescribed by, or in consultation with, a hematologist; **AND**
      2. Use of extended half-life factor VIII is planned for one of the following indications:
         i. On-demand treatment and control of bleeding episodes **AND** the number of factor VIII units requested does **not** exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
         ii. Perioperative management of bleeding; **OR**
         iii. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
            a. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
            b. Member has had more than one documented episode of spontaneous bleeding; **AND**
         iv. Dose and frequency do not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval; **AND**

3. Prior treatment with a standard half-life factor VIII product administered at the FDA approved dose for at least 50 exposure days was ineffective for the treatment or prevention of bleeding episodes; **OR**
    i. There is clinical documentation that all available standard half-life factor VIII products are inappropriate; **AND**
4. 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 trails. All are effective for reduction in annualized bleeding rates when used prophylactically compared to on-demand treatment.

VI. Extended half-life factor VIII products were developed to extend the half-life and allow for longer infusion intervals. The majority of published clinical trial evidence evaluating extended half-life products have included previously treated patients with a minimum of 50 exposure days and no history of inhibitors.

VII. There is no evidence that extended half-life factor replacement products are safer or more efficacious than standard half-life products. However, there are no head-to-head trials comparing extended half-life products and standard half-life products to definitively establish superior safety or efficacy.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of extended half-life factor VIII products in any other condition.

References

1. Adynovate® [Prescribing Information]. Westlake Village, CA: Shire; May 2018
2. Afstyla® [Prescribing Information]. Kankakee, IL: CSL Behring; September 2017
3. Esperoct® [Prescribing Information]. Novo Nordisk Inc: Plainsboro, NJ. October 2019.
4. Eloctate® [Prescribing Information]. Waltham, MA: Bioverativ Therapeutics; December 2017
5. Jivi® [Prescribing Information]. Whippany, NJ: Bayer; August 2018
6. National Hemophilia Foundation. Hemophilia A. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed July 5, 2019.
7. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
8. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Action and Summary of Changes	Date
Esperoct added to policy	05/2020
New policy created for extended half-life factor products	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP030

Description

Alphanate, Humate-P, and Wilate are factor VIII concentrates containing von Willebrand factor (VWF) for the treatment of von Willebrand disease (vWD) and/or hemophilia A.

Length of Authorization

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

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit[‡]
Alphanate, antihemophilic factor/von Willebrand factor complex (human)	250, 500, 1000, 1500, 2000 IU FVIII	**Control and prevention of bleeding – hemophilia A**[δ]: Up to 50 IU factor VIII/kg twice daily for at least three to five days. Following this, factor VIII levels should be maintained at 25 IU factor VIII/kg twice daily until healing has been achieved. Major hemorrhages may require treatment for up to ten days. Intracranial hemorrhages may require prophylaxis therapy for up to six months.	**Control and prevention of bleeding in hemophilia A:** Up to the number of doses requested every 28 days
		Perioperative management – hemophilia A: Up to 50 IU factor VIII/kg prior to surgery, then up to 50 IU factor VIII/kg twice daily for the next seven to ten days, or until healing has been achieved	**Perioperative management in hemophilia A:** Up to the number of doses requested for 28 days
		Control and prevention of bleeding and perioperative management – vWD[γ]**:** Pre-operative/pre-procedure dose: • Adults: Up to 60 IU VWF:RCo/kg body weight • Pediatrics: Up to 75 IU VWF:RCo/kg body weight Maintenance: • Adults: Up to 60 IU VWF:RCo/kg body weight at eight to 12 hour intervals as clinically needed for at least three to seven days	**Control and prevention of bleeding and perioperative management in vWD:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		• Pediatrics: Up to 75 IU VWF:RCo/kg body weight at eight to 12 hour intervals as clinically needed for at least three to seven days	
Humate-P, antihemophilic factor/von Willebrand factor complex (human)	600, 1200, 2400 IU vWF:RCo	**Control and prevention of bleeding – hemophilia A*:** • Minor: Up to 15 IU factor VIII:C/kg to achieve a factor VIII: C plasma level of approximately 30% of normal. One infusion may be sufficient. If needed, half of the loading dose may be given one or twice daily for one to two days • Moderate: Up to 25 15 IU factor VIII:C/kg to achieve a factor VIII: C plasma level of approximately 50% of normal, followed by 15 IU factor VIII:C/kg every eight to 12 hours for the first one to two days to maintain the factor VIII:C plasma level at 30% of normal. Continue the same dose one or twice for up to seven days or until adequate wound healing is achieved • Major: Initially up to 50 IU factor VIII:C/kg, followed by up to 25 IU factor VIII:C/kg every eight hours to maintain the factor VIII:C plasma level at 80-100% of normal for seven days. Continue the same dose one or twice daily for another seven days to maintain the factor VIII:C level at 30-50% of normal **Control and prevention of bleeding – vWD:** Up to 80 IU vWF:RCo (corresponding to 17 to 33 IU factor VIII in Humate-P) per kg body weight every eight to 12 hours. Adjust as needed based on the extent and location of bleeding. Repeat doses as long as necessary. **Perioperative management – vWD:** <u>Loading</u>: • Major: vWF:RCo target peak plasma level – 100 IU/dL; Target factor VIII:C activity – 80-100 IU/dL	**Control and prevention of bleeding – hemophilia A:** Up to the number of doses requested every 28 days **Control and prevention of bleeding – vWD:** Up to the number of doses requested every 28 days **Perioperative management – vWD:** Up to the number of doses requested for 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit[‡]
		• Minor: vWF:RCo target peak plasma level – 50-60 IU/dL; Target factor VIII:C activity – 40-50 IU/dL • Emergency: vWF:RCo target peak plasma level – 100 IU/dL; Target factor VIII:C activity – 80-100 IU/dL. Administer a dose of 50-60 IU vWF:RCo/kg body weight <u>Maintenance</u>: Initial maintenance dose should be half the loading dose, irrespective of additional dosing required to meet factor VIII:C targets. Subsequent doses should be based on the patient's vWF:RCo and factor VIII levels	
Wilate, von Willebrand factor/coagulation factor VIII complex (human)		**Control of bleeding episodes – vWD**[€]: Up to 60 IU/kg initially, followed by up to 40 IU/kg every 12 to 24 hours until vWF:Rco and factor VIII activity trough levels > 50%, for up to five to seven days **Perioperative management of bleeding – vWD**: Up to 60 IU/kg initially, followed by up to 40 IU/kg every 12 to 24 hours until wound healing achieved, up to six days or more. vWF:Rco and factor VIII activity trough levels > 50% and peak levels 100% until wound healing is achieved, up to six days or more	**Control of bleeding episodes – vWD:** Up to the number of doses requested every 28 days **Perioperative management of bleeding – vWD:** Up to the number of doses requested for 28 days

[‡]Allows for +5% to account for assay and vial availability

[δ] Dose (IU) = body weight (kg) x desired factor VIII rise (IU/dL or % normal) x 0.5 (IU/kg per IU/dL)

[ν] The ratio of VWF:RCo to factor VIII varies by lot, so with each new lot, check the IU vWF:RCo/Vial to ensure accurate dosing

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

[ψ] Target peak plasma vWF:RCo level – baseline plasma vWF:RCo level) – body weight (kg)/in vivo recovery. If the in vivo recovery is not available, assume an in vivo recovery of 2 IU/dL per IU/kg and calculate the loading dose as follows: (100 – baseline plasma vWF:RCo) x body weight (kg)/2

[€] The ratio between vWF:RCo and factor VIII activities is approximately 1:1. The dosage should be adjusted according to the extent and location of the bleeding.

Initial Evaluation

von Willebrand Disease

I. **Alphanate** or **Humate-P** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologists; **AND**
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
   C. Use is planned for one of the following indications:
      1. Treatment of spontaneous and trauma-induced bleeding episodes; **OR**
      2. Used as surgical bleeding prophylaxis during major or minor procedures when desmopressin (DDAVP) is either ineffective or contraindicated; **AND**
      3. **Alphanate** will not be used for severe (type 3) vWD undergoing major surgery

II. **Wilate** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologists; **AND**
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
   C. Use is planned for one of the following indications:
      1. Perioperative management of bleeding; **OR**
      2. For the treatment of spontaneous and trauma-induced bleeding episodes when one of the following is met:
         i. Member has severe vWD; **OR**
         ii. Member has mild or moderate vWD and the use of desmopressin (DDAVP) is known or suspected to be ineffective or contraindicated; **AND**
   D. Wilate will not be used for the routine prophylactic treatment of spontaneous bleeding episodes; **AND**
   E. Wilate is not being used for hemophilia A

Hemophilia A (congenital factor VIII deficiency)

I. **Alphanate** or **Humate-P** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   B. A diagnosis of hemophilia A has been confirmed by blood coagulation testing; **AND**
   C. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding episodes **AND** the number of factor VIII/VWF units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
      2. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
         i. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
         ii. Member has had more than one documented episode of spontaneous bleeding; **OR**
      3. Perioperative management of bleeding; **AND**

D. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; **AND**
E. Dose and frequency does not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval

II. Alphanate, Humate-P, and Wilate are considered investigational when used for any other condition.

Renewal Evaluation

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

Supporting Evidence

von Willebrand Disease

I. Von Willebrand disease (vWD) is the most common of the inherited bleeding disorders. Although vWD is common, only a fraction of patients seek medical attention due to bleeding symptoms due to the mild nature of the disease in many patients, and to the lack of bleeding challenges.
II. There are three types of inherited vWD:
    - Type 1 – The most common type that accounts for about 70% of cases. It reflects a quantitative deficiency of von Willebrand factor (vWF). The clinical presentation varies from mild to moderately severe.
    - Type 2 – Accounts for 25-30% of cases and is characterized by several qualitative abnormalities of vWF (e.g. altered size rations or biologic properties).
    - Type 3 – The most severe type of disease with very low or undetectable levels of vWF. Patients typically present with severe bleeding involving both the skin and mucous membrane surfaces and soft tissues and joints. Replacement therapy with vWF is usually required.
III. Choice of therapy begins with an accurate and complete diagnosis of vWD, plus patient-specific factors must be taken to account (e.g. history of bleeding, response to prior therapies).
IV. A trial of desmopressin (DDAVP) should be considered in all patients with type 1 and most with type 2, but not in patients with type 3 vWD. Typically, minor bleeding episodes can be treated with DDAVP without further therapeutic intervention. Major surgery typically requires replacement with vWF. However, Alphanate is not indicated for patients with severe vWD undergoing major surgery.
V. Patients with type 3 vWD, those with more severe type 1, and many of those with certain subtypes of type 2 disease often require replacement therapy with a vWF-containing product to control bleeding. However, vWF is not generally given as long-term prophylaxis like is done in patients with hemophilia A.

VI. The safety and efficacy of factor VIII/vWF complex products were established based on open-label, non-randomized trails. All replacement are effective in restoring hemostasis.

Hemophilia A

I. Hemophilia A (factor VIII deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. The availability of factor replacement products has dramatically improved care for those with hemophilia A.

II. There are varying severities of hemophilia A depending on the level of factor produced by the patient. Hemophilia A is divided into the following categories based on severity:

   i. **Severe**: <1% factor activity (<0.01 IU/mL)
   ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
   iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL

III. There are three general approaches to bleeding management in those with hemophilia A:

   i. Episodic ("on demand") treatment that is given at the time of clinically evident bleeding
   ii. Perioperative management of bleeding for those undergoing elective surgery/procedures
   iii. Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia A is to replace the deficient coagulation factor either through episodic ("on demand") treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor VIII products are the treatment of choice for hemophilia A as recommended by The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia A. Therapy should be initiated early with the goal of keeping the trough factor VIII level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. The safety and efficacy of the standard half-life products were established based on open-label, non-randomized trails. All replacement products can produce satisfactory hemostasis.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of factor VIII/vWF complex products in any other condition.

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Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	Date
New policy created for factor VIII/vWF complex products	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP083

Split Fill Management*

Description

Fedratinib (Inrebic) is an orally administered kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
fedratinib (Inrebic)	100 mg tablets	Myelofibrosis	120 tablets/30 days	207644

Initial Evaluation

I. Fedratinib (Inrebic) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by or in consultation with a hematologist or oncologist; **AND**
   B. A diagnosis of **intermediate- to high-risk myelofibrosis (MF)** when the following are met:
      1. The member's myelofibrosis is characterized by one of the following: primary MF, post-polycythemia vera MF, or post essential thrombocytopenia MF; **AND**
      2. Treatment with ruxolitinib (Jakafi) has been ineffective, contraindicated, or not tolerated; **AND**
      3. Starting platelet count, measured within the past 30 days, is greater than or equal to 50,000/microL (50 X 10^9/L); **AND**
      4. Baseline spleen volume has been measured and documentation has been submitted with medication request

II. Fedratinib (Inrebic) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Symptomatic low-risk myelofibrosis (MF)
   B. Acute myeloid leukemia
   C. Polycythemia vera

Renewal Evaluation

I. Documentation of reduction in spleen volume or palpable spleen length; **AND**
II. Documentation of improvement in symptoms

Supporting Evidence

I. 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).
II. JAKARTA was a Phase 3, double-blind, randomized, placebo-controlled trial that met its primary endpoint of spleen response (defined as a >35% reduction in spleen volume from baseline as determined by magnetic resonance imaging or computed tomography) at week 24 and confirmed 4 weeks later; achieved by 36 % and 40% of patients in the fedratinib (Inrebic) 400 mg and 500 mg groups, vs 1% in the placebo group (P < .001).
    - The secondary endpoint of reduction of at least 50% in the total symptom score (TSS) from baseline to week 24 was 36%, 34%, and 7% in the 400 mg, 500 mg, and placebo groups, respectively.
III. JAKARTA-2 was a single-arm, open-label, non-randomized, Phase 2 trial in ruxolitinib (Jakafi) resistant or intolerant patients which reported a spleen response (≥35% reduction in spleen volume from baseline) in 46 (55%, 95% CI 44–66) of 83 patients at week 24.
    - The secondary endpoint of reduction of at least 50% in the total symptom score from baseline to week 24 was achieved in 26% of patients (23 of 90 evaluable for symptom response).
IV. Though patients in the clinical trials were previously on hydroxyurea, hydroxyurea does not play a role in the treatment of an intermediate-2 or high-risk myelofibrosis patient as its benefits are minimal. It is typically used in patients who have thrombocytosis/and are ineligible for ruxolitinib (Jakafi). However, anemia is worsened by this agent and will prevent most patients from being able to utilize it. Additionally, NCCN states that hydroxyurea has only a limited role in a patient who may benefit from cytoreduction in the low-risk category. Therefore previous treatment with hydroxyurea is not required in the intermediate-2 or high-risk myelofibrosis setting.
V. As of September 2019, NCCN guidelines recommend treatment with fedratinib (Inrebic) in patients with intermediate-2 or high-risk MF and a platelet count greater than 50,000 microL (category 2B recommendation) or in those with no response or loss of response to ruxolitinib (Jakafi) (category 2A recommendation).
VI. Unlike ruxolitinib (Jakafi), fedratinib (Inrebic) carries a black box warning for encephalopathy including Wernicke's, due to seven cases of Wernicke's encephalopathy during fedratinib (Inrebic) trials. As a result the fedratinib (Inrebic) program was previously placed on clinical hold.
VII. There is currently no evidence that fedratinib (Inrebic) is superior to ruxolitinib (Jakafi) as initial therapy for the treatment of myelofibrosis. As noted above NCCN guidelines provide ruxolitinib (Jakafi) a 2A recommendation in the first line setting and fedratinib (Inrebic) a 2B. Ruxolitinib (Jakafi) has a longer time on the market providing a more clear safety picture and through additional studies has been shown to improve survival in this disease state. Additionally, the

treatment paradigm of using ruxolitinib (Jakafi) in the first line setting allows members to have a second-line option with fedratinib (Inrebic). As JAKARTA-2 indicates fedratinib (Inrebic) has activity in ruxolitinib (Jakafi) resistant patients, but there is no evidence to say the reverse is true. Lastly, the cost of one year of treatment with ruxolitinib (Jakafi) is approximately $159,517, while the cost of fedratinib (Inrebic) is $255,500.

VIII. During the JAKARTA trial, fedratinib (Inrebic) showed dose interruptions due to adverse events in 21% of patients, dose reductions in 19%, and permanent discontinuation in 14% of patients.

IX. NCCN guidelines recommend consideration of clinical trial participation in patients with platelet counts less than 50, 000/microL. Guidelines state that patients with a platelet count less than 50, 000/microL experience a greater symptom burden and might benefit from symptomatically guided treatment options. However, at present time there are no effective treatment options for this group of patients since the majority of clinical trials evaluating treatment options for MF have excluded this group of patients, which is the case of fedratinib (Inrebic) trials.

Investigational or Not Medically Necessary Uses

I. Currently, there is no high-quality published clinical trial evidence supporting the safety or efficacy of fedratinib (Inrebic) in the following settings:
   A. Symptomatic low-risk myelofibrosis (MF)
   B. Acute myeloid leukemia
   C. Polycythemia vera

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

References

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Policy Implementation/Update:

Date Created	September 2019
Date Effective	November 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

fenfluramine (Fintepla®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

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: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
fenfluramine (Fintepla)	2.2 mg/ml solution	Dravet syndrome	360 ml/30 days

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. Provider attestation fenfluramine (Fintepla) will not be used in combination with cannabidiol (Epidiolex); **AND**
   D. A diagnosis of **Dravet syndrome** when the following are met:
      1. At least two of the following have been ineffective, not tolerated or all are contraindicated:
         i. clobazam (Onfi)
         ii. valproate (Depakote)
         iii. cannabidiol (Epidiolex)
         iv. stiripentol (Diacomit)

II. Fenfluramine (Fintepla) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Epileptic encephalopathies associated with SCN1A mutations
   B. Lennox-Gastaut syndrome
   C. Seizure disorders other than Dravet syndrome
   D. Use in combination with cannabidiol (Epidiolex)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Provider 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 the use in patients aged two years and older. This agent is being reintroduced at a lower strength. It was originally introduced as a weight-loss agent and was pulled from the market due to reports of cardiovascular adverse events. Given the serious 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. Dravet syndrome is a rare epileptic disease that can be misdiagnosed as other conditions such as cerebral palsy, Lennox-Gastaut syndrome, or vaccine encephalopathy; therefore, fenfluramine (Fintepla) must be prescribed, or in consultation with a neurologist.
III. Use of fenfluramine (Fintepla) is contraindicated with monoamine oxidase inhibitors due to increased risk of serotonin syndrome. Moreover, concomitant use with other serotonergic drugs such as selective serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), bupropion, triptans, and dietary supplements (e.g., St. John's Wort, tryptophan) will also increase risk of serotonin syndrome.
IV. 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.
V. Trial one (Lagae L, et al. 2019) was a Phase 3, randomized, double-blind, placebo-controlled, multicohort, multi-country trial that studied 119 patients ages two to 18 years, who had at least four convulsive seizures in a four-week period for the past 12 weeks prior to screening and were stable for at least four weeks prior to screening and throughout the trial on valproate, clobazam, topiramate, or levetiracetam. This trial excluded patients who were on concomitant stiripentol (Diacomit) therapy. Patients were randomized 1:1:1 to either fenfluramine 0.7 mg/kg/day, fenfluramine 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 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 0.2 mg/kg/day versus placebo ($p=0.0209$).

VI. 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 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 versus placebo arm. The primary efficacy outcome was the difference between fenfluramine 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%) ($p <0.001$).

VII. Fenfluramine (Fintepla) may be used as monotherapy, or concomitantly with stiripentol (Diacomit), or concomitantly as triple-therapy with stiripentol (Diacomit) and clobazam. However, concomitant use with cannabidiol (Epidiolex) has not been studied. Therefore, efficacy and safety of fenfluramine (Fintepla) used in combination with cannabidiol (Epidiolex) remains unknown.

VIII. There are no formal treatment guidelines published for Dravet syndrome; however, the consensus panel recommends clobazam and valproate as first-line therapy, with topiramate as second-line.

IX. 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. Lennox-Gastaut syndrome
   C. Seizure disorders other than Dravet syndrome

Appendix

I. Table 1: fenfluramine (Fintepla) Recommended Titration Schedule

	Without concomitant stiripentol	With concomitant stiripentol and clobazam

	Weight-based Dosage	Maximum Total Daily Dosage	Weight-based Dosage	Maximum Total Daily Dosage
Initial Dosage	0.1 mg/kg twice daily	26 mg	0.1 mg/kg twice daily	17 mg
Day 7	0.2 mg/kg twice daily	26 mg	0.15 mg/kg twice daily	17 mg
Day 14	0.35 mg/kg twice daily	26 mg	0.2 mg/kg twice daily	17 mg

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®)

UMP POLICY

Uniform Medical Plan

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP185

Description

Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®) is an opioid agonist FDA approved for the treatment of breakthrough cancer pain in those who are tolerant to, or already receiving, constant opioid treatment for continual cancer pain.

Length of Authorization

- Initial: Up to 12 months
- Renewal: Up to 12 months

Quantity Limits

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

	800 mcg lozenge handle		120 lozenges/30 days
	1200 mcg lozenge handle		120 lozenges/30 days
	1600 mcg lozenge handle		120 lozenges/30 days

Initial Evaluation

I. Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, fentanyl citrate) may be considered medically necessary when the following criteria are met:
   A. Member has a diagnosis of **chronic pain associated with cancer**; **AND**
   B. Member is enrolled into the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) program**; AND**
   C. Member is 18 years of age or older; **OR**
      1. If request is for fentanyl citrate (Actiq), member is 16 years of age or older; **AND**
   D. Medication is prescribed by, or in consultation with, an oncologist or pain specialist; **AND**
   E. Member is opioid tolerant; **AND**
   F. Member is <u>currently experiencing</u> 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 <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. Non-tolerant opioid members
   B. Any indication that is not for treatment of breakthrough pain in patients experiencing chronic pain associated with cancer

Renewal Evaluation

I. See initial evaluation section.

Supporting Evidence

I. Based off clinical trials, there is currently no evidence to support the use of fentanyl citrate (Abstral®, Fentora®, Lazanda®, Subsys®) in any age group below 18 years of age, with the exception of fentanyl citrate (Actiq®, fentanyl citrate) which was studied in those aged 16 years and older.

II. Due to the FDA indication, Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS), and strict dosing guidelines, these agents are not to be prescribed without the consultation or direct supervision of a pain specialist or oncologist.
III. All fentanyl citrate products, and the parties involved in their use (i.e., outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors) are required to be enrolled into the TIRF REMS program, in accordance with FDA guidelines.
IV. The policy aligns with recommendations of the Centers for Disease Control, the Washington State Agency Medical Directors Group, and the Bree Collaborative around safe and appropriate opioid prescribing.
V. This policy is in full compliance with UMP's regulations and mandates regarding the chronic use of opioids.
VI. This policy applies to all groups under UMP, including Public Employees Benefit Board (PEBB) and School Employees Benefits Board (SEBB).

Investigational or Not Medically Necessary Uses

I. Fentanyl citrate (Abstral) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraines dental pain, or use in the emergency department
II. Fentanyl citrate (Actiq)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraines and dental pain
III. Fentanyl citrate (Fentora)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain, including headache/migraine and dental pain
IV. fentanyl citrate (Lazanda)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraine and dental pain, or in emergency department
V. fentanyl citrate (Subsys)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraine and dental pain, or in emergency department

Appendix

I. Table 1: Product dosing schedule and conversion from lozenge (Actiq) to other formulation

Product Name	Titration Dosing Schedule
fentanyl citrate (Abstral)	**Start:** 100mcg, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half

	hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Please see chart below for conversion when switching from Actiq to Abstral*	
	200mcg	2x 100mcg, *or* 1x 200mg tab
	300mcg	3x 100mcg, *or* 1x 300mg tab
	400mcg	4x 100mcg, *or* 2x 200mcg, *or* 1x 400mg tab
	600mcg	3x 200mcg, *or* 1x 600mg tab
	800 mcg	4x 200mcg, *or* 1x 800mg tab

Initial Dosing Recommendations for Patients on ACTIQ	
Current ACTIQ Dose (mcg)	**Initial Abstral Dose (mcg)**
200	100 mcg
400	200 mcg
600	200 mcg
800	200 mcg
1200	200 mcg
1600	400 mcg

Product Name	**Titration Dosing Schedule**	
fentanyl citrate (Actiq)	**Start:** 200mcg taken over 15 minutes, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 200mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Note: No more than six units is allowed to be dispensed at one time until maintenance dose is found.*	
	400 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	600 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	800 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	1200 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
	1600 mcg lozenge handle	Same instructions as above **Note: No more then six units is allowed to be dispensed at one time until maintenance dose is found.*
Product Name	**Titration Dosing Schedule**	

	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.*	
fentanyl citrate (Fentora)	200 mcg buccal tablet 2x 100mcg, *or*	1x 200mg tab
	400 mcg buccal tablet	4x 100mcg, *or* 2x 200mg tab, *or* *1x 400mg tab*
	600 mcg buccal tablet	3x 200mcg, *or* 1x 600mg tab
	800 mcg buccal tablet	4x 200mcg, *or* 1x 800mg tab
Initial Dosing Recommendations for Patients on ACTIQ		
Current ACTIQ Dose (mcg)		**Initial Fentora Dose (mcg)**
200		100 mcg
400		100 mcg
600		200 mcg
800		200 mcg
1200		2x 200 mcg
1600		2x 200 mcg
For patients converting from ACTIQ doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg FENTORA tablet and should proceed using multiples of this tablet strength		
Product Name		**Titration Dosing Schedule**
fentanyl citrate (Lazanda)	**Start:** 100mcg (one spray in each nostril) if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Due to differences in pharmacokinetic properties and individual variability, do not switch patients on a mcg per mcg basis from any other fentanyl product to Lazanda as Lazanda is not equivalent with any other fentanyl product, nor is Lazanda a generic version of any other fentanyl product.*	
	200 mcg nasal spray *Note: Only comes in a 100mcg and 400mcg bottle, these strengths are achieved by intervals of 100mcg or 400mcg*	2 x 100 mcg spray (1 in each nostril)
	400 mcg nasal spray	1 x 400 mcg
	800 mcg nasal spray *Note: Only comes in a 100mcg and 400mcg bottle, these strengths are achieved by intervals of 100mcg or 400mcg*	2 x 400mcg (1 in each nostril)
Product Name		**Titration Dosing Schedule**

fentanyl citrate (Subsys)	**Start:** 100mcg, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Please see chart below for conversion when switching from Actiq to Subsys.*	
	100 mcg sublingual spray	1 × 100 mcg unit
	200 mcg sublingual spray	1 × 200 mcg unit
	400 mcg sublingual spray	1 × 400 mcg unit
	600 mcg sublingual spray	1 × 600 mcg unit
	800 mcg sublingual spray	1 × 800 mcg unit
	1200 mcg sublingual spray	2 × 600 mcg unit
	1600 mcg sublingual spray	2 × 800 mcg unit

Initial Dosing Recommendations for Patients on ACTIQ	
Current ACTIQ Dose (mcg)	**Initial Subsys Dose (mcg)**
200	100 mcg
400	100 mcg
600	200 mcg
800	200 mcg
1200	400 mcg
1600	400 mcg

a. For patients converting from Actiq doses 400 mcg and below, titration should be initiated with 100 mcg SUBSYS and should proceed using multiples of this strength.
b. For patients converting from Actiq doses of 600 and 800 mcg, titration should be initiated with 200 mcg SUBSYS and should proceed using multiples of this strength.
c. For patients converting from Actiq doses of 1200 and 1600 mcg, titration should be initiated with 400 mcg SUBSYS and should proceed using multiples of this strength

Product Name	**Titration Dosing Schedule**	
fentanyl citrate (fentanyl citrate)	**Start:** 200mcg taken over 15 minutes, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 200mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher. **Note: No more than six units is allowed to be dispensed at one time until maintenance dose is found.*	
	200 mcg lozenge handle	1 × 200 mcg unit
	400 mcg lozenge handle	1 × 400 mcg unit
	600 mcg lozenge handle	1 × 600 mcg unit
	800 mcg lozenge handle	1 × 800 mcg unit
	1200 mcg lozenge handle	1 × 1200 mcg unit
	1600 mcg lozenge handle	2 × 1600 mcg unit

References

1. Abstral® [Prescribing Information]. Solana Beach, CA: Sentynl Therapeutics, Inc. October 2019.
2. Actiq® [Prescribing Information]. North Wales, PA: Teva Pharmaceuticals USA, Inc. October 2019.
3. Fentora® [Prescribing Information]. North Wales, PA: Teva Pharmaceuticals USA, Inc. October 2019.
4. Lazanda® [Prescribing Information]. Northbrook, IL: West Therapeutic Development, LLC October 2019.

5. Subsys® [Prescribing Information]. Chandler, AZ: Insys Therapeutics, Inc. October 2019.
6. Washington State Agency Medical Directors Group. Interagency Guideline on Prescribing Opioids for Pain. 3rd Edition, June 2015. Available: www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed attestation criteria following UMP guidance, as cancer is exempt diagnosis for the attestation requirement. Per UMP guidance, left in baseline and ongoing pain assessments, mental health and substance abuse screening, and provider check of Prescription Drug Monitoring Program (PDMP) for any other opioid use and concurrent use of benzodiazepines and other sedatives.	06/2020
Converted to policy, added in REMS question, age limitation question, and clarified prescribing provider specialty needed for approval.	04/2020
Previous reviews	11/15/13, 12/28/17
Criteria created	12/2011

filgrastim (Neupogen®, Zarxio®, Nivestym™, Granix®)

UMP POLICY

Uniform Medical Plan

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP031

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

Dosage Form	Indication	Quantity Limit
Self-Administered Agents		
Neupogen (filgrastim) 300mcg/mL; 480mcg/1.6mL; 300mc/0.5mL; 480mcg/0.8mL Vial; 300mcg/0.5mL;480mcg/0.8mL Syringe	• Bone marrow transplant • Peripheral progenitor cell (PBPC) mobilization and transplant • Prophylactic use in patients with non-myeloid malignancy • Treatment of chemotherapy-induced febrile neutropenia • Neutropenic complications from prior cycle • Acute myeloid leukemia (AML) patient following induction or consolidation chemotherapy • Bone marrow transplantation failure or engraftment delay • Severe chronic neutropenia • Myelodysplastic syndrome • Exposure to myelosuppressive doses of radiation	15 prefilled syringes or 15 vials per 30-day supply
Zarxio (filgrastim-sndz)* 300mcg/0.5mL; 480/0.8mL Syringe		15 prefilled syringes or 15 vials per 30-day supply
Nivestym (filgrastim-aafi) 300mcg/mL; 480mcg/1.6mL Vial; 300mcg/0.5mL; 480/0.8mL Syringe		15 prefilled syringes or 15 vials per 30-day supply
Granix (tbo-filgrastim) 300mcg/mL; 480mcg/1.6mL Vial; 300mcg/0.5mL; 480/0.8mL Syringe		15 prefilled syringes or 15 vials per 30-day supply
Leukine (sargramostim) 250mcg; 500mcg/mL vial		15 vials per 30-day supply

**No PA required*

Initial Evaluation

I. Products may be considered medically necessary when the following criteria below are met:

Zarxio is the preferred short-acting G-CSF • **Patients must have failed, have contraindication to, or intolerance of Zarxio prior to the consideration of any other short-acting G-CSF.**   ○ There is no prior authorization required for Zarxio unless requesting above the quantity limit noted above.

A. A diagnosis of:
   1. **Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant**; **OR**
   2. Patient who experienced a **neutropenic complication from a prior cycle of the same chemotherapy**; **OR**
   3. **Bone Marrow Transplant (BMT)**; **OR**
   4. **Bone Marrow Transplantation (BMT) failure or Engraftment Delay**; **OR**
   5. Patients acutely exposed to **myelosuppressive doses of radiation** (Hematopoietic Subsyndrome of Acute Radiation Syndrome); **OR**
   6. **Acute Myeloid Leukemia (AML)** patient following induction or consolidation chemotherapy; **OR**
   7. **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**
      ii. Patient is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 10% or greater **AND** one or more of the following co-morbidities:
         a. Elderly patients (age 65 or older) receiving full dose intensity chemotherapy
         b. History of recurrent febrile neutropenia from chemotherapy
         c. Extensive prior exposure to chemotherapy
         d. Previous exposure of pelvis, or other areas of large amounts of bone marrow, to radiation
         e. Pre-existing neutropenia (ANC ≤ 1000/mm3) or bone marrow involvement with tumor
         f. Patient has a condition that can potentially increase the risk of serious infection (i.e. HIV/AIDS)
         g. Infection/open wounds
         h. Recent surgery
         i. Poor performance status
         j. Poor renal function (creatinine clearance <50)
         k. Liver dysfunction (elevated bilirubin >2.0)
         l. Chronic immunosuppression in the post-transplant setting including organ transplant; **OR**
   8. **Myelodysplastic Syndrome**; **AND**
      i. Endogenous serum erythropoietin level of ≤500 mUnits/mL; **AND**

ii. Patient has lower risk disease (i.e., defined as IPSS-R [Very Low, Low, Intermediate], IPSS [Low/Intermediate-1], WPSS [Very Low, Low, Intermediate]); **AND**

iii. Used for treatment of symptomatic anemia in patients without del(5q); **AND**

iv. Patient is receiving concurrent therapy with Erythropoiesis Stimulating Agents (ESAs); **AND**

a. Patient has ring sideroblasts < 15% and will use in combination with lenalidomide following no response (despite adequate iron stores) or loss or response to an ESA alone; **OR**

b. Patient has ring sideroblasts ≥ 15%; **OR**

9. **Treatment of chemotherapy-induced febrile neutropenia**; **AND**

i. Patient has been on prophylactic therapy with filgrastim; **OR**

ii. Patient has not received prophylactic therapy with a granulocyte colony stimulating factor; **AND**

a. Patient has one or more of the following risk factors for developing infection-related complications:

i. Sepsis Syndrome

ii. Age >65

iii. Absolute neutrophil count [ANC] <100/mcL

iv. Duration of neutropenia expected to be greater than 10 days

v. Pneumonia or other clinically documented infections

vi. Invasive fungal infection

vii. Hospitalization at the time of fever

viii. Prior episode of febrile neutropenia; **OR**

10. **Severe chronic neutropenia**; **AND**

i. Patient must have an absolute neutrophil count (ANC) < 500/mm3; **AND**

ii. Patient must have a diagnosis of one of the following:

a. Congenital neutropenia

b. Cyclic neutropenia

c. Idiopathic neutropenia; **OR**

11. **Management of CAR-T related Toxicity**; **AND**

i. Patient has been receiving therapy with CAR T-cell therapy (e.g. tisangenleclecleucel (Kymriah), Axicabtagene Ciloleucel (Yescarta), etc.); **AND**

ii. Patient is experiencing neutropenia related to their therapy.

Renewal Evaluation

I. Renewal criteria

A. Same as initial prior authorization policy criteria

Supporting Evidence

I. All indications listed follow FDA labeled indications or compendia indications
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

1. Neupogen [package insert]. Thousand Oaks, CA; Amgen Inc; June 2016. Accessed March 2018.
2. Zarxio [package insert]. Princeton, NJ; Sandoz Inc; December 2017. Accessed July 2018.
3. Nivestym [package insert]. Lake Forest, IL; Hospira Inc; July 2018. Accessed July 2018
4. Neulasta [package insert]. Thousand Oaks, CA; Amgen Inc; June 2018. Accessed July 2018
5. Fulphila [package insert]. Zurich, Switzerland; Mylan GmbH; September 2018. Accessed October 2018.
6. Udenyca [package insert]. Redwood City, California; Coherus Biosciences; November 2018. Accessed November 2018.
7. Leukine [package insert]. Bridgewater, NJ; sanofi-aventis US LLC; February 2017. Accessed March 2018.
8. Granix [package insert]. North Wales, PA; Teva Pharmaceuticals USA, Inc.; June 2017. Accessed March 2018.
9. 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
10. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Myeloid Growth Factors. Version 1.2018. National Comprehensive Cancer Network, 2017. 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.
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12. Wisconsin Physicians Service Insurance Corporation. Local Coverage Determination (LCD): Human Granulocyte/Macrophage Colony Stimulating Factors (L34699). Centers for Medicare & Medicaid Services, Inc. Updated on 1/23/2018 with effective date 02/1/2018. Accessed March 2018.
13. First Coast Service Options, Inc. Local Coverage Determination (LCD): G-CSF (Neupogen®, Granix™, Zarxio™) (L34002). Centers for Medicare & Medicaid Services, Inc. Updated on 6/10/2016 with effective date 7/5/2016. Accessed March 2018.
14. National Government Services, Inc. Local Coverage Article: Filgrastim, Pegfilgrastim, Tbofilgrastim, Filgrastim-sndz (e.g., Neupogen®, Neulasta™, Granix™, Zarxio™) - Related to LCD L33394 (A52408). Centers for Medicare & Medicaid Services, Inc. Updated on 9/23/2016 with effective date 10/1/2016. Accessed March 2018.
15. Palmetto GBA. Local Coverage Determination: White Cell Colony Stimulating Factors (L37176). Centers for Medicare & Medicaid Services, Inc. Updated on 12/7/2017 with effective date 2/26/2018. Accessed March 2018.

Policy Implementation/Update:

Date Created	February 2018
Date Effective	February 2017
Last Updated	December 2019
Last Reviewed	12/28/2018, 10/15/2019, 12/2019

Action and Summary of Changes	Date
Updated quantity level limit to allow 15 doses per 30 day supply	12/2019
Policy title change, designate Zarxio as a preferred product, add "No PA Required" to Initial Evaluation Section 1 boxed information	10/2019

Added Nivestym, biosimilar to Neupogen	10/2018
Criteria update. Zarxio is the preferred short-acting G-CSF	02/2017

fostemsavir (Rukobia)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP204

Description

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

Length of Authorization

I. Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
fostemsavir (Rukobia)	600 mg extended-release tablets	Human immunodeficiency virus type 1 (HIV-1) infection	60 tablets/30 days

Initial Evaluation

I. Fostemsavir (Rukobia) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an infectious disease or HIV specialist; **AND**
   C. Provider attestation that fostemsavir (Rukobia) will be used in combination with at least one other antiretroviral medication; **AND**
   D. Member has a diagnosis of **human immunodeficiency virus type 1 (HIV-1) infection** when all of the following are met:
      1. Provider attests the member is heavily treatment-experienced as indicated by treatment failure, contraindication, intolerance, and/or resistance to medications in three or more classes of HIV therapies; **AND**
      2. Provider attests the member has two or less remaining medications that are fully active and available to construct a viable treatment regimen; **AND**
      3. The member is failing their current treatment regimen, as defined by HIV-1 RNA viral load greater than, or equal to, (≥) 200 copies/mL; **AND**
      4. The member does not have concurrent untreated hepatitis B infection.

II. Fostemsavir (Rukobia) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of disease response to treatment defined by improvement or stability of disease symptoms [e.g., decreased HIV-1 RNA, increased CD4 cell count from baseline].

Supporting Evidence

I. Fostemsavir (Rukobia) has not been studied in randomized controlled trials in pediatric patients <18 years of age.
II. In the pivotal Phase 3 trial (BRIGHTE), subjects were given fostemsavir (Rukobia) in combination with other antiretroviral(s). Per the National Institute for Health recommendations, HIV-1 infections should never be treated with monotherapy. Fostemsavir (Rukobia) is not approved as monotherapy and must be used in combination with other antiretroviral(s).
III. In the BRIGHTE trial, subjects were included if they had documented resistance, contraindication, or intolerance to three or more antiretroviral classes and had two or less fully active and available antiretroviral agents in two or fewer classes of which a treatment regimen could be constructed. Fostemsavir (Rukobia) is only approved for use in heavily treatment-experienced individuals.
IV. The primary efficacy endpoint in the BRIGHTE trial was the adjusted mean $\log_{10}$ change in HIV-1 RNA from baseline after Day 8 which was -0.17 in the placebo group and -0.79 in the fostemsavir (Rukobia) group (difference: -0.625; 95% CI: -0.810, -0.441; p<0.0001). Increase in CD4 count was found to be clinically significant after 96 weeks. The mean increase was 204.7 c/mm3 and 119.1 for randomized and non-randomized cohorts, respectively. Patients with the lowest CD4 counts at baseline (<20 c/mm3) showed the largest increase by week 96 with a mean of 239.8 c/mm3, a clinically meaningful improvement.
V. In clinical trials HIV-1 RNA suppression was seen after Day 8, thus the initial authorization of three months ensures that there is adequate time to respond to treatment and that the therapy remains safe and effective.
VI. The National Institute for Health defines virologic failure as the inability to maintain suppression of HIV RNA <200 copies/mL and persistent viral loads at this level are often indicative of the viral evolution and drug-resistance mutations.
VII. Subjects with chronic, untreated hepatitis B (HBV) co-infection were excluded from the BRIGHTE trial. Elevations in hepatic transaminases were more commonly observed in subjects with HBV co-infection and consistent with HBV reactivation, particularly when anti-hepatitis therapy was discontinued.

Investigational or Not Medically Necessary Uses

I. Fostemsavir (Rukobia) has not been sufficiently studied for safety and efficacy for any other condition to date.

References

1. Rukobia [Prescribing Information]. Research Triangle Park, NC: ViiV Healthcare. July 2020.
2. NIH AIDSInfo. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV (2019)
3. Rukobia (fostemsavir) Integrated Review. FDA. 2020
4. Fostemsavir in adults with multi-drug resistant HIV-1 infection (BRIGHTE). *N Engl J Med*. 2020 Mar 26;382(13):1232-1243. (NCT 02362503)

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of HIV-specialist to criterion 1B, addition of establishing therapy through a different health plan in the renewal criteria, removal of requirement for HIV resistance assessment from renewal criteria as response to treatment is already being assessed via decrease HIV RNA, addition of supporting evidence V.	03/2021
Policy created	11/2020

Policy Type: PA Pharmacy Coverage Policy: UMP197

Description
Gabapentin ER (Gralise) is an orally administered anticonvulsant. Gabapentin enacarbil (Horizant) is a prodrug of gabapentin.

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

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
gabapentin ER (Gralise)	300 mg tablets	Postherpetic neuralgia	90 tablets/30 days
	600 mg tablets		
gabapentin enacarbil (Horizant)	300 mg tablets	Postherpetic neuralgia; Restless leg syndrome	30 tablets/30 days
	600 mg tablets		60 tablets/30 days

Initial Evaluation

I. Gabapentin ER (Gralise) or gabapentin enacarbil (Horizant) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. A diagnosis of one of the following:
      1. **Postherpetic neuralgia (PHN); AND**
         i. Treatment with gabapentin, greater than or equal to, 1800 mg per day has been ineffective, contraindicated, or not tolerated; **AND**
         ii. Treatment with pregabalin has been ineffective, contraindicated, or not tolerated; **OR**
      2. **Moderate-to-severe primary restless leg syndrome**; **AND**
         i. Request is for gabapentin enacarbil (Horizant); **AND**
         ii. Treatment with **all** of the following has been ineffective, contraindicated, or not tolerated:
            a. pramipexole; **AND**
            b. ropinirole; **AND**
            c. pregabalin

II. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) are considered investigational when used for all other conditions, including but not limited to:
   A. Diabetic peripheral neuropathy
   B. Postmastectomy pain syndrome

C. Seizures
D. Other neuropathic pain

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
III. A diagnosis of one of the following:
- **Restless Leg Syndrome (RLS); AND**
  i. Member has exhibited improvement or stability of restless leg syndrome symptoms [e.g., improved pain, sleep, fatigue]; **OR**
- **Postherpetic neuralgia (PHN); AND**
  1. Member has exhibited improvement or stability of symptoms [e.g. improved pain, skin sensitivity].

Supporting Evidence

I. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for safety and efficacy in pediatric patients under the age of 18 years.
II. A phase 3, placebo-controlled, randomized trial has shown gabapentin ER (Gralise) to be efficacious in decreasing pain associated with postherpetic neuralgia over placebo (p=0.013). Phase 4 studies have similarly suggested effectiveness in pain reduction in patients with postherpetic neuralgia.
III. A phase 3, placebo-controlled, randomized trial has shown gabapentin enacarbil (Horizant) to be efficacious in reducing pain associated with postherpetic neuralgia over placebo (p=0.013) after 13 weeks.
IV. Guidelines for postherpetic neuralgia recommend immediate release gabapentin as a first line treatment option. It is recommended patients trial gabapentin IR before switching to an extended-release gabapentin product such as gabapentin ER (Gralise) or gabapentin enacarbil (Horizant).
V. Standard of care for treatment of postherpetic neuralgia includes use of pregabalin as first line therapy.
VI. A phase 4, placebo-controlled randomized trial found gabapentin enacarbil (Horizant) to improve restless leg syndrome symptoms on patient reported scales (IRLS) over placebo (p=0.014) as well as clinician-assessed (CGI-I) scales (p=0.004) after 12 weeks of treatment.
VII. Restless leg syndrome guidelines, as published by the American Academy of Neurology (AAN), recommend dopamine agonists (e.g. pramipexole, ropinirole, rotigotine) and gabapentin enacarbil (Horizant) as first line treatment options. A small (n=39) double-blind, placebo-controlled trial investigated a possible reduced response to gabapentin enacarbil (Horizant) following long-term dopaminergic treatment. A significant difference (p=0.045) in restless leg syndrome symptoms (IRLS) was found between dopamine treatment-naïve and dopamine treatment-experienced individuals when treated with gabapentin enacarbil (Horizant). Patients

who were dopamine-experienced had been treated with a dopamine agonist for at least 90% of the past 5 consecutive years. Although gabapentin enacarbil (Horizant) is recommend as a first-line therapy along with dopamine agonists, due to the small sample size, as well as the unknown effects of shorter-term uses of dopamine agonists on gabapentin enacarbil (Horizant) responses, enacarbil (Horizant) should not be chosen as a first-line agent over a dopamine agonist.

VIII. Restless leg syndrome guidelines as published by the American Academy of Neurology (AAN) also lists pregabalin as having moderate evidence for use in treatment of RLS aligned with ropinirole, a dopamine agonist.

Investigational or Not Medically Necessary Uses

I. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   - A. Diabetic peripheral neuropathy
     - i. A placebo-controlled, randomized trial found no significant difference in efficacy from placebo and three different doses of gabapentin enacarbil (Horizant) in subjects with diabetic peripheral neuropathy.
   - B. Postmastectomy pain syndrome
     - i. A small (n=21) open-label study found a small positive improvement in pain intensity after 8 weeks with gabapentin ER (Gralise). Further placebo-controlled, randomized trials are needed to validate efficacy and safety for this indication.
   - C. Seizures
     - i. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for efficacy and safety in the treatment of seizures.
   - D. Other neuropathic pain
     - i. Gabapentin ER (Gralise) and gabapentin enacarbil (Horizant) have not been adequately studied for efficacy and safety in the treatment of neuropathic pain not associated with postherpetic neuralgia or restless leg syndrome.

References

1. Gralise [Prescribing Information]. Menlo Park, CA: Depomed. September 2012.
2. Horizant [Prescribing Information]. Research Triangle Park, NC: GSK. March 2013.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Update to new policy format, addition of pregabalin as required agent to try and fail, removal of renal status related criteria	10/2020
Previous review	11/2011

gilteritinib (XOSPATA®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP032

Description

Gilteritinib (Xospata) is an orally administered FLT3 Tyrosine Kinase Inhibitor.

Length of Authorization

- Initial: 6 months
- Renewal: Twelve months

Quantity limits

gilteritinib (Xospata)	Indication	Quantity Limit	DDID
40 mg tablets	Relapse/Refractory FLT3 AML	90 tablets/30 days	204950

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 <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   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

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

1. Xospata [Prescribing Information]. Northbrook, Illinois: Astellas Pharma; November 2018.
2. NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. Version 3.2018. National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed January 10, 2019.
3. Rydapt [Prescribing Information]. East Hanover, New Jersey: Novartis pharmaceuticals; June 2018.
4. ClinicalTrials.gov

Policy Implementation/Update:

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

Action and Summary of Changes	Date

Policy Type: PA/SP Pharmacy Coverage Policy: UMP033

Description

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

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity limits

glasdegib (Daurismo)	Indication	Quantity Limit	*DDID*
25 mg tablets	Acute myeloid leukemia	60 tablets/30 days	204939
100 mg tablets	Acute myeloid leukemia	30 tablets/30 days	204938

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 <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   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

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

1. Cortes JE, Heidel FH, Hellmann A, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2018
2. Daurismo [prescribing information]. Pfizer Labs, Inc.: New York, NY. November 2018.
3. Venclexta [prescribing information]. Genentech: San Francisco, CA. November 2018.
4. U.S. Food and Drug Administration. FDA approves new treatment for patients with acute myeloid leukemia. Published November 21, 2018. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm626443.htm
5. NCCN Clinical Practice Guideline in Oncology: Acute Myeloid Leukemia. Version 3.2018. National Comprehensive Cancer Network. Available at: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Updated November 30, 2018.
6. Cortes, J. E., Heidel, F. H., Heuser, M., et al. A Phase 2 Randomized Study of Low Dose Ara-C with or without Glasdegib (PF-04449913) in Untreated Patients with Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome. Blood, 128(22), 99. Accessed December 03, 2018.
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Policy Implementation/Update:

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

Action and Summary of Changes	Date

glycerol phenylbutyrate (Ravicti®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP034

Description

Glycerol phenylbutyrate (Ravicti) is an orally administered nitrogen-binding agent.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

glycerol phenylbutyrate (Ravicti)	Indication	Quantity Limit	DDID
1.1 g/mL (25 mL bottle)	Urea Cycle Disorder	500 mL (20 bottles)/30 days	177929

Initial Evaluation

I. Glycerol phenylbutyrate (Ravicti) may be considered medically necessary when the following criteria below are met:
   A. Age two months and older; **AND**
   B. A diagnosis of:
      1. **Urea Cycle Disorder**; **AND**
         i. Has tried and failed to be managed by dietary protein restriction and amino acid supplementation, or has a contraindication to those therapies; **AND**
         ii. Has tried and failed sodium phenylbutryrate (Buphenyl); **AND**
         iii. Has plasma ammonia level >100 µmol/L

Renewal Evaluation

I. Patient has previously received treatment with glycerol phenylbutyrate (Ravicti); **AND**
II. The patient's chronic hyperammonia is being properly manage with glycerol phenylbutyrate; **AND**
III. Absence of unacceptable toxicity from the medication
IV. Documentation that the patient's plasma ammonia level is <35 µmol/L

Supporting Evidence

I. Glycerol phenylbutyrate (Ravicti) is indicated for use as a nitrogen-binding agent for chronic management of patient with urea cycle disorder (UCD) that cannot be managed by dietary protein restriction and/or dietary supplementation alone.

II. An elevated plasma ammonia level of 150 µmol/L (>260 µg/dl) or higher in neonates and > 100 µmol/l (175 µg/dl) in older children and adults, is a strong indication for the presence of a urea cycle disorder.

III. Clinical study results showed ammonia values ranged from 9-35 µmol/L following treatment with glycerol phenylbutrate (Ravicti).

References

1. Ravicti [Prescribing Information]. South San Francisco, CA: Hyperion Therapeutics Inc.;January 2013.
2. Lee B. Urea Cycle Disorder: Management. UpToDate [database online]. Available at
   a. <http://www.uptodate.com/home/index.html> Updated March 26, 2013. [Accessed on July 22, 2013].
3. Urea Cycle DisordersTreatment Guidelines. Rare Disease Clinical Research Network. Available at < http://rarediseasesnetwork.epi.usf.edu/ucdc/physicians/guidelines-main.htm> [Accessed on July 22, 2013].

Policy Implementation/Update:

Date Created	July 2013
Date Effective	August 2013
Last Updated	January 2019
Last Reviewed	

Action and Summary of Changes	Date
Criteria update: Included new FDA expanded indication for pediatric patients 2 months and older. Glycerol phenylbutyrate (Ravicti) was originally approved for pediatric patients 2 years and older. Additionally, a question was added to the renewal portion of this policy to assess for toxicity.	01/2019

Glycopyrronium (Qbrexza™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP035

Description

Glycopyrronium (Qbrexza) is an anticholinergic that works to reduce sweating by inhibiting the action of acetylcholine on sweat glands.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
glycopyrronium (Qbrexza)	Topical 2.4% single-use pre-moistened cloth	Primary axillary hyperhidrosis	30 cloths/30 days	203316 203275

Initial Evaluation

I. Glycopyrronium (Qbrexza) may be considered medically necessary when the following criteria below are met:
   A. Member is nine years of age or older; **AND**
   B. The medication is prescribed by or in consultation with a dermatologist; **AND**
   C. Member has a confirmed diagnosis of primary axillary hyperhidrosis; **AND**
   D. Member has a history of medical complications such as skin infections or significant functional impairments due to condition; **OR**
   E. Member has a significant impact to activities of daily living due to condition; **AND**
   F. Member has tried and failed or have a contraindication to both of the following:
      1. Over-the-counter topical antiperspirant therapy (e.g. Drysol Solution, Hypercare Solution, or Aluminum Chloride Hexahydrate 20% Solution); **AND**
      2. Oral anticholinergics (e.g. oxybutynin tablet, glycopyrrolate tablet)

Renewal Evaluation

I. Member has experienced a reduction in spontaneous axillary sweat production; **AND**
II. Member has experienced an improvement in activities of daily living.

Supporting Evidence

I. Glycopyrronium (Qbrexza) is the first topical anticholinergic agent FDA-approved for treatment of axillary hyperhidrosis. The drug was studied in two, phase III, randomized, double-blind, vehicle controlled, parallel group trials, ATMOS-1 (N=344) and ATMOS-2 (N=353) evaluating daily glycopyrronium (Qbrexza) application to each axilla over 4 weeks. ASDD responder rate at week 4 was significantly greater for glycopyrronium (Qbrexza) versus vehicle in both trials.
    - ATMOS-1: 52.8% vs 28.3%; *P*=<0.001
    - ATMOS-2: 66.1% vs 26.9%; *P*=<0.001

II. Safety and efficacy of glycopyrronium (Qbrexza) has been established in patients older than nine years of age.

III. Glycopyrronium (Qbrexza) is FDA approved in the setting of primary hyperhidrosis. Secondary causes of hyperhidrosis should be ruled out. Patients with generalized, secondary hyperhidrosis usually present as adults and report sweating that occurs both while awake and sleeping. Medications should be carefully reviewed, as many can cause generalized sweating

IV. Topical antiperspirants offer a localized treatment approach with a favorable side effect profile compared to other therapies. Although glycopyrronium (Qbrexza) is a topical formulation, it carries a similar side effect profile to oral anticholinergics (e.g. oxybutynin).

References

1. Qbrexza [prescribing information]. Menlo Park,CA: Dermira; June 2018.
2. Glaser DA, Hebert AA, Nast A, Werschler WP, Green L, Mamelok R, Drew J, Quiring J, Pariser DM, Topical Glycopyrronium Tosylate for the Treatment of Primary Axillary Hyperhidrosis: Results from the ATMOS-1 and ATMOS-2 Phase 3 Randomized Controlled Trials, Journal of the American Academy of Dermatology (2018), doi: 10.1016/j.jaad.2018.07.002.
3. UpToDate, Inc. Primary focal hyperhidrosis. UpToDate [database online]. Waltham, MA. Updated January 16, 2018. Available at: http://www.uptodate.com/home/index.html. Accessed October 2, 2018.
4. Hornberger J, Grimes K, Naumann M, Glaser DA, Lowe NJ, Naver H, et al. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. Journal of the American Academy of Dermatology. 2004;51(2):274–86.
5. Baumgartner, Fritz J. Hyperhidrosis [Internet]. London: BMJ Publishing Group Ltd. 2015. Available from: Best Practice. Accessed October 3, 2018
6. International Hyperhidrosis Society. Primary Axillary Hyperhidrosis Clinical Guidelines. Available at: https://www.sweathelp.org/pdf/IHhS%20Axillary%20Hh%20Treatment%20Algorithm%20Aug-2018.pdf. Accessed October 3, 2018

Policy Implementation/Update:

Date Created	October 2018
Date Effective	November 2018
Last Updated	September 2019
Last Reviewed	09/2019

Action and Summary of Changes	**Date**
Transition from criteria to policy	09/2019
Criteria created	10/2018

Gonadotropin-releasing hormone (GnRH)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP092

Description

The listed treatments are synthetic gonadotropin-releasing hormone (GnRHs) analog that exhibits a potent reversible inhibition of gonadotropin secretion through suppression of testicular and ovarian steroidogenesis.

Length of Authorization and Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit	Duration of approval
naferlin (Synarel)	2 mg/mL nasal spray	Endometriosis	16 mL/30 days	6 months
		Central Precocious Puberty	40 mL/30 days	6 months
leuprolide acetate (Lupron)	1 mg/0.2mL kit	Central Precocious Puberty	1 kit/14 days	6 months
Leuprolide acetate (Lupron Depot)	3.75 mg/syringe kit	Endometriosis, Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	1 syringe kit/30 days	6 months for all indications EXCEPT - 3 months for uterine leiomyoma -2 months for Endometrial Thickness
	7.5 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/30 days	6 months
	11.25 mg/syringe kit	Advanced Prostate Cancer, Advanced Breast Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	1 syringe kit/90 days	6 months for all indications EXCEPT - 3 months for Uterine Leiomyoma -2 months for Endometrial Thickness
	22.5 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/90 days	6 months
	30 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/120 days	6 months
	45 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/180 days	6 months
Leuprolide acetate (Lupron Depot-Ped)	7.5 mg/syringe kit	Central Precocious Puberty	1 syringe kit/30 days	6 months
	11.25 mg/syringe kit	Central Precocious Puberty	1 syringe kit/30 days OR 1 syringe kit/90 days	6 months

	15 mg/syringe kit	Central Precocious Puberty	1 syringe kit/30 days	6 months
	30 mg/syringe kit	Central Precocious Puberty	1 syringe kit/90 days	6 months
Leuprolide acetate (Eligard)	7.5 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/30 days	6 months
	22.5 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/90 days	6 months
	30 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/120 days	6 months
	45 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/180 days	6 months
Leuprolide-norethindrone (Lupaneta)	3.75-5 mg/syringe	Endometriosis	1 syringe kit/30 days	6 months
	11.25-5 mg/syringe	Endometriosis	1 syringe kit/90 days	6 months
Renewal				
naferlin (Synarel)	2 mg/mL nasal spray	Central Precocious Puberty	40 mL/30 days	6 months
leuprolide acetate	1 mg/0.2mL kit (each kit contains 2.8 mL of leuprolide acetate and 14 disposable syringes)	Central Precocious Puberty	1 kit/14 days	6 months
Leuprolide acetate (Lupron Depot)	3.75 mg/syringe kit	Endometriosis, Advanced Breast Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	1 syringe kit/30 days	- 12 months for Advanced Breast Cancer and Gender Dysphoria EXCEPT - 6 months for Endometriosis (**MAX #1 renewal allow**) - NO RENEWAL for Uterine leiomyoma and Endometrial Thickness
	7.5 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/30 days	12 months
	11.25 mg/syringe kit	Advanced Prostate Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria	1 syringe kit/90 days	- 12 months for Advanced Breast Cancer and Gender Dysphoria EXCEPT - 6 months for Endometriosis (**MAX #1 renewal**)

				- NO RENEWAL for Uterine leiomyoma and Endometrial Thickness
	22.5 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/90 days	12 months
	30 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/120 days	12 months
	45 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/180 days	12 months
Leuprolide acetate (Lupron Depot-Ped)	7.5 mg/syringe kit	Central Precocious Puberty	1 syringe kit/30 days	6 months
	11.25 mg/syringe kit	Central Precocious Puberty	1 syringe kit/30 days OR 1 syringe kit/90 days	6 months
	15 mg/syringe kit	Central Precocious Puberty	1 syringe kit/30 days	6 months
	30 mg/syringe kit	Central Precocious Puberty	1 syringe kit/90 days	6 months
Leuprolide acetate (Eligard)	7.5 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/30 days	12 months
	22.5 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/90 days	12 months
	30 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/120 days	12 months
	45 mg/syringe kit	Advanced Prostate Cancer	1 syringe kit/180 days	12 months
Leuprolide-norethindrone (Lupaneta)	3.75-5 mg/syringe	Endometriosis	1 syringe kit/30 days	6 months
	11.25-5 mg/syringe	Endometriosis	1 syringe kit/90 days	6 months (**MAX #1 renewal allow**)

Initial Evaluation

I. Synthetic gonadotropin-releasing hormones (GnRHs) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with 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. Member has clinical diagnosis of CPP and documented onset of secondary sexual characteristics (any physical characteristic developing at puberty) made when:
      a. The FEMALE member was < 8 years of age, and is currently less than 11 years of age; **OR**
      b. The MALE member was < 9 years of age, and is currently less than 12 years of age; **AND**
   ii. Member's diagnosis of CPP has been confirmed by a pubertal response to a GnRH stimulation test; **AND**
   iii. Member has bone age advanced at least one year beyond chronological age; **AND**
   iv. Tumor has been ruled out by ALL of the following:
      a. Beta human chorionic gonadotropin (HCG) level
      b. Adrenal and pelvic ultrasound or testicular ultrasound
      c. Computerized tomography (CT) of the head; **AND**
   v. The request is for leuprolide acetate 1 mg/0.2mL, Lupron Depot-Ped, or Synarel; **OR**
4. **Advanced prostate cancer; AND**
   i. The request is for Lupron-Depot, or Eligard; **OR**
5. **Advanced breast cancer in premenopausal women; AND**
   i. The request is for Lupron-Depot 11.25 mg; **OR**
6. **Reduction of endometrial thickness prior to endometrial ablation; AND**
   i. The request is for Lupron Depot (3.75 mg, 11.25 mg), **OR**
7. **Gender Dysphoria.**

II. Gonadotropin-releasing hormone (GnRH) analogs are considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. In vitro fertilization
   B. Premenstrual syndrome

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. 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**
      3. Male member is less than 12 years of age; **OR**
   C. **Advanced prostate cancer; AND**
      1. Provider attest that member has exhibited improvement in or stability of disease symptoms; **OR**
   D. **Advanced breast cancer in premonopausal women**; **AND**
      1. Provider attests that member has exhibited improvement in or stability of disease symptoms; **OR**
   E. Gender Dysphoria; AND
      1. A renewal approval of 12 months is allowed.

Supporting Evidence

I. In clinical trials, leuprolide acetate (Lupron Depot), when compared to danazol 800 mg per day, significantly reduced symptoms of endometriosis (e.g., pelvic pain, dysmenorrhea, dyspareunia, pelvic tenderness, and induration) and inducing 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 mg 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 there, safety and efficacy has not been established beyond 6 months.

III. In a randomized study, leuprolide acetate (Lupron depot) plus iron demonstrated clinical response ((HCT of 36% or greater and Hb of 12 g/dL or greater) compared with iron alone at week 4 (40% vs 17%), week 8 (71% vs 39%), and week 12 (75% vs 49%). In the leuprolide acetate (Lupron depot) arm: excessive vaginal bleeding decreased in 80% of patients at 3 months; uterine and myoma volume decreases of 25% or greater occurred in 60% and 54% of patients, respectively; and mean fibroid diameter decreased from 6.3 cm to 5.6 cm. The use of leuprolide acetate (Lupron depot) for uterine leiyomyoma should not exceed a FDA max of 3 months therapy.

IV. 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.

V. 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.

VI. 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.

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Policy Implementation/Update:

Date Created	October 2014
Date Effective	October 2014
Last Updated	October 2019
Last Reviewed	08/2017, 10/2019

Action and Summary of Changes	**Date**
Criteria transitioned into policy format. With the following updates made: added supporting evidence, added indications that are medically not necessary, added renewal criteria, limit renewal for endometriosis to a total duration of 12 months, limit initial approval for uterine leiomyoma to 3 months per FDA max, require bone mineral density evaluation upon renewal for the treatment of endometriosis, require concomitant iron therapy for uterine leiomyoma indication, updated Lupron-depot strength for advanced breast cancer, and no renewal for uterine leiyomyoma and endometrial thickness.	10/2019

Growth Hormone, Human

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

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 others: Six months
- Renewal: 12 months
  - i. AIDS wasting syndrome: three months only
  - ii. Short bowel syndrome: no renewal allowed
  - iii. All others: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
somatropin (Genotropin)	5 mg/mL cartridge	• Prader-Willi syndrome • Turner syndrome • Growth failure in children • Growth hormone deficiency, adults • Idiopathic short stature	0.32 mg/kg/28 days
	12 mg/mL cartridge		
somatropin (Genotropin MiniQuick)	0.2 mg/0.25 mL syringe		
	0.4 mg/0.25 mL syringe		
	0.6 mg/0.25 mL syringe		
	0.8 mg/0.25 mL syringe		
	1 mg/0.25 mL syringe		
	1.2 mg/0.25 mL syringe		
	1.4 mg/0.25 mL syringe		
	1.6 mg/0.25 mL syringe		
	1.8 mg/0.25 mL syringe		
	2 mg/0.25 mL syringe		
somatropin (Humatrope)	5 mg vial	• Turner syndrome • Growth failure in children	0.35 mg/kg/28 days
	6 mg cartridge		
	12 mg cartridge		

	24 mg cartridge	• Growth hormone deficiency, adults • Idiopathic short stature • Short stature homeobox-containing gene (SHOX) deficiency	
somatropin (Norditropin FlexPro)	5 mg/1.5 mL pen injector 10 mg/1.5 mL pen injector 15 mg/1.5 mL pen injector 30 mg/3 mL pen injector	• Noonan syndrome • Prader-Willi syndrome • Turner syndrome • Growth failure in children • Growth hormone deficiency, adults • Idiopathic short stature	0.448 mg/kg/28 days
somatropin (Nutropin AQ)	5 mg/2 mL pen injector 10 mg/2 mL pen injector 20 mg/2 mL pen injector	• Growth failure associated with chronic renal insufficiency (CRI) • Turner syndrome • Growth failure in children • Growth hormone deficiency, adults • Idiopathic short stature	**35 years and younger:** 0.7 mg/kg/28 days **36 years or older:** 0.35 mg/kg/28 days
somatropin (Omnitrope)	5.8 mg vial 5 mg/1.5 mL cartridge 10 mg/1.5 mL cartridge	• Prader-Willi syndrome • Turner syndrome • Growth failure in children • Growth hormone deficiency, adults • Idiopathic short stature	0.32 mg/kg/28 days
somatropin (Saizen)	5 mg vial 8.8 mg vial	• Growth failure in children • Growth hormone deficiency, adults	0.28 mg/kg/28 days
somatropin (Saizen Click Easy)	8.8 mg/1.51 mL cartridge		
somatropin (Saizenprep)	8.8 mg cartridge		
somatropin (Serostim)	4 mg vial 5 mg vial 6 mg vial	• Wasting or cachexia associated with HIV	168 mg/28 days
somapacitan (Sogroya)	10 mg/1.5 mL pen	• Growth hormone deficiency, adults	6 mL/28 days
somatropin (Zomacton)	5 mg vial	• Turner syndrome • Growth failure in children	0.35 mg/kg/28 days

	10 mg vial	• Growth hormone deficiency, adults • Idiopathic short stature • Short stature homeobox-containing gene (SHOX) deficiency	
somatropin (Zorbtive)	8.8 mg vial	• Short bowel syndrome	224 mg/28 days

Growth Hormone Therapy in Children and Adolescents

Initial Evaluation

Omnitrope is the preferred growth hormone agents.
- There is no prior authorization required on the 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**
         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 Omnitrope has been ineffective, contraindicated, or not tolerated; **OR**
            a. The request is for Humatrope or Zomacton for SHOX gene deficiency; **OR**
            b. The request is for Nutropin AQ for chronic renal insufficiency; **OR**
            c. The request is for Norditropin for Noonan Syndrome; **OR**
         iii. **Growth Hormone Deficiency; AND**
            a. Member has signs or symptoms of growth hormone deficiency such as growth velocity two SD below the age-appropriate mean **OR** height two SD below the age-appropriate mean; **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**

ii. Member has had hypothalamic-pituitary defect (such as major congenital malformation [ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk], tumor, or irradiation), and deficiency of at least one additional pituitary hormone; **OR**

b. Member is a neonate with hypoglycemia and does not attain a serum GH concentration above 5 micrograms/L and has deficiency of at least one additional pituitary hormone; **AND**

c. Treatment with Omnitrope has been ineffective, contraindicated, or not tolerated; **OR**

iv. **Growth failure in children born small for gestational age (SGA); AND**

a. Member failed to manifest catch-up growth by two years of age; **AND**

b. Birth weight and/or length is less than two SD below the mean for gestational age; **AND**

c. Height remains less than two SD below the mean age and gender at two years of age; **AND**

d. Treatment with Omnitrope has been ineffective, contraindicated, or not tolerated

Growth Hormone Therapy in Adults

Initial Evaluation

Omnitrope is the preferred growth hormone agents.

- There is no prior authorization required on the 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 <u>one</u> 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 <u>TWO</u> 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 <u>BOTH</u> of the following:
            1. A subnormal response (less than 10 ng/ml) to any <u>TWO</u> 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 Omnitrope has been ineffective, contraindicated, or not tolerated

II. Growth hormone is considered <u>not medically necessary</u> when used for all other conditions, including but <u>not limited to</u>:
   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 short stature associated with Turner Syndrome, Prader-Willi Syndrome, Noonan Syndrome, SHOX Gene Deficiency, Chronic Renal Insufficiency, Children with Growth Hormone Deficiency, 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 Omnitrope 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**
   B. **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**

C. Adult Growth Hormone Deficiency; AND

a. Treatment with Omnitrope 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. Sogroya (somapacitan), provides the option of weekly administration; 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 I GF-I also increases the likelihood that this diagnosis is correct.

FDA Approved Indications for Growth Hormone Products

Brand	GHD		TS	ISS	SGA	PWS	CKD	NS	SHOX	HIV	SBS
	Ch	Ad									
Genotropin	x	x	x	x	x	x					
Humatrope	x	x	x	x	x				x		
Norditropin	x	x	x		x			x			
Nutropin AQ	x	x	x	x			x				
Omnitrope	x	x	x	x	x	x					
Saizen	x	x									
Zomacton	x	x	x	x	x				x		
Sogroya		x									
Serostim										x	
Zorbtive											x

GHD = Growth Hormone Deficiency (Ch = Children, Ad = Adult)
TS = Turner Syndrome
ISS = Idiopathic Short Stature
SGA = Growth failure in children born Small for Gestational Age
PWS = Prader-Willi Syndrome in children
CKD = Growth failure due to chronic kidney disease
NS = Noonan Syndrome
SHOX = Short stature homeobox-containing gene deficiency
HIV = HIV-associated Wasting or Cachexia
SBS = Short Bowel Syndrome

Investigational or Not Medically Necessary Uses

I. Idiopathic short stature
   A. Growth hormone therapy for certain conditions may not be approved when growth hormone 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 children who are short compared to others in their age- and gender appropriate reference range for unknown or hereditary reasons. 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.

II. Increased athletic performance in adults
   A. The AACE recommends that GH should only be prescribed to patients with clinical features suggestive of adult GHD. Administration of GH to patients for improvement of athletic performance or for any reason other than its approved medical uses is not recommended.

III. There is insufficient or inconclusive medical and scientific evidence to support the safety and efficacy of growth hormone therapy in the listed conditions:
   A. Growth hormone insensitivity (Laron Syndrome)
   B. Constitutional growth delay
   C. Children with growth failure caused by glucocorticoids
   D. Children who are not growth hormone deficient but have short stature associated with chronic disease
   E. Children with chromosomal and genetic disorders (except Turner's and Prader Willi Syndromes) or familial short stature
   F. Russell Silver syndrome
   G. Altered body habitus or lipodystrophy associated with antiviral therapy
   H. Precocious puberty
   I. Obesity
   J. Cystic fibrosis
   K. Idiopathic dilated cardiomyopathy
   L. Juvenile idiopathic arthritis

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15. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab. 2000;85(11):3990-3.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new product Sogroya in non-preferred position	02/2021
Added further supporting evidence to duration of therapy with Serostim in the setting of HIV/AIDS associated wasting or cachexia. Updated renewal section to require previous Omnitrope.	11/2020
Updated to policy format. Updated growth hormone stimulation requirements to align with guideline recommendations (Molitch 2011 and Grimberg 2016). Added requirement of treatment to be prescribed by specialist. Removed route for coverage in the setting of idiopathic short stature as growth hormone therapy for certain conditions may not be approved when growth hormone use is not expected to correct a significant functional deficit OR when reduced growth is not due to an underlying medical condition.	11/2019
Criteria update: updated criteria to new format, deleted question defining HIV wasting, added routing questions for growth failure in children born small for gestational age added clinical notes to questions.	03/2018
Criteria Created	08/2014

Policy Type: PA/SP Pharmacy Coverage Policy: UMP036

Description

The listed treatments for Hepatitis C are for orally administered Direct-Acting Antiviral (DAA) therapies.

Length of Authorization

- Initial: 8-16 weeks based on liver status*
- Renewal: none

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*
glecaprevir/pibrentasvir (Mavyret)	100 mg/40 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	84 tablets/28 days
sofosbuvir (Sovaldi)	200 mg oral tablet	HCV Genotype 2 or 3 Treatment naïve or experienced	28 tablets/28 days
	400 mg oral tablet	HCV Genotype 1, 2, 3, 4 Treatment naïve or experienced	
ledipasvir/sofosbuvir (Harvoni)	45 mg /200 mg tablet	HCV Genotype 1, 4, 5, 6 Treatment naïve or experienced	28 tablets/28 days
	90 mg /400 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	
ledipasvir/sofosbuvir (authorized generic)	45 mg /200 mg tablet	HCV Genotype 1, 4, 5, 6 Treatment naïve or experienced	28 tablets/28 days
	90 mg /400 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	
velpatasvir/sofosbuvir (Epclusa)	100 mg/400 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	28 tablets/28 days
velpatasvir/sofosbuvir (authorized generic)	100 mg/400 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	28 tablets/28 days
daclatasvir (Daklinza)	30 mg, 60 mg, 90 mg tablet	HCV Genotype 1, 3	28 tablets/28 days

elbasvir/grazoprevir (Zepatier)	50 mg /100 mg tablet	HCV Genotype 4	28 tablets/28 days
velpatasvir/sofosbuvir/ voxilaprevir (Vosevi)	100 mg/400 mg/ 100 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment experienced	28 tablets/28 days
simeprevir (Olysio)	150 mg capsule	HCV Genotype 1 Treatment naïve or experienced	28 capsules/28 days
ombitasvir/paritaprevir/ ritonavir/dasabuvir (Viekira Pak)	12.5/75/50 mg oral tablet and dasabuvir 250 mg tablet	HCV Genotype 1a, 1b Treatment naïve or experienced	1 box/ 28 days
ombitasvir/paritaprevir/ ritonavir/dasabuvir (Viekira XR)	12.5/75/50 mg oral tablet and dasabuvir 250 mg tablet	HCV Genotype 1a, 1b Treatment naïve or experienced	1 box/28 days
ombitasvir/paritaprevir/ ritonavir (Technivie)	12.5/75/50 mg tablet	HCV Genotype 4	1 box/28 days

*See appendix for specific treatment durations

Initial Evaluation

Hepatitis C treatments may be considered medically necessary when the following criteria are met:

I. Patient has confirmed diagnosis of Hepatitis C and a quantifiable HCV RNA test >15 IU/mL within the last 12 months; **AND**

II. Required documentation for confirmation of treatment duration, as confirmed by a clinical pharmacist, include:
   A. HCV Genotype; **AND**
   B. Current HCV RNA viral load less than 12 months old; **AND**
   C. 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**
   D. If fibrosis level F4 (cirrhosis): Documentation decompensated or previous episodes of decompensated liver disease; **AND**
   E. Documentation of treatment history including:
      1. Prior treatment regimen; **AND**
      2. Duration of prior treatment; **AND**
      3. Response to treatment; **AND**
      4. Dates of prior treatment; **AND**
   F. Documentation, if available, of the presence or absence of resistant mutations in treatment experienced patients; **AND**
   G. The request is for treatment with the preferred product **Mavyret**; **OR**
   H. The request is for **Vosevi and the** member meets one of the specific settings below:
      1. Member has previously failed treatment with elbasvir-grazoprevir (Zepatier) or glecaprevir/pibrentasvir (Mavyret); **OR**
      2. Member has HCV genotype 3 and was previously treated with sofosbuvir

III. 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

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Policy Implementation/Update:

Action and Summary of Changes	Date

Updated to include specific scenarios for Vosevi approval	06/2021
Appendix updated to follow Mavyret label update indicating an 8-week treatment duration in treatment naïve, compensated cirrhosis patients. Add newly available lower doses of Solvaldi and Harvoni.	10/2019
Updated to remove provider specialty and F0 requirements	06/10/2019
Updated preferred products to only include Mavyret, sofosbuvir/velpatasvir (authorized generic to Epclusa), and Vosevi.	04/01/2019
Previous reviews	04/2015 11/2014 11/2015 12/2015 04/2016 06/2016 08/2016 09/2016 06/2017 11/2017 02/2018
Policy created	02/2014

Appendix:

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

Genotype	Regimen	Please select:
Genotype 1		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced^+ No cirrhosis	Mavyret x 16 weeks	
	Other:	
Treatment experienced^ + Cirrhosis	Mavyret x 16 weeks	
	Other:	
Treatment experienced‡ + No cirrhosis	Mavyret x 12 weeks	
	Other:	
Treatment experienced‡ + Cirrhosis	Mavyret x 12 weeks	
	Other:	
Treatment experienced' + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced' + Cirrhosis	Mavyret x 12 weeks	
	Other:	
Genotype 2		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced^ + No cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced^ + Cirrhosis	Vosevi x 12 weeks	

	Other:	
Treatment experienced‡ + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced‡ + Cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced' + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced' + Cirrhosis	Mavyret x 12 weeks	
	Other:	
Genotype 3		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced^+ No cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced^ + cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced‡ + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced‡ + cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced' + No cirrhosis	Mavyret x 16 weeks	
	Other:	
Treatment experienced' + Cirrhosis	Mavyret x 16 weeks	
	Other:	
Genotype 4		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced^+ No cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced^ + cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced‡ + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced‡ + Cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	

	Other:	
Treatment experienced[!] + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced[!] + Cirrhosis	Mavyret x 12 weeks	
	Other:	
Genotype 5		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced[^]+ No cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced[^] + cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced[‡] + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced[‡] + Cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced[!] + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced[!] + Cirrhosis	Mavyret x 12 weeks	
	Other:	
Genotype 6		
Treatment naïve + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment naïve + Cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced[^]+ No cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced[^] + cirrhosis	Vosevi x 12 weeks	
	Other:	
Treatment experienced[‡] + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced[‡] + Cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks	
	Other:	
Treatment experienced[!] + No cirrhosis	Mavyret x 8 weeks	
	Other:	
Treatment experienced[!] + Cirrhosis	Mavyret x 12 weeks	
	Other:	

[^]Treatment experienced after only NS5A (ledipasvir, velpatasvir, daclatasvir, elbasvir, ombitasvir) containing regimen
[‡]Treatment experienced after only NS3/4A PI (simeprevir, boceprevir, telaprevir) containing regimen
[!]Treatment experienced after peginterferon/ribavirin containing regimen with or without sofosbuvir
***Payment consideration for Daklinza with Sovaldi is reserved for no more than a 12 week course of treatment*

Hereditary Angioedema

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP075

Description

C1 esterase inhibitors (Cinryze, Haegarda, Berinert, Ruconest) are injectable medications that regulate the activation of various systems that are thought to modulate the increased vascular permeability during HAE attacks by preventing the generation of bradykinin.

Lanadelumab (Takhzyro), icatibant (Firazyr), 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) and icatibant (Firazyr) are injectable medications, and berotralstat (Orladeyo) is orally administered.

Length of Authorization

- Initial: Three months
- Renewal: Six months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
C1 esterase inhibitor (Cinryze)	500 unit single use vial for IV administration	HAE prophylaxis	20 vials/30 days
C1 esterase inhibitor (Haegarda)	2000 unit single use vial for SQ administration		Weight based 60 iu/kg twice weekly, refer to chart below for quantity
	3000 unit single use vial for SQ administration		
lanadelumab (Takhzyro)	300 mg/2 mL single dose vial for SQ administration		4 mL/28 days
berotralstat (Orladeyo)	110 mg capsules		28 capsules/28 days
	150 mg capsules		
C1 esterase inhibitor (Berinert)	500 unit single use vial for IV administration	Treatment of acute HAE attacks	Weight based 20 iu/kg, refer to chart below
C1 esterase inhibitor (Ruconest)	2100 unit single use vial for IV administration		16 vials/30 days
icatibant (Firazyr)	30 mg/3 mL SQ prefilled syringe		9 syringes (27 mL)/30 days

Medication	Body Weight (kg)	Vial Configuration	Vials per Dose	Number of Vials per 30 days
Haegarda	Up to 33 kg	2000 unit	1	8
	34-50	3000 unit	1	8
	51-67	2000 unit	2	16
	68-100	3000 unit	2	16
	101-133	2000 unit	4	32
	134-150	3000 unit	3	32
Berinert	Up to 25	500 unit	1	4

	25 - 50		2	8
	50 - 75		3	12
	75 - 100		4	16
	100-125		5	20
	125-150		6	24

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
               iii. tranexamic acid; **AND**
            d. "On demand" therapy (e.g., icatibant [Firazyr], 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) OR Berinert are requested; **OR**
    a. Ruconest is requested; **AND**
    b. Treatment with Berinert AND generic icatibant 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], 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 (Firazyr)**: the member is ≥ 18 years of age; **AND**
    a. Generic icatibant is prescribed; **OR**
    b. Brand Firazyr is prescribed and treatment with generic icatibant 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);
    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.; **AND**
III. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
IV. The medication is prescribed by, or in consultation with one of the following specialists: allergist, immunologist, dermatologist, hematologist, pulmonologist, medical geneticist; **AND**
V. The member continues to be evaluated for potentially treatable triggers of HAE attacks and is being managed to avoid triggers; **AND**
VI. The member has been seen and evaluated for medication efficacy and safety in the past 12 months; **AND**
VII. 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**
VIII. Documentation the member has experienced functional improvement AND improvement in the number, severity, or duration of attacks; **AND**
IX. **For prophylactic treatment of HAE**:
    - The member has not been prescribed more than one medication FDA-approved for HAE prophylaxis (Cinryze, Haegarda, Takhzyro, Orladeyo), etc.; **AND**
    - **For Haegarda**: documentation of current weight (within the last three months, to calculate appropriate dose); **OR**
    - **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**
    - The request is for **Orladeyo**; **OR**
X. **For acute treatment of HAE attacks:**
    - The member has not been prescribed more than one medication FDA approved for HAE treatment (e.g., icatibant [Firazyr], Berinert, Ruconest, Kalbitor); **AND**
    - **For brand Firazyr:** the member has tried and failed, not tolerated, or has contraindication to generic icatibant; **OR**
    - **For Berinert**: documentation of current weight within the last three months, to calculate appropriate dose

Supporting Evidence

I. Hereditary angioedema (HAE) is a rare disease characterized by recurrent and sometimes severe episodes of angioedema without urticarial or pruritus. Skin and mucosal tissues in the upper respiratory and gastrointestinal tracks are often affected and may have airway involvement leading to asphyxiation if not treated appropriately. It should be noted that it is not uncommon for patients to have mild and/or self-limiting attacks that do not require treatment. Non-pharmacologic and pharmacologic management of HAE is very complex and requires confirmatory tests and monitoring by, or in close consultation with, a specialist.

II. Patients with HAE may have one of three types indicated as types 1-3. Types 1-2 may be detected through laboratory levels noted in criteria above; however, although rare, the remaining forms of HAE show normal complement lab measurements. Clinical trials have only evaluated HAE therapies in types 1-2.

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] – available generic), and kallikrein inhibitor (Kalbitor). Only one of these therapies should be prescribed and used at one time.

VI. 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.

VII. 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.

VIII. 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.

IX. Lanadelumab (Takhzyro) was evaluated in two phase 3 studies in patients aged 12 years and older with HAE.

- Study DX2930-03 was a phase 3, multicenter, randomized, double-blind, placebo-controlled parallel-group study. The 26-week study included 125 patients 12 years of age and older with HAE-I or HAE-II who experienced at least one investigator-confirmed attack per 4 weeks during the run-in period. During the study run-in period, attack rates of ≥3 attacks/month were observed in 52% of patients. The primary endpoint was mean monthly attack rate from day 0 to 182, those in the

Takhzyro 150 mg every 4 weeks arm had 0.48 mean monthly attack rate, those in the Takhzyro 300 mg every 4 weeks arm had 0.53 mean monthly attack rate and 0.26 mean monthly attack rate was observed in those who received Takhzyro 300 mg ever 2 weeks, while those in the placebo arm had a 1.97 mean monthly attack rate (p<0.001). This secondary endpoint of the study was mean number of monthly attacks requiring acute treatment from day 0 to 182. Clinically meaningful and statistically significant outcomes were observed across all Takhzyro arms. Participants in the placebo arm had a mean of 1.64 monthly attacks requiring acute treatment, compared to 0.31 (150 mg every 4 weeks), 0.42 (300 mg every 4 weeks) and 0.21 (300 mg every 2 weeks) [p<0.001] as observed across all Takhzyro arms.

- The open-label phase 3 extension study DX2930-04 evaluated the long-term safety of lanadelumab 300 mg Q2W in Types I and II HAE patients. The study consisted of rollover subjects who completed the double-blind treatment period of Trial DX2930-03 and non-rollover subjects who enrolled directly into the OLE study. A secondary objective of the study was to characterize the outer bounds of dosing frequency in the rollover subjects. The primary objective of the study was to provide long-term safety data which include adverse events/serious adverse events, clinical labs (hematology, chemistry, LFTs, UA, coagulation, pregnancy), ECG, vital signs, physical exam, and ADA testing.

X. Berotralstat (Orladeyo) was evaluated in a three-part phase 3 study, and the approval was based on data submitted from part 1 (24 weeks).Parts 2 and 3 of this study are still ongoing to evaluate the long-term efficacy and safety or berotralstat (Orladyo), additional data on laboratory tests of interest from part 1 (such as LFT elevations) and HAE attack data.

- APeX-2 was a double-blind, randomized, placebo-controlled trial in 121 patients with type I or type II HAE. The primary efficacy outcome of part 1 was the rate of investigator confirmed HAE attacks per month at week 24, which was 1.31 (p< 0.001) for the berotralstat 150 mg arm, 1.65 (p=0.024) for the berotralstat 110 mg arm and 2.35 for placebo. Although berotralstat (Orladyeo) met its primary efficacy endpoint, the study failed to meet statistical significance in its secondary endpoint, which was the change from baseline of AE-QOL total scores at 24 weeks. The long-term efficacy and safety of this product is currently unknown due to the lack of published long-term data. The distribution of on-demand medication use during the study across all study arms was not provided; therefore, there is a risk the concomitant therapies confounded the outcome results.

XI. There are no direct head-to-head studies comparing lanadelumab (Takhyzro) and berotralstat (Orladeyo) to establish superior safety or efficacy of one product over the other; however, lanadelumab (Takhzyro) has a more established safety profile, and favorable quality of evidence for efficacy.

Investigational or Not Medically Necessary Uses

I. Use of two or more therapies for the same indication (e.g., acute or prophylactic) has not been evaluated for safety and efficacy.

II. The medications listed in this policy have not been sufficiently evaluated for safety and efficacy outside of hereditary angioedema.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added Orladeyo criteria for prophylactic treatment of HAE for P&T, added renewal criteria requiring initial policy criteria needs to be met, no continuation based on samples and must have had prior approval by plan.	02/2021
Age for Haegarda expanded down to six years of age (from previous 12)	10/2020
Added age restriction to Takhzyro of ≥ 12 years of age	03/2020
Policy created and criteria added to initial and renewal portions. Takhzyro combined with other agents. Specification on inappropriateness of dual therapy use, medical necessity of therapy, and addition of generic icatibant to the policy and use required prior to brand payment consideration.	10/2019
Takhzyro criteria created for P&T.	10/2018
Criteria updated to include Cinryze prophylactic therapy for patients six years of age and older, a new FDA approved age range.	01/2018
HAE indication review completed, agents included in policy were updated and questions added to align with clinical appropriateness and medical criteria.	11/2017
Criteria created	10/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP127

Description
Human chorionic gonadotropin (hCG) stimulates production of gonadal steroid hormones by causing production of androgen by the testes and the development of secondary sex characteristics in males. In females, hCG acts as a substitute for luteinizing hormone (LH) to stimulate ovulation.

Length of Authorization
- Initial: 12 months (for hypogonadotropic hypogonadism); six months (for cryptorchidism)
- Renewal: 12 months (for hypogonadotropic hypogonadism)*
  * Other indications are not eligible for renewal

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
human chorionic gonadotropin (human chorionic gonadotropin)	10,000 unit vial	Hypogonadotropic hypogonadism Ovulation induction* Prepubertal cryptorchidism	5 vials/30 days
human chorionic gonadotropin (Novarel)	5,000 unit vial		10 vials/30 days
human chorionic gonadotropin (Pregnyl)	10,000 unit vial		5 vials/30 days

**Drugs used in the treatment of fertility are excluded from coverage. Please refer to the member handbook/certificate of coverage for further information.*

Initial Evaluation

I. Human chorionic gonadotropin (Novarel; Pregnyl) may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      1. **Hypogonadotropic hypogonadism; AND**
         i. Two sub-normal testosterone concentration levels taken on two separate mornings while fasting; **AND**
         ii. Treatment with **all** of the following has been ineffective, contraindicated, or not tolerated:
            a. Generic injectable testosterone (i.e. testosterone cypionate, testosterone enanthate); **AND**
            b. Generic topical testosterone (i.e. generic testosterone 1% gel); **OR**
      2. **Prepubertal cryptorchidism; AND**
         i. Not due to anatomical obstruction

II. Human chorionic gonadotropin (Novarel; Pregnyl) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Men with low testosterone concentration and without clinical symptoms and signs consistent with testosterone deficiency. The routine assessment of testosterone level in the absence of hypogonadal symptoms is not advised.
   B. Men with a single, sub-normal testosterone concentration that is not repeatable per the U.S. Endocrine Society.
   C. Men with symptoms of hypogonadism; however, current testosterone level is within normal range.

III. Human chorionic gonadotropin (Novarel; Pregnyl) is considered investigational when used for all other conditions including but not limited to:
   A. Age-related hypogonadism
   B. Men with type 2 diabetes mellitus with low testosterone for the purpose of improving glycemic control
   C. Obesity

Renewal Evaluation

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

Supporting Evidence

I. Human chorionic gonadotropin (Novarel; Pregnyl) is FDA approved for the treatment of hypogonadotropic hypogonadism, prepubertal cryptorchidism, and ovulation induction. Coverage of medications used in the treatment of fertility is an excluded benefit; thus, criteria for coverage in the setting of ovulation induction is unrepresented within this policy.
II. There are several dosing regimen options in the setting of prepubertal cryptorchidism; however the label only supports a six week course with the potential of another series given one month later if the initial course was not successful.
III. Per the 2018 AUA guidelines, diagnosis of hypogonadism should be confirmed prior to initiating testosterone replacement therapy. Testosterone levels should be drawn ideally between 8 and 10 AM while fasting due to the diurnal fluctuation of testosterone and its sensitivity to glucose ingestion. A separate, confirmatory measurement is recommended.
IV. Thirty percent of men with an initial testosterone concentration in the hypogonadal range can have a measurement within the normal range on repeat measurement.
V. The Endocrine Society strongly advises against “trial periods” of testosterone in men with a single sub-normal testosterone concentration and vague symptoms of deficiency.

VI. In patients within normal range, or have low testosterone concentration due to age, obesity or otherwise, the benefit of increased testosterone has not been shown. Rather, in this patient population with low testosterone and an intact gonadal system, increasing testosterone is associated with an increase of certain health risks, including cardiovascular disease. Because of this, the FDA has required manufacturers to label testosterone products warning of the increased risk for heart attack and stroke.

Investigational or Not Medically Necessary Uses

I. All of the aforementioned conditions listed in the not medically necessary section are considered to be excluded from coverage.
II. In the conditions listed, there is insufficient information, or, information reports inconclusive evidence, to support the safety and efficacy of using human chorionic gonadotropin (Novarel; Pregnyl).

References

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Policy Implementation/Update:

Date Created	December 2019
Date Effective	December 2019
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date

hydrocortisone (Alkindi Sprinkle™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP212

Description

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

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
hydrocortisone (Alkindi Sprinkle)	0.5mg capsules	Adrenocortical insufficiency	10 mg/m^2/day*
	1mg capsules		
	2mg capsules		
	5mg capsules		

*limited to three capsules a day

Initial Evaluation

I. **Hydrocortisone (Alkindi Sprinkle)** may be considered medically necessary when the following criteria below are met:
   A. The member is 17 years of age or younger; **AND**
   B. The medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. A diagnosis of an **Adrenocortical insufficiency** (e.g. primary adrenal insufficiency, Addison's Disease, secondary adrenal insufficiency) and the following are met:
      1. The request is for hydrocortisone (Alkindi Sprinkle) 0.5 mg, 1 mg, or 2 mg capsules; **AND**
         i. Each individual dose is less than 5 mg (of note, when a 5 mg dose is reached, member is required to transition to generic hydrocortisone oral tablets, unless contraindicated); **AND**
         ii. Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated; **OR**
      2. The request is for hydrocortisone (Alkindi Sprinkle) 5 mg capsules;
         i. Treatment with generic hydrocortisone oral tablet is contraindicated (documentation must be attached); **AND**
         ii. Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated

II. Hydrocortisone (Alkindi Sprinkle) is considered not medically necessary when the following are met:

A. Total daily dose requirement for hydrocortisone may be met using hydrocortisone (Cortef) oral tablets (5 mg, 10 mg, or 20 mg) or hydrocortisone compound (solution or suspension)
B. Treatment requiring hydrocortisone (Alkindi Sprinkle) 5 mg capsules

III. Hydrocortisone (Alkindi Sprinkle) is considered investigational when used for all other conditions, including but not limited to:

A. Treatment of members 18 years of age or older, requiring hydrocortisone therapy
B. Chemotherapy induced nausea and vomiting

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The request is for hydrocortisone (Alkindi Sprinkle) 0.5 mg, 1 mg, or 2 mg capsules; **AND**
    - Each individual dose is less than 5 mg (of note, when a 5 mg dose is reached, member is required to transition to generic hydrocortisone oral tablets, unless contraindicated); **AND**
    - Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated; **OR**
IV. The request is for hydrocortisone (Alkindi Sprinkle) 5 mg capsules;
    - Treatment with generic hydrocortisone oral tablet is contraindicated (documentation must be attached); **AND**
    - Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated
V. Provider attests that the member remains ineligible to transition to generic hydrocortisone tablets and compounded hydrocortisone products (solution or suspension); **AND**
VI. Member has exhibited improvement or stability of disease symptoms (e.g. improved cortisol levels over baseline, improvement in symptoms such as hypotension, hyponatremia)

Supporting Evidence

I. Hydrocortisone (Alkindi Sprinkles) is a corticosteroid, indicated as a replacement therapy in pediatric patients (less than 17 years of age) with adrenocortical insufficiency. Alkindi Sprinkle is a granular formulation of hydrocortisone, which was designed to overcome the barrier of inaccuracy of dosing (when using currently available hydrocortisone formulations) for younger patients.
II. Pediatric patients (neonate to <17 years old) usually require less than 5 mg of total daily dose of hydrocortisone. The daily dose of hydrocortisone is usually divided into two to three doses with initial dose of 8mg/m^2 to 10mg/m^2 per day. Hydrocortisone (Alkindi Sprinkle) is supplied in a pack size of 50 capsules to be stored in the original bottle (unbreakable package). Quantity limit

for hydrocortisone (Alkindi Sprinkles) is based on total daily dose divided into two to three individualized doses and should be rounded up to the nearest pack size.

III. Currently there are no published clinical trial or treatment regimens for children with Primary Adrenal Insufficiency (PAI). The Journal of Endocrinology and Metabolism guideline recommends that treatment in children is aimed at managing and controlling symptoms of adrenal insufficiency with optimal doses that allow for growth and pubertal development. Because PAI is a complex disease state, management and treatment monitoring of PAI in pediatric patients must be in consultation with an endocrinologist or a healthcare provider with endocrine expertise.

IV. Differential diagnose of PAI requires confirmation with the Corticotropin simulation test, which is considered the gold standard due to its higher degree of specificity and sensitivity. A confirmed diagnosis of PAI is determined by low morning serum cortisol concentrations (≤ 140 *n*Mol/L) and high adrenocorticotropic hormone (ACTH) levels (≥ 66 *p*mol/L).

V. While glucocorticoid monotherapy is a typical initial treatment approach, many patients also require a mineralocorticoid as an add-on agent. The Journal of Endocrinology and Metabolism guideline recommends use of 100 µg per day of fludrocortisone. Mineralocorticoids are essential in maintaining water and electrolyte homeostasis; however, use in PAI has not been studied systematically. The rationale is to dose fludrocortisone in the mornings to mimic aldosterone levels, which are generally high in the morning due to circadian rhythms.

VI. Patients with PAI are at high risk of developing Adrenal crisis, an acute etiology that develops due to inability of the adrenal gland to produce enough cortisol in response to an increased need. Clinical features of adrenal crisis consist of volume depletion and hypotension. In such cases, parenteral injections ($50mg/m^2$) of hydrocortisone may be required.

VII. Hydrocortisone (Alkindi Sprinkle) received FDA approval for pediatric patients (<17 years of age) based on the ease of dosing and proposed accuracy of dosing as it is available in smaller doses (0.5 mg, 1 mg, 2 mg, and 5 mg). Hydrocortisone (Alkindi Sprinkle) was granted FDA-approval as a new dosage form of hydrocortisone and was limited to the indication of adrenocortical insufficiency. There are no independent prospective clinical trials to support efficacy and safety of hydrocortisone (Alkindi Sprinkle) for any other conditions. As such, until now, patients requiring a daily dose of hydrocortisone > 5 mg per day have been managed using hydrocortisone (Cortef) oral tablets (intact or crushed and mixed with liquid), or compounded formulations of hydrocortisone (oral solution or suspension). Notably, the compounded formulations of hydrocortisone have been successfully used in pediatric populations to fulfill the need for optimum daily doses less than 5 mg. These formulations provide accuracy of dosing as well as ease of administration. Although hydrocortisone (Alkindi Sprinkle) is a new formulation that provides administrative convenience, use of this formulation is cost-prohibitive. Given the long-standing efficacy, safety, accuracy of dosing, cost, and clinical experience, compounded formulations of hydrocortisone are considered standard and practical high-value treatment options in this space and should be preferred over hydrocortisone (Alkindi Sprinkle).

Investigational or Not Medically Necessary Uses

I. There are no direct head-to-head clinical trials comparing efficacy and safety of glucocorticoid drugs used in in long term treatment of PAI in children. The Endocrine Societal Guidelines recommend children should be treated with hydrocortisone because of its optimal pharmacokinetic profile, and short half-life, furthermore overtreatment should be avoided.

Doses of ≥ 5mg daily are considered not medically necessary for children aged less than 17 years of age due to risk of growth retardation. Therefore, close monitoring of glucocorticoid dosing is advised in children with increasing body surface area.

II. Hydrocortisone (Alkindi Sprinkle) is not considered medically necessary in any other disease state other than adrenocortical insufficiency. Epidemiology in this setting largely involves pediatric population. Based on the scope of FDA-approval, hydrocortisone (Alkindi Sprinkle) is deemed medically necessary only for pediatric patients diagnosed with adrenocortical insufficiency, for whom, the total daily dose requirement may not be met using generic hydrocortisone tablets or compounded hydrocortisone formulations.

III. Use of hydrocortisone has been widely recommended in many inflammatory conditions including chemotherapy induced nausea, prostate cancer, chronic lung disease and gout. However, it should be noted that typical daily dose requirement of hydrocortisone in the treatment of these conditions is higher than 5 mg per day. As such, use of hydrocortisone (Alkindi Sprinkle) in these settings over traditionally used hydrocortisone formulations (e.g. generic Cortef oral tablet) is not practical and FDA-approved, given the lack of the clinical superiority data for the former, as well as, higher cost of therapy.

IV. Efficacy and Safety of hydrocortisones (Alkindi Sprinkle) for treatment of conditions other than adrenocortical insufficiency have not been studied and remain unknown.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	12/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP175

Description

Hydroxyprogesterone caproate (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

Product Name	Dosage Form	Indication	Quantity Limit
hydroxyprogesterone caproate (Makena, hydroxyprogesterone caproate)	Intramuscular solution: 250 mg/mL, 1250 mg/5mL Subcutaneous auto-injector: 275 mg/1.1mL	Preterm birth	Intramuscular solution: 250 mg/mL (4 vials/28 days), 1250 mg/5 mL (1 vial/35 days) Subcutaneous auto-injector: 4 auto-injectors/28 days ***See additional clinical notes***

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:

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%; RR¼0.87 [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

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Policy Implementation/Update:

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

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

ibrutinib (Imbruvica)	Indication	Quantity Limit
560 mg tablets	Mantle Cell Lymphoma, previously treated; Marginal Zone Lymphoma, relapsed/refractory	30 tablets/30 days
420 mg tablets	Chronic Graft versus Host Disease (refractory); Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; Waldenström Macroglobulinemia	30 tablets/30 days
280 mg tablet	Dose modification	30 tablets/30 days
140 mg tablet	Dose modification	30 tablets/30 days
140 mg capsule	Dose modification	60 capsules/30 days
70 mg capsule	Dose modification	30 capsules/30 days

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. Medication will not be used in combination with any other oncology therapy unless outlined below (e.g. with obinutuzumab for chronic lymphocytic leukemia); **AND**
   F. 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. **Marginal Zone Lymphoma (MZL)**; **AND**
   i. Member has received at least one prior anti-CD20-based therapy (e.g., rituximab, obinutuzumab, ofatumumab); **AND**
   ii. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
3. **Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Leukemia (SLL); AND**
   i. The member does <u>not</u> 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**
      c. The request is for use in combination with obinutuzumab in the first-line 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**
4. **Waldenström Macroglobulinemia (WM); AND**
   i. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
   ii. Ibrutinib (Imbruvica) will be used with rituximab; **OR**
5. **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 <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia in combination with rituximab only

III. Ibrutinib (Imbruvica) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Relapsed/refractory Hodgkin lymphoma
   B. Mantle Cell Lymphoma, frontline
   C. Mantle Cell Lymphoma, combination therapy
   D. Marginal Zone Lymphoma, combination therapy
   E. Diffuse Large B Cell Lymphoma
   F. Relapsed/refractory Multiple Myeloma
   G. Hairy Cell Leukemia
   H. Primary CNS lymphoma
   I. Esophagogastric carcinoma
   J. Gliobalastoma
   K. Non-small-cell lung carcinoma
   L. 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 patient has exhibited improvement or stability of symptoms [e.g., manifestations of disease to the skin, oral cavity, musculoskeletal system]; **OR**
    - For oncology indications: The patient 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 an 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 65.8% with ibrutinib (Imbruvica) therapy.
III. In the setting of MZL, ibrutinib (Imbruvica) was studied in an open-label, multi-center, single-arm trial of 63 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.
IV. 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, a randomized, multicenter, open-label, phase 3 study of ibrutinib (Imbruvica) versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia/small lymphocytic lymphoma was conducted in patients with previously treated CLL or 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. 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.

- The iLLUMINATE study was a randomized, open-label, active-controlled, multicenter, Phase 3 trial of ibrutinib (Imbruvica) in combination with obinutuzumab in 229 patients with treatment naïve CLL/SLL. 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.
- In the HELIOS and E1912 trials patients with del17p were excluded. In the iLLUMINATE trial, all patients included in the study were considered unsuitable for fludarabine based chemoimmunotherapy because they were aged 65 years or older or younger than 65 years with at least one of the following coexisting conditions: cumulative illness rating scale score greater than 6, creatinine clearance of less than 70 mL/min, presence of del17p confirmed by FISH, or TP53 mutation. The majority of high-risk patients included in iLLUMINATE had unmutated IGVH (65%) while only 16% of patients had a del17p or TP53 mutation.
- There have been no direct comparisons between ibrutinib (Imbruvica) monotherapy and ibrutinib (Imbruvica) in combination with obinutuzumab.
- NCCN CLL/SLL guidelines recommend ibrutinib (Imbruvica) monotherapy as a Category 1 recommendation in in the relapsed/refractory setting in patients with or without 17p deletion/TP53 mutation. In the first-line setting monotherapy also carries a Category 1 recommendation in patients without 17p deletion/TP53 mutation, with a 2A recommendation in those with the deletion/mutation. NCCN guidelines do not list combination ibrutinib (Imbruvica) with rituximab, ibrutinib (Imbruvica) with rituximab and bendamustine, or ibrutinib (Imbruvica) with obinutuzumab in members with 17p deletion/TP53 mutation as a treatment option. All regimens carry 2B recommendations in CLL/SLL without del17p/TP53 mutation.

V. 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).

VI. 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.

VII. 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 or obinutuzumab. 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. Relapsed/refractory Hodgkin lymphoma
      i. Subject of current ongoing trials.
   C. Mantle cell lymphoma, frontline
      i. Ibrutinib (Imbruvica) is being investigated as a first-line treatment for patients with MCL in the phase III SHINE trial (NCT01776840), evaluating the safety and efficacy of ibrutinib plus bendamustine and rituximab (Rituxan) in older patients with newly-diagnosed MCL who are not eligible for stem cell transplant. SHINE has fully enrolled, but there is no data available yet. The trial is expected to read out in 2021.
   D. Mantle cell lymphoma, combination therapy
      i. 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.
   E. Marginal zone lymphoma, combination therapy

F. 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. 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 need 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 (Imbruivca) to standard R-CHOP chemotherapy regimen in the DLBCL first-line setting failed to meet its primary endpoint of improving event-free survival (EFS) when compared to R-CHOP alone in the phase III PHOENIX (NCT01855750) study.
G. 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.
H. 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.
I. 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.
J. Esophagogastric carcinoma
    i. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

II. Gliobalastoma
    A. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

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

IV. T-cell Lymphoma
    A. 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

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12. Grommes C, Pastore A, Palaskas N, et al. Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma. Cancer Discov. 2017;7(9):1018-1029.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of split-fill requirement, updated initial approval back to 3 months. Included requirement the member has not progressed on a previous BTK inhibitor. Updated policy based on new indication in combination with rituximab for CLL/SLL as not medically necessary. Criteria for CLL/SLL updated to focus on diagnosis and mutation status over use in combination with other agents. Updated criteria for MCL and MZL to only be used as monotherapy. Removed toxicity renewal requirement and added disease stability renewal examples for GVHD patients.	06/2020
Updated criteria to policy format, specified combination therapy in CLL/SLL patients to be used in members without 17p deletion/TP53 mutation, addition of trial and failure of 140mg capsules prior to use of 140 mg or 280 mg tablets. In MCL, marginal zone lymphoma, and graft versus host disease, added more detail on	03/2019

type of prior therapy required. For Waldenström macroglobulinemia added use to be as monotherapy or with rituximab.	
Updated formatting, extended initial approval from 3 months to 6 months.	01/2018
Previous updates	08/2014 02/2015 04/2015 08/2017
Criteria created	02/2014

idelalisib (Zydelig®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP168

Description

Idelalisib (Zydelig) is an orally administered PI3Kδ kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
idelalisib (Zydelig)	100 mg tablets	Relapsed Chronic Lymphocytic Leukemia; Relapsed Follicular B-cell non-Hodgkin Lymphoma; Relapsed Small Lymphocytic Lymphoma	60 tablets/30 days
	150 mg tablets		

Initial Evaluation

I. Idelalisib (Zydelig) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. A diagnosis of one of the following:
      1. Relapsed Chronic Lymphocytic Leukemia (CLL); AND
         i. Documentation of use of at least <u>one</u> prior therapy; **AND**
         ii. Use is in combination with rituximab; **AND**
         iii. Will not be used with any other oncology therapy; **OR**
      2. Relapsed Small Lymphocytic Lymphoma (SLL); AND
         i. Treatment with <u>two</u> prior therapies for SLL has been ineffective, contraindicated, or not tolerated; **AND**
         ii. Medication will be used as monotherapy; **OR**
      3. **Relapsed Follicular B-cell non-Hodgkin Lymphoma (FL); AND**
         i. Treatment with <u>two</u> prior therapies for FL has been ineffective, contraindicated, or not tolerated; **AND**
         ii. Medication will be used as monotherapy.

II. Idelalisib (Zydelig) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Use in combination with bendamustine and rituximab for the indication of CLL/SLL
   B. Idelalisib as monotherapy for the treatment of relapsed or refractory CLL/SLL
   C. Use as treatment naïve or first line therapy for any indication
   D. In combination with other medications for any indication outside of dual therapy with rituximab for the indication of relapsed CLL

E. Marginal zone lymphoma
F. Lymphoplasmacytic lymphoma with or without Waldenstrom's macroglobulinemia
G. Immunoglobulin M (IgM) associated primary amyloidosis
H. Hodgkin Lymphoma
I. Acute Lymphoblastic Leukemia
J. Non-Small Cell Lung Cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms; **AND**
IV. Member has a diagnosis of one of the following:
   A. **Relapsed Chronic Lymphocytic Leukemia (CLL)**; **AND**
      1. Use is in combination with rituximab; **OR**
   B. **Relapsed Small Lymphocytic Lymphoma; AND**
      1. Medication will be used as monotherapy; **OR**
   C. **Relapsed Follicular B-cell non-Hodgkin Lymphoma (FL); AND**
      1. Medication will be used as monotherapy.

Supporting Evidence

I. Safety and efficacy of idelalisib (Zydelig) has not been studied or established in the pediatric population.
II. Treatment for CLL, SLL, or FL are difficult to treat conditions requiring consultation with an oncologist or hematologist.
III. Idelalisib (Zydelig) was studied in a Phase III, randomized, double blind placebo controlled clinical trial in combination with rituximab in patients with relapsed chronic lymphocytic leukemia (CLL). Patients were given idelalisib (Zydelig) 150mg twice daily until disease progression or unacceptable toxicity. Nearly all patients had prior treatment with anti-CD20 monoclonal antibodies, and most patients also had prior treatment with bendamustine/rituximab, fludarabine/cyclophosphamide/rituximab, or rituximab monotherapy. Primary outcome was progression free survival and overall response rate with the median duration of response not reached.
IV. Idelalisib (Zydelig) was studied in a Phase II, open label, single group clinical trial including patients with small lymphocytic leukemia (SLL) who had relapsed within six months following rituximab and an alkylating agent and had at least two prior treatments. The most common prior treatments included rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, fludarabine/cyclophosphamide/rituximab, and bendamustine/rituximab. Primary outcome was overall response rate with the median duration of response of 11.9 months
V. 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.

Investigational or Not Medically Necessary Uses

I. 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.
II. Idelalisib (Zydelig) was not found to be beneficial in combination with bendamustine and/or rituximab for the treatment of FL. Label does not support the use in combination with bendamustine and/or rituximab
III. Idelalisib (Zydelig) was not found to be beneficial as first line therapy in patients with SLL. Label does not support use as first line treatment.
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

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3. ClinicalTrials.gov. Efficacy and Safety Study of Idelalisib in Participants With Indolent B-Cell Non-Hodgkin Lymphomas. NCT01282424.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy updated to require use of one prior therapy for CLL; removed history of toxic epidermal necrolysis	02/2020
Previous reviews	11/2014

imatinib (Gleevec®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP128

Description

Imatinib (Gleevec) is an orally administered protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase to suppress proliferation and promote apoptosis of cancer cells.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

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

		Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, after failure of interferon-alpha therapy; Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, newly diagnosed; Systemic mast cell disease, aggressive, D816V c-Kit mutation negative or unknown	

Initial Evaluation

I. Imatinib may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older for all indications except the following;
      1. Philadelphia chromosome-positive acute lymphoblastic leukemia, newly diagnosed, in combination with chemotherapy
      2. Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, newly diagnosed;
      AND
   B. Medication is prescribed by, or in consultation with, an oncologist **AND**
   C. Not used in combination with other oral oncolytic therapies (e.g., sunitinib [Sutent], regorafenib [Strivarga], bosutinib [Bosulif], nilotinib [Tasigna]); **AND**
   D. Generic imatinib is prescribed, unless generic has been tried and failed, is not tolerated or contraindicated [documentation required] (note: imatinib is the interchangeable AB-rated generic of Gleevec); **AND**
   E. A diagnosis of one of the following:
      1. **Chronic eosinophilic leukemia**
      2. **Dermatofibrosarcoma protuberans, unresectable, recurrent, and/or metastatic**
      3. **Gastrointestinal stromal tumor, Kit (CD117)-positive, adjuvant treatment**
      4. **Gastrointestinal stromal tumor, Kit (CD117)-positive, unresectable or metastatic disease**
      5. **Hypereosinophilic syndrome**
      6. **Myelodysplastic syndrome, PDGFR gene rearrangement**
      7. **Myelodysplastic syndrome, chronic, PDGFR gene rearrangement**
      8. **Philadelphia chromosome-positive acute lymphoblastic leukemia, newly diagnosed, in combination with chemotherapy**
      9. **Philadelphia chromosome-positive acute lymphoblastic leukemia, relapsed/refractory**
      10. **Philadelphia chromosome positive chronic myelogenous leukemia, accelerated phase or blast crisis**
      11. **Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, after failure of interferon-alpha therapy**
      12. **Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, newly diagnosed**

13. **Systemic mast cell disease, aggressive, D816V c-Kit mutation negative or unknown**

II. Imatinib (Gleevec) is considered investigational when used for all other conditions, including but not limited to:
   A. Breast cancer
   B. Cervical cancer
   C. Graft-versus-host disease
   D. Malaria
   E. Melanoma
   F. Mesothelioma
   G. Multifocal leukoencephalopathy
   H. Multiple sclerosis
   I. Neurofibromas
   J. Non-Hodgkin's lymphoma
   K. Ovarian or peritoneal cancers
   L. Pancreatic cancer
   M. Renal cancers
   N. Sickle cell anemia
   O. Thyroid cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescribed by, or in consultation with, an oncologist; **AND**
IV. Member has exhibited improvement or stability of disease with lack of disease progression; **AND**
V. For imatinib (Gleevec) brand: generic imatinib has been tried and failed, not tolerated, or is contraindicated [documentation required] (note: imatinib is the interchangeable AB-rated generic of Gleevec).

Supporting Evidence

I. Imatinib (Gleevec) is a tyrosine kinase inhibitor, indicated in a variety of disease states in adults, and two indications have been evaluated with treatment of imatinib (Gleevec) in pediatric patients. Dosing is indication specific, but ranges from 100 mg to 800 mg per day, with standard dosing ranging from 400 mg to 800 mg per day.. Dose adjustments may be warranted in the setting of toxicity or organ dysfunction/impairment. Imatinib (Gleevec) may be used as

monotherapy or in addition to chemotherapy for certain indications. Use with other oral tyrosine kinase oncolytic therapies has not been evaluated for safety and/or efficacy to date.

II. Overarching indications include chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), gastrointestinal stromal tumor (GIST), eosinophilic leukemia and syndromes, dermatofibrosarcoma protuberans, myelodysplastic syndromes, and systemic mast cell disease. An extensive number of clinical trials have been completed for imatinib (Gleevec).

III. Generic imatinib is available and is recognized as the AB-rated interchangeable generic to Gleevec. It provides better value and is a cost effective option compared to brand Gleevec with no known safety or efficacy differences at this time. Payment consideration for brand is reserved for those that have had inefficacy, intolerance, or contraindication to generic imatinib. Occurrence of toxicities known to be in the adverse event profile of imatinib (Gleevec), does not meet medical necessity for brand over generic exception. If toxicity occurs, consistent with the imatinib (Gleevec) adverse event profile, dose reduction or discontinuation may be appropriate.

Investigational or Not Medically Necessary Uses

I. Imatinib (Gleevec) has not been sufficiently evaluated for safety and/or efficacy and/or is in clinical trials for the following indications:
   A. Breast cancer
   B. Cervical cancer
   C. Graft-versus-host disease
   D. Malaria
   E. Melanoma
   F. Mesothelioma
   G. Multifocal leukoencephalopathy
   H. Multiple sclerosis
   I. Neurofibromas
   J. Non-Hodgkin's lymphoma
   K. Ovarian or peritoneal cancers
   L. Pancreatic cancer
   M. Renal cancers
   N. Sickle cell anemia
   O. Thyroid cancer

References

1. Gleevec [Prescribing Information]. East Hanover, NF. Novartis Pharmaceuticals Corp. September 2017.
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Policy Implementation/Update:

Date Created	August 2008
Date Effective	August 2008
Last Updated	November 2019
Last Reviewed	02/2016, 03/2016, 05/2017, 11/2018, 11/2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format, new indications added/specified, age edit added, addition of specialist provider, and limitation of dual oral therapy.	11/2019
Generic imatinib preferred therapy indicated for initial and continuation of therapy, unless medical necessity for brand met.	11/2018
Criteria questions rearranged and clarified.	08/2017
Criteria updated to prefer generic imatinib for initial approval.	05/2017
Criteria updated for new disease states.	02/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP039

Description

inotersen (Tegsedi) is a subcutaneously administered antisense oligonucleotide inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

inotersen (Tegsedi)	Indication	Quantity Limit	*DDID*
284 mg/1.5 mL syringe	hereditary transthyretin-mediated amyloidosis	6 mL/28 days	204500

Initial Evaluation

I. inotersen (Tegsedi) may be considered medically necessary when the following criteria are met:
   A. Prescribed by or in consultation with a neurologist or cardiologist; **AND**
   B. A diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) when the following are met:
      1. Age 18 years and older; **AND**
      2. Documented transthyretin variant (TTR mutation) by genotyping (e.g., V30M); **AND**
      3. Documented amyloid deposit by biopsy; **AND**
      4. Patient has a platelet count > 100 × 109/L; **AND**
      5. Documentation of one of the following:
         i. Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb
         ii. Patient has a baseline FAP Stage 1 or 2
         iii. Patient has a baseline neuropathy impairment (NIS) score ≥ 10 and ≤ 130

         AND
      6. Presence of clinical signs and symptoms of the disease (e.g., peripheral sensorimotor polyneuropathy, autonomic neuropathy, motor disability, etc.); **AND**
      7. No prior liver transplant or anticipated liver transplant; **AND**
      8. New York Heart Association (NYHA) functional classification of <3; **AND**
      9. Does not have presence of known type 1 or type 2 diabetes mellitus; **AND**
      10. Does not have renal insufficiency (defined as CrCl <60 mL/min); **AND**
      11. Patient has tried and failed or has a contraindication to patisiran (Onpattro); **AND**
      12. Inotersen (Tegsedi) will not be used in combination with patisiran (Onpattro) or tafamidis meglumine (Vyndaqel)

II. inotersen (Tegsedi) is considered investigational when used for all other conditions, including but not limited to:
   A. Cardiac amyloidosis due to wild-type or mutant TTR

Renewal Evaluation

I. Patient has previously received treatment with inotersen (Tegsedi); **AND**
II. Documentation of one of the following:
   A. Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb; **OR**
   B. Patient has a baseline FAP Stage 1 or 2; **OR**
   C. Patient has a baseline neuropathy impairment (NIS) score ≥ 10 and ≤ 130

   AND
III. Documentation that the patient has experienced a positive clinical response to inotersen (Tegsedi) (e.g., improved neurologic impairment, motor function, quality of life, slowing of disease progression, etc.); **AND**
IV. Inotersen (Tegsedi) will not be used in combination with patisiran (Onpattro) or tafamidis meglumine (Vyndaqel); **AND**
V. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. In the pivotal NEURO-TTR trial leading to approval, inotersen (Tegsedi) was studied in adults with stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) hereditary transthyretin amyloidosis with polyneuropathy.
II. Diagnosis of the hereditary form of ATTR requires demonstration of a TTR gene mutation. Although mass spectrometry can demonstrate a mass difference between wild-type and TTR protein variants in serum, it does not specify the site and kind of amino acid substitution in a number of disease-related *TTR* gene mutations; thus, DNA sequencing is usually required.
III. Use of inotersen (Tegsedi) is contraindicated in patients with platelet count less than 100 x 109/L, history of acute glomerulonephritis caused by inotersen (Tegsedi), or history of hypersensitivity reaction to inotersen (Tegsedi).
IV. Patients with a PND score greater than IIIb (i.e. PND of IV) are confined to a wheelchair or bedridden. Patients with FAP stage 1 have unimpaired ambulation, stage 2 require assistance with ambulation, and FAP stage 3 patients are wheelchair bound or bedridden. As mentioned above, all patients included in the study were ambulatory. Patents included also had a baseline NIS score ≥ 10 and ≤ 130.
V. Additional exclusion criteria in the NEURO-TTR trial consisted of prior liver transplant or anticipated liver transplant, New York Heart Association (NYHA) functional classification of <3, presence of known type 1 or type 2 diabetes mellitus, and renal insufficiency (defined as CrCl <60 mL/min).
VI. Inotersen (Tegsedi) carries two black box warnings related to potential for life-threatening thrombocytopenia and glomerulonephritis that may require immunosuppressive treatment and may result in dialysis. Tegsedi is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) program because of these risks. Patisiran (Onpattro) is also indicated and FDA approved for the polyneuropathy of hATTR in adults and provides a more favorable safety profile. Onpattro efficacy was evaluated in a randomized, double-blind,

placebo-controlled trial in adults with polyneuropathy caused by hATTR amyloidosis. Onpattro met its primary endpoint of change from baseline to Month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7).

VII. Use of inotersen (Tegsedi) in combination with other therapies for hATTR (e.g., patisiran (Onpattro) or tafamidis meglumine (Vyndaqel) has not been studied.

Investigational or Not Medically Necessary Uses

I. Cardiac amyloidosis due to wild-type or mutant TTR
   A. Pivotal trials leading to FDA approval were specifically in the hereditary transthyretin-mediated amyloidosis setting. Wild-type TTR is not considered hereditary. Inotersen (Tegsedi) in this setting is under investigation, trials have not yet started recruiting.

References

1. Tegsedi [Prescribing Information]. Carlsbad, CA: Ionis Therapeutics, Inc., 2018.
2. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. NEJM. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153.
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6. Benson MD, Waddington-cruz M, Berk JL, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379(1):22-31.
7. Coelho T, Ericzon B, Falk R, et al. A Guide to Transthyretin Amyloidosis. Available at: http://www.amyloidosis.org/wp-content/uploads/2017/05/2017-ATTR-guide.pdf.
8. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8(1):1-18. doi:10.1186/1750-1172-8-31.

Policy Implementation/Update:

Date Created	January 2019
Date Effective	February 2019
Last Updated	January 2019
Last Reviewed	01/2019

Action and Summary of Changes	Date
Criteria created	01/2019

istradefylline (Nourianz™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP084

Description

Istradefylline (Nourianz) is an orally administered adenosine receptor antagonist.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
istradefylline (Nourianz)	20 mg tablets	Parkinson's disease	30 tablets/30 days	207954
	40 mg tablets		30 tablets/30 days	207955

Initial Evaluation

I. Istradefylline (Nourianz) may be considered medically necessary when the following criteria below are met:
   A. 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 <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:

A. Parkinson's disease WITHOUT documentation of motor fluctuations, "wearing off"

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

1. Nourianz [Prescribing Information]. Kyowa Kirin Inc.: Bedminster, NJ. August 2019.

2. Fox, SH, et al. International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease. Movement Disorders 2018; 00:1-16. Available at: www.movementdisorders.org/MDS-Files1/Resources/PDFs/TreatmentsforMotorSymptomsofPD-2018.pdf
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4. UpToDate, Inc. Medical management of motor fluctuations and dyskinesia in Parkinson's disease. UpToDate [database online]. Waltham, MA. Last updated May 17, 2019 Available at: http://www.uptodate.com/home/index.html.
5. Food and Drug Administration [online press release]. FDA approves new add-on drug to treat off episodes in adults with Parkinson's disease. Available at: www.fda.gov/news-events/press-announcements/fda-approves-new-add-drug-treat-episodes-adults-parkinsons-disease. Updated August 27, 2019.
6. LeWitt PA, Guttman M, Tetrud JW, et al. Adenosine A2A receptor antagonist istradefylline (KW-6002) reduces "off" time in Parkinson's disease: a double-blind, randomized, multicenter clinical trial (6002-US-005). Ann Neurol 2008;63:295-302.
7. Hauser RA, Shulman LM, Trugman JM, et al. Study of istradefylline in patients with Parkinson's disease on levodopa with motor fluctuations. Mov Disord 2008;23:2177-2185.
8. Stacy M, Silver D, Mendis T, et al. A 12-week, placebo-controlled study (6002-US-006) of istradefylline in Parkinson disease. Neurology 2008;70:2233-2240.
9. Pourcher E, Fernandez HH, Stacy M, Mori A, Ballerini R, Chaikin P. Istradefylline for Parkinson's disease patients experiencing motor fluctuations: results of the KW-6002-US-018 study. Parkinsonism Relat Disord 2012;18:178-184.

Policy Implementation/Update:

Date Created	September 2019
Date Effective	November 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	**Date**

Ivabradine (Corlanor®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP040

Description

Ivabradine (Corlanor) is an orally administered direct and selective inhibitor of the hyperpolarization-activated cyclic nucleotide-gated (HCN-gated) channels, or the f-channels that are located in the cardiac sinoatrial node which results in a lowering of the heart rate.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
ivabradine (Corlanor)	5 mg tablets	Heart Failure in Adult Patients	60 tablets/30 days	188210
	7.5 mg tablets		60 tablets/30 days	188211
	5 mg/5 mL solution	Heart Failure in Pediatric Patients	450 mL/30 days	Not available yet

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 <u>not medically necessary</u> 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 <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Non-stable, asymptomatic chronic heart failure
   B. Pediatric heart failure not due to dilated cardiomyopathy

Renewal Evaluation

I. **Heart Failure in adults, heart failure in pediatrics, inappropriate sinus tachycardia**; **AND**
   A. Member has previously received treatment with ivabradine (Corlanor); **AND**
   B. Continues to meet criteria identified in section I of the initial Evaluation; **AND**
   C. Provider attest to stabilization of disease (e.g. heart rate reduction, reduction in hospitalization due to worsening heart failure); **AND**
   D. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. Ivabradine (Corlanor) is indicated to reduce the risk of hospitalization for worsening heart failure in adult patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use.

II. ACC/AHA 2015 guideline recommends the use of ivabradine (Corlanor) [moderate evidence] over the historical standard treatment of beta-blockers [weak evidence] for the treatment of inappropriate sinus tachycardia.

Investigational or Not Medically Necessary Uses

I. Coronary artery disease
   A. In the BEAUTIFUL and SIGNIFY trials, no benefits were found in patients with stable coronary artery disease with or without stable heart failure, who were given ivabradine (Corlanor).

II. Non-stable, asymptomatic chronic heart failure
   A. Ivabradine (Corlanor) has not been studied in patients with non-stable, asymptomatic chronic heart failure; therefore, it would be considered investigational when Corlanor is requested in that setting.

III. Pediatric heart failure not due to dilated cardiomyopathy
   A. Ivabradine (Corlanor) has not been studied in pediatric patients with heart failure that is not due to dilated cardiomyopathy; therefore, it would be considered investigational when Corlanor is requested in that setting.

References

1. Corlanor [Prescribing Information]. Thousand Oaks, CA: Amgen, Inc. April 2019.
2. Fox K, Ford I, Steg G, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Sep 6;372(9641):807-16. doi: 10.1016/S0140-6736(08)61170-8.
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:

Date Created	May 2015
Date Effective	May 2015
Last Updated	August 2015
Last Reviewed	06/2019

Action and Summary of Changes	Date
Transitioned criteria to policy. In this transition, the following updates were made: added new indication for pediatric heart failure due to dilated cardiomyopathy, incorporated the approvable off-label indication of inappropriate sinus tachycardia, and added renewal criteria.	06/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP123

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
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
enasidenib (Idhifa)	50 mg tablets	Acute myeloid leukemia, relapsed/refractory	30 tablets/30 days
	100 mg tablets		
ivosidenib (Tibsovo)	250 mg capsule	Acute myeloid leukemia, relapsed/refractory Acute myeloid leukemia, newly diagnosed	60 capsules/ 30 days

Initial Evaluation

I. Enasidenib (Idhifa) or ivosidenib (Tibsovo) 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. Will not be used in combination with other oncologic agents (i.e. as monotherapy); **AND**
   C. 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**
            a. Request is for ivosidenib (Tibsovo); **OR**
         iii. Presence of IDH-2 mutation as detected by an FDA-approved test; **AND**
            a. Request is for enasidenib (Idhifa); **OR**

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

II. Enasidenib (Idhifa) and/or ivosidenib (Tibsovo) is/are considered investigational when used for all other conditions, including but not limited to:
    A. Advanced cholangiocarcinoma
    B. Chondrosarcomas
    C. Myelodysplastic Syndrome (MDS)

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., became independent of red blood cell and platelet transfusion).

Supporting Evidence

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. 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.

II. NCCN Guideline preferred therapies for the treatment of recurrent/relapse AML include the following: clinical trial, systemic chemotherapy, or allogenic hematopoietic stem cell transplant.

III. 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).

IV. 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 preclude 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.

Investigational or Not Medically Necessary Uses

I. Advanced cholangiocarcinoma
   A. Limited to proof-of-concept
   B. Mutations of isocitrate dehydrogenase have been identified only.

II. Chondrosarcomas
   A. Clinical trials currently ongoing and limited to proof-of-concept.

III. 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.

References

1. Tibsovo [prescribing information]. Cambridge, MA: Agios Pharmaceuticals, Inc.; July 2018.
2. Idhifa [package insert]. Cambridge, MA: Agios Pharmaceuticals & Celgene Corporation; August 2017.
3. DiNardo C, Stein EM, Botton S, et al. Durable Remssions with Ivosidenib in *IDH1*-mutated Relapsed or Refractory AML. *N Engl J Med.* 2018 June: 378:2386-2398. DOI: 10.1056/NEJMoa1716984
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5. NCCN Clinical Practice Guidelines in Oncology™. Acute Myeloid Leukemia v.3.2020. [cited 02/05/2020]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/aml_blocks.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria update: To improve the clinical flow of the policy, the indication of relapse/refractory AML was separated from newly diagnosed AML. For clinical appropriateness and standard of practice, the requirement for both chemotherapy "AND" allogenic stem cell transplant for relapsed or refractory AML, was changed to an "OR;" therefore, either one prior regimen would satisfy that requirement. For the newly diagnosed AML diagnosis, additional information around comorbidities has been included in the policy to help better determine the comorbidities that may preclude newly diagnosed AML patients from intensive induction chemotherapy. Based on current clinical trials that are being conducted, myelodysplastic syndrome (MDS) has been added to the investigation/experimental section of this policy and supporting evidence has been updated to reflect the rationale for the addition. The supporting evidence in this whole policy has been updated to reflect the pivotal trials. The references section has been updated to include the pivotal trials and NCCN guideline for AML.	02/2020
Policy created. Tibsovo and Idhifa was combined into one policy.	12/2019

ixazomib (Ninlaro®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP129

Description

Ixazomib (Ninlaro) is an orally administered reversible proteasome inhibitor that binds and inhibits chymotrypsin-like activity of the beta 5 subunit of the 20s proteasome.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
ixazomib (Ninlaro)	2.3 mg capsule	Previously treated multiple myeloma, in combination with lenalidomide and dexamethasone	3 capsules/28 days
	3 mg capsule		
	4 mg capsule		

Initial Evaluation

I. Ixazomib (Ninlaro) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND**
   C. A diagnosis of **Previously treated multiple myeloma** when the following are met:
      1. The member has relapsed or refractory disease; **AND**
      2. The member has progressed on at least one prior therapy (e.g., melphalan, thalidomide, bortezomib, stem cell transplant, etc.); **AND**
      3. The member has **not** previously progressed on or after lenalidomide (Revlimid); **AND**
      4. Ixazomib (Ninlaro) will be used in combination with lenalidomide (Revlimid) AND dexamethasone; **AND**
      5. Ixazomib (Ninlaro) will be **not** be used with any other oncolytic medication other than those noted above.

II. Ixazomib (Ninlaro) is considered investigational when used for all other conditions, including but not limited to:
   A. Graft-Versus-Host Disease
   B. AL Amyloidosis
   C. Non-Hodgkin lymphoma
   D. Follicular lymphoma

E. Breast cancer
F. Mantle cell lymphoma
G. Sarcoma
H. Kidney cancer
I. Central nervous system cancers

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Ixazomib (Ninlaro) is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
IV. Clinical documentation of response to treatment such as stabilization or improvement in disease or symptoms; **AND**
V. Will be used in combination with lenalidomide (Revlimid) AND dexamethasone; **AND**
VI. Will **not** be used in combination with any other oncolytic medication other than lenalidomide (Revlimid).

Supporting Evidence

I. The safety and efficacy of ixazomib (Ninlaro) was evaluated in a randomized, double-blind, placebo controlled trial.
    - Ixazomib (Ninlaro) was evaluated in combination with lenalidomide (Revlimid) and dexamethasone for multiple myeloma in adults. Subjects were relapsed or refractory to at least one prior therapy, with those who were refractory to lenalidomide (Revlimid) excluded from the trial. The label indicates 69% of participants in each group had previously progressed on bortezomib (Velcade), 44-47% had progressed on thalidomide (Thalomid), 80-81% had progressed on melphalan therapy, and 55-59% had previous stem cell transplantation.
    - A total of 722 subjects were randomized and treated until disease progression or unacceptable toxicity with ixazomib (Ninlaro)on days one, eight, and 15 of the 28-day cycles.
    - The primary endpoint was progression-free survival (PFS) according to the 2011 International Myeloma Working Group (IMWG) Consensus Uniform Response Criteria, assessed by a blinded independent review committee. The PFS for ixazomib (Ninlaro) was 20.6 months (17, NE) versus 14.7 months (12.9, 17.6) [HR 0.74 (0.59-0.94), p<0.012].
    - A statistically significant survival benefit has not been demonstrated with ixazomib (Ninlaro).

II. National Comprehensive Cancer Network guidelines indicate that treatment with a three drug regimen is standard of care; however, for those that have low performance status, initiation with a two-drug regimen may be appropriate until performance improves.

III. Clinical resources indicate ixazomib (Ninlaro) is approved for multiple myeloma maintenance therapy for newly diagnosed disease; however, the label does not indicate this use. A clinical trial for maintenance therapy after hematopoietic stem cell transplant shows preliminary results for PFS; however, clinically relevant data, such as overall survival, are unknown at this time.

Investigational or Not Medically Necessary Uses

I. Ixazomib (Ninlaro) has not been sufficiently studied for safety and efficacy, and/or are is currently being evaluated in clinical trials for the following indications:
   A. Graft-Versus-Host Disease
   B. AL Amyloidosis
   C. Non-Hodgkin lymphoma
   D. Follicular lymphoma
   E. Breast cancer
   F. Mantle cell lymphoma
   G. Sarcoma
   H. Kidney cancer
   I. Central nervous system cancers

References

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4. Dimopolulos MA., Gay F., Schjesvold F., et al. Oral ixazomib maintenance following autologous stem cell transplant (TOURMALINE-MM3): a double-blind, randomized, placebo-controlled phase 3 trial. *Lancet*. 2019; 393(10168):253-264.

Policy Implementation/Update:

Date Created	December 2015
Date Effective	February, 2016
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format. Age requirement added, as well as clarification on place in therapy and appropriate combination therapy. Renewal requirements changed to include specialist prescriber, and appropriate place in therapy and combination therapy.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP076

Description

Lapatinib (Tykerb) is an orally administered tyrosine kinase inhibitor against epidermal growth factor receptors HER1 and HER2.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
lapatinib (Tykerb)	250 mg tablets	Breast cancer, HER2 overexpression, advanced or metastatic in combination with capecitabine after prior therapy	105 tablets/21 days
		Breast cancer, HR-positive, HER2 overexpression, in postmenopausal women, in combination with letrozole	168 tablets/28 days

Initial Evaluation

I. **Lapatinib (Tykerb)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Lapatinib (Tykerb) will <u>not</u> 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 <u>ALL</u> of the following therapies: anthracycline therapy (e.g., doxorubicin), taxane therapy (e.g., paclitaxel, docetaxel), trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.); **AND**
            a. Will be used in combination with capecitabine; **AND**
            b. Request is for generic lapatinib; **OR**
               i. Member has an intolerance or contraindication to generic labatinib; **OR**
         ii. Initial therapy in the metastatic setting; **AND**

a. The member is a postmenopausal female (natural or pharmacotherapy induced [e.g., GnRH therapy used concomitantly [e.g., Lupron]); **AND**
b. The disease is hormone receptor (HR)-positive; **AND**
c. Will be used in combination with letrozole or trastuzumab (Herceptin, Trazimera, Kanjinti, etc.); **AND**
d. Request is for generic lapatinib; **OR**
    i. Member has an intolerance or contraindication to generic labatinib

II. Lapatinib (Tykerb) is considered investigational when used for all other conditions, including but not limited to:
    A. HER2(–) breast cancer
    B. Concurrent use with therapies outside of those listed above
    C. Ovarian, uterine, endometrial cancer
    D. Peritoneal cancer
    E. Pancreatic cancer
    F. Melanoma
    G. Central nervous system cancers
    H. Head and neck cancer
    I. Gastrointestinal cancer
    J. Bladder, urothelial, renal cancer

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member has received a previous prior authorization approval for this agent; **AND**
III. The medication is prescribed by or in consultation with, an oncologist; **AND**
IV. Lapatinib (Tykerb) will not be used in combination with any other oncolytic medication with the exception of an letrozole, capecitabine or trastuzumab; **AND**
III. Documentation is provided indicating disease response to therapy, as defined by stabilization of disease, decrease in the size of the tumor, or tumor spread; **AND**
    A. Request is for generic lapatinib; **OR**
        1. Member has an intolerance or contraindication to generic labatinib

Supporting Evidence

I. Lapatinib (Tykerb) was evaluated in in combination with capecitablne for HER2(+), metastatic breast cancer. The trial was a Phase 3, randomized study versus capecitabine monotherapy in subjects that had previous exposure to anthracyclines, taxanes, and trastuzumab. The primary

endpoint was time to progression and the results were statistically significant in favor of lapatinib (Tykerb).

II. Overall survival data was not mature at time of assessment, and future results are likely to be confounded as subjects on placebo were allowed to cross over to active therapy during the trial.

III. In two randomized trials, lapatinib (Tykerb) showed to be less effective than trastuzumab-based chemotherapy regimens. The package label indicates subjects should have disease progression on trastuzumab prior to initiation of lapatinib (Tykerb) when used in combination with capecitabline for those with advanced or metastatic, HER2(+) disease.

IV. Lapainib (Tykerb) in combination with letrozole was evaluated in a double-blind, placebo-controlled study. The trial included women with HR+, HER2(+), metastatic breast cancer who had not received prior therapy for metastatic disease. The primary outcome was progression-free survival (PFS) which was statistically significant in favor of lapatinib (Tykerb).

V. Another trial evaluated lapatinib (Tykerb) in combination with an aromatase inhibitor, again evaluating in HR+, HER2(+), metastatic disease. These subjects had progressed after trastuzumab chemotherapy and endocrine therapies. The treatment arms included lapatinib (Tykerb) + trastuzumab + AI, trastuzumab + AI, or lapatinib (Tykerb) + AI. The results were statistically significant in PFS for the triple therapy, followed by lapatinib (Tykerb) + AI, then trastuzumab + AI. Additionally, lapatinib (Tykerb) has demonstrated a statistically significant improvement in PFS in HER2(+) breast cancer when added to trastuzumab compared to lapatinib (Tykerb) alone.

Investigational or Not Medically Necessary Uses

I. Lapatinib (Tykerb) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. HER2(–) breast cancer
   B. Concurrent use with therapies outside of those listed above
   C. Ovarian, uterine, endometrial cancer
   D. Peritoneal cancer
   E. Pancreatic cancer
   F. Melanoma
   G. Central nervous system cancers
   H. Head and neck cancer
   I. Gastrointestinal cancer
   J. Bladder, urothelial, renal cancer

References

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2. Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol. 2017;18(6):732-742.
3. Pivot X, Manikhas A, Żurawski B, et al. CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2015;33(14):1564-73.

4. Johnston S, Pippen J, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J Clin Oncol. 2009;27(33):5538-46.
5. NCCN Clinical Practice Guideline in Oncology: Breast Cancer. Version 3.2019. National Comprehensive Cancer Network. Available at https://www.nccn.org/professionals/ physician_gls/pdf/breast.pdf. Updated September 6, 2019.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria to prefer generic lapatinib over brand Tykerb unless contraindicated or not tolerated	06/2021
Criteria transitioned to policy. Policy updated to include the following requirement: specialist prescriber, age, concurrent therapies, specified place in therapy.	10/2019
Previous Reviews	09/2013 08/2013 08/2011 10/2008
Policy Created	09/2008

Policy Type: PA/SP Pharmacy Coverage Policy: UMP042

Split Fill Management*

Description

Larotrectinib (Vitrakvi) is an orally administered tropomyosin receptor kinase (TRK) inhibitor; specifically TRKA, TRKB, and TRKC.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
larotrectinib (Vitrakvi)	25 mg capsule	Neuotrophic receptor tyrosine kinase gene fusion positive solid tumor, metastatic	180 tablets/30 days
	100 mg capsule		60 tablets/30 days
	20 mg/1 mL solution		Quantity calculated to 100 mg/m2 of body surface area

Initial Evaluation

I. Larotrectinib (Vitrakvi) may be considered medically necessary when the following criteria are met:
   A. Prescribed by, or in consultation with, an oncologist; **AND**
   B. Medication will **not** be used in combination with any other oncolytic medication; **AND**
   C. The member has **not** previously progressed on other NTRK gene fusion medications (e.g., entrectinib [Rozlytrek]); **AND**
   D. A diagnosis of solid tumor with confirmed **NTRK gene fusion; AND**
   E. Member has metastatic disease, or surgical resection is likely to result in severe morbidity (i.e., tumor is unresectable); **AND**
   F. The member does **not** have an acquired resistance mutation (resistant mutations include, but may not be limited to: G595R, G623R, G696A, F617L); **AND**
   G. **All** alternative therapies for diagnosis and stage of cancer have been exhausted, as defined by:
      1. Progression following all appropriate treatments; **OR**
      2. Nonresponse to all available therapies; **OR**
      3. All available therapies are contraindicated or not tolerated; **OR**
      4. No standard or satisfactory treatments exist; **AND**
   H. The member has intolerance to or contraindication to entrectinib (Rozlytrek); **OR**

1. Member is less than 12 years of age

II. Larotrectinib (Vitrakvi) is considered not medically necessary when criteria above are not met and/or when used for the following:
   A. When used for a resistance mutation (resistant mutations include, but may not be limited to G595R, G623R, G696A, F617L)

III. Larotrectinib (Vitrakvi) is considered investigational when used for all other conditions, including but not limited to:
   A. Oncolytic indications as an adjunct therapy
   B. Non-small cell lung cancer without NTRK fusion gene rearrangements
   C. Solid tumors that do not harbor NTRK gene fusions
   D. Leukemias or lymphomas

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescribed by, or in consultation with, an oncologist; **AND**
IV. Medication will **not** be used in combination with any other oncolytic medication; **AND**
V. Response to therapy as indicated by stabilization of disease or decrease in tumor size or spread; **AND**
VI. Member does **not** have unacceptable medication toxicity (e.g., hepatotoxicity, severe delirium or gait disturbances, etc.); **AND**
VII. Documentation of absence of acquired resistance

Supporting Evidence

I. Per the landmark trials LOXO-TRK-14001 (SCOUT and NAVIGATE): All subjects were diagnosed with measurable or evaluable metastatic or locally advanced solid tumors, had progressed beyond all effective and available therapies per the National Comprehensive Cancer Network (NCCN), had no therapies available for the diagnosis per NCCN guidelines, or surgical resection would result in significant morbidity.
II. Subjects were without acquired resistance mutations to NTRK-inhibitors, without active cardiovascular disease or history of myocardial infarction within the prior six months, and were not on concurrent CYP3A4 inhibitors or inducers.
III. The NTRK gene fusion mutation was confirmed using a validated laboratory testing method. Testing methods for NTRK gene fusion include NGS, RT-PCR, FISH, or Immunohistochemistry (ICH). The use of ICH may lead to a false positive result. ICH uses the presence of a surrogate marker (TRK proteins) to establish the likelihood of a NTRK gene fusion. The FISH method

requires the visual assessment of an experienced pathologist of several tests and is considered more subjective than NGS or RT-PCR.

IV. The trials were single-arm, open-label studies that included 55 patients with solid tumors. The tumor types that had represented AND reported a measurable Overall Response Rate (ORR) were the following:
    - Salivary gland cancer
    - Soft tissue sarcoma (STS)
    - Infantile fibrosarcoma (IFS)
    - Gastrointestinal Stromal Tumor (GIST)
    - Non-small cell lung cancer (NSCLC)
    - Colorectal cancer (CRC)
    - Melanoma
    - Thyroid carcinoma
    - Colon cancer

V. Tumors that were evaluated in one or more subjects but did not show an ORR includ cholangiocarcinoma, appendix, breast and pancreatic cancer.

VI. Adverse reactions were common with larotrectinib (Vitrakvi), and included fatigue, pyrexia, peripheral edema, CNS, gastrointestinal, respiratory, musculoskeletal, and laboratory disturbances (e.g., ASK, ALT). Adverse events leading to dose discontinuation, interruption or reduction occurred in 37% of subjects. The safety profile of larotrectinib (Vitrakvi) is likely not fully developed given the small number of subjects in the clinical trials and short trial duration. Additionally, due to rarity of the NTRK gene fusion mutation, post-marketing information is likely to remain limited.

VII. There are currently two available therapies for NTRK gene fusion positive mutations. Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek), currently there is no direct comparison data showing safety and/or efficacy differences between these therapies OR safety or efficacy of using them sequentially after progression. Additionally, caution should be exercised when making cross trial comparisons. At this time, entrectinib (Rozlytrek) provides a better value for general populations with NTRK gene fusion positive tumors given the sum of safety, efficacy, and cost information currently available.

VIII. It should also be noted that due to single-arm, open-label trial designs, as well as outcomes evaluated, no NTRK gene fusion therapies available have been shown to improve health outcomes to date.

IX. Entrectinib (Rozlytrek) is FDA-approved down to 12 years of age, but has been, and will continue to be, evaluated in younger populations. Larotrectinib (Vitrakvi) FDA-approval is nonspecific to pediatrics and adults.

Investigational or Not Medically Necessary Uses

I. Larotrectinib (Vitrakvi) does not have sufficient activity in those with resistance mutations. As of December 2019, known resistance mutations include: G595R, G623R, G696A, F617L.

II. Larotrectinib (Vitrakvi) has not been sufficiently evaluated for safety and efficacy in the following settings:
    A. Oncolytic indications as an adjunct therapy

B. Non-small cell lung cancer without NTRK fusion gene rearrangements
C. Solid tumors that do not harbor NTRK gene fusions
D. Leukemias or lymphomas

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

References

1. Vitrakvi [Prescribing Information]. Stamford, CT: Loxo Oncology,Inc. November 2018.
2. Rozlytrek [Prescribing Information]. Genentech. San Francisco, CA. 2019.
3. Gatalica Z, Swensen J, Kimbrough J, et. al. AACR-NCI-EORTC 2017. Abstract A047: Molecular characterization of the malignancies with targetable NTRK gene fusions. Available at: http://mct.aacrjournals.org/content/17/1_Supplement/A047. Accessed December 5, 2018.
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Policy Implementation/Update:

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

Action and Summary of Changes	**Date**
Policy updated to newest formatting. Initial approval duration changed to three months from six months given safety concerns and split-fill designation, quantity limit for solution now based on BSA, removal of designated test requirement, removed requirements for lab value monitoring, requirement for lack of CV comorbidities and CNS symptoms. Addition of monotherapy requirement, documentation of intolerance of contraindication to entrectinib (Rozlytrek) and requirement the member has not previously progressed on other NTRK therapies.	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP111

Description

Thalidomide (Thalomid) is an oral immunomodulatory medication that inhibits FGF-dependent angiogenesis in vivo and exhibits antineoplastic activity. Lenalidomide (Revlimid) and pomalidomide (Pomalyst) are orally administered thalidomide analogues. These agents are thought to attack multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis, and cytokine circuits, among others.

Length of Authorization

- Initial:
  - i. Lenalidomide (Revlimid)
    1. Follicular lymphoma/Marginal zone lymphoma: 12 months
    2. All other indications: Six months
  - ii. Pomalidomide (Pomalyst) and thalidomide (Thalomid)
    1. All indications: Three months
- Renewal:
  - i. Lenalidomide (Revlimid)
    1. Follicular lymphoma/Marginal zone lymphoma: Cannot be renewed
    2. All other indications: 12 months
  - ii. Pomalidomide (Pomalyst)
    1. All indications: 12 months
  - iii. Thalidomide (Thalomid)
    1. Cutaneous manifestations of moderate to severe Erythema Nodosum Leprosum (ENL): Three months
    2. Multiple myeloma: Six months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
lenalidomide (Revlimid)	2.5 mg capsules	Follicular lymphoma; Marginal zone lymphoma; Multiple myeloma; Myelodysplastic syndromes	28 capsules/28 days
	5 mg capsules	Follicular lymphoma; Mantle cell lymphoma; Marginal zone lymphoma; Multiple myeloma; Multiple myeloma maintenance therapy following auto-HSCT; Myelodysplastic syndromes;	28 capsules/28 days
	10 mg capsules		28 capsules/28 days
	15 mg capsules		28 capsules/28 days
	20 mg capsules		21 capsules/28 days
	25 mg capsules	Mantle cell lymphoma; Multiple myeloma	21 capsules/28 days
	1 mg capsules	Multiple Myeloma	21 capsules/28 days

pomalidomide (Pomalyst)	2 mg capsules		
	3 mg capsules		
	4 mg capsules		
Thalidomide (Thalomid)	50 mg capsules	Multiple Myeloma	28 capsules/28 days
	100 mg capsules		
	150 mg capsules		
	200 mg capsules		
	50 mg capsules	Erythema Nodosum Leprosum	60 capsules/30 days
	100 mg capsules		
	150 mg capsules		
	200 mg capsules		

Initial Evaluation

I. **Lenalidomide (Revlimid)** 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 <u>with</u> del(5q) abnormality; **OR**
         ii. MDS <u>without</u> del(5q) abnormality; **AND**
            a. Serum erythropoietin levels are <u>less than</u> 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 <u>greater than</u> 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 in patients with relapsed MM who were refractory to both lenalidomide (Revlimid) and bortezomib. The primary endpoint, PFS, was significantly longer in patients who received pomalidomide (Pomalyst) and low-dose dexamethasone compared to those who received high-dose dexamethasone (4.0 vs 1.9 months; P < 0.0001). Overall survival was significantly longer in the pomalidomide (Pomalyst) group also (12. 7 vs 8.1 months; P = 0.0285).

- A Phase 2, randomized open-label trial evaluated the safety and efficacy of pomalidomide (Pomalyst) alone or pomalidomide (Pomalyst) with low-dose dexamethasone in patients with relapsed or refractory MM. The ORR was 29.2% in patients who received combination therapy versus 7.4% in the monotherapy arm.
- Additional data regarding single agent pomalidomide (Pomalyst) therapy is available but is considered low quality. Pomalidomide (Pomalyst) monotherapy was evaluated in a Phase 1 trial of 24 patients and demonstrated an ORR of 50%. In a subsequent Phase 1 study, the ORR was much lower at 15%.
- Immunomodulatory agents are usually given in combination with dexamethasone and/or other agents, but the NCCN Multiple Myeloma Panel suggests considering pomalidomide (Pomalyst) monotherapy in patients who are steroid-intolerant.

Thalidomide (Thalomid)

- Although thalidomide (Thalomid) was the first immunomodulatory agent to show efficacy in MM, other agents such as lenalidomide (Revlimid) and pomalidomide (Pomalyst) have since been developed and offer a more favorable safety profile.
- The efficacy and safety of thalidomide (Thalomid) plus dexamethasone vs dexamethasone alone in multiple myeloma was evaluated in two open-label studies in symptomatic patients with newly diagnosed multiple myeloma. In one study, response rates (based on serum or urine paraprotein measurements) were significantly higher in the combination arm (52% vs 36%). In another study, the time to progression (TTP) was statistically significantly longer in the combination arm.
- The NCCN Guideline for Multiple Myeloma does not include thalidomide (Thalomid)-based regimens as preferred or recommended for any setting. Regimens containing thalidomide (Thalomid) may be useful in certain circumstances when used in combination with other active multiple myeloma agents (e.g. bortezomib). The combination of bortezomib, thalidomide (Thalomid), and dexamethasone is a Category 1 recommendation as primary therapy for transplant candidates in certain circumstances.
- There is no evidence to support the use of thalidomide (Thalomid) as monotherapy for the treatment of multiple myeloma.

II. **Myelodysplastic syndromes (MDS):**

- Lower-risk MDS <u>with</u> del(5q) generally has a relatively good prognosis and is highly responsive to lenalidomide (Revlimid) therapy.
    i. A Phase 3 trial in 205 patients demonstrated superiority of lenalidomide (Revlimid) compared to placebo for achieving RBC transfusion-independence.

1. Patients with transfusion-dependent, lower risk MDS with del(5q) were treated with low dose lenalidomide (Revlimid) (10 mg), lower dose lenalidomide (Revlimid) (5 mg), and placebo.
2. The rates of transfusion-independence for greater than 26 weeks were 57%, 37%, and 2% respectively for low dose lenalidomide (Revlimid), lower dose lenalidomide (Revlimid), and placebo.
3. The risk of transformation to acute myeloid leukemia (AML) was not significantly different between lenalidomide (Revlimid) and placebo.

ii. Additionally, a Phase 2 trial in anemic transfusion-dependent patients with del(5q) also reported similar hematologic responses in two-thirds of the 148 patients with del(5q).

- The safety and efficacy of lenalidomide (Revlimid) for lower-risk MDS <u>without</u> del(5q) was evaluated in a Phase 3 trial in 239 patients with transfusion-dependent MDS.
  i. Patients receiving lenalidomide (Revlimid) compared to placebo had a higher rate of transfusion-independence (26.9% vs 2.5%; $p < 0.001$). Transfusion reduction of four or more units of packed RBCs was seen in 22% of lenalidomide (Revlimid)-treated patients while no reduction was seen in the placebo group.
  ii. Incidence of treatment-related mortality was 2.5% in both groups, but the incidence of myelosuppression was higher in the lenalidomide-treated group. Furthermore, when comparing lenalidomide (Revlimid) to placebo, the incidence of grade 3 or 4 neutropenia was 61.9% vs 12.7%, respectively, and the rate of thrombocytopenia was 35.6% vs 3.8%, respectively.

III. **Mantle cell lymphoma (MCL):**

- Lenalidomide (Revlimid) is approved for the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.
- The safety and efficacy of single-agent lenalidomide (Revlimid) for relapsed or refractory MCL was evaluated in a Phase 2, open-label trial in 134 patients with prior bortezomib therapy. The ORR was 28% and a median duration of response (DoR) was 16.6 months.
- An additional Phase 2 trial included 254 patients with relapsed MCL who were not candidates for intensive therapy were randomized to receive single-agent lenalidomide (Revlimid) or single-agent of the investigator's choice (e.g. rituximab, gemcitabine, fludarabine, chlorambucil, cytarabine) and were allowed to receive lenalidomide (Revlimid) at the time of progression. After a median follow-up of 15.9 months, PFS was 8.7 months for lenalidomide (Revlimid) verses 5.2 months for the control arm.
- The NCCN B-Cell Lymphomas guideline suggests the use of lenalidomide (Revlimid) outside of the relapsed/refractory setting, including as initial treatment or in the second-line setting. However, there is limited evidence to support use outside of the relapsed/refractory setting. A small Phase 2 study evaluated the use of lenalidomide (Revlimid) plus rituximab as initial therapy for patients with MCL. The ORR in the

intention-to-treat population (n = 38) was 87% and 92% in the population that could be evaluated (n = 36).

IV. **Previously treated follicular lymphoma (FL)/marginal zone lymphoma (MZL):**

- The efficacy of lenalidomide (Revlimid) with rituximab in patients with relapsed or refractory follicular and marginal zone lymphoma was evaluated in the AUGMENT (NCT01938001) and MAGNIFY (NCT01996865) trials.
- AUGMENT was a randomized, double-blind, multicenter trial (n=358) in patients with relapsed or refractory follicular or marginal zone lymphoma who received lenalidomide (Revlimid) and rituximab or rituximab and placebo for a maximum of 12 cycles or until unacceptable toxicity.
    i. Efficacy results in the follicular and marginal zone lymphoma population reported a PFS of 39.4 months in the lenalidomide (Revlimid) and rituximab arm versus 14.1 months in the rituximab plus placebo arm.
- MAGNIFY is an open-label, multicenter trial (n=232) in which patients with relapsed or refractory follicular, marginal zone, or mantle cell lymphoma received 12 induction cycles of lenalidomide (Revlimid) and rituximab.
    i. Overall response by investigator assessment was 59% (104/177) [95% CI: 51, 66] for patients with follicular lymphoma. Median DoR was not reached within a median follow-up time of 7.9 months [95% CI: 4.6, 9.2]. With an overall response of 51% (23/45) [95% CI: 36, 66] for patients with marginal zone lymphoma and median DoR not reached within a median follow-up time of 11.5 months [95% CI: 8.0, 18.9].

V. **Erythema nodosum leprosum (ENL)**

- Erythema nodosum leprosum (ENL) is a serious immunological complication of leprosy, causing inflammation of skin, nerves, other organs, and general malaise. There is limited high-quality, prospective data supporting the use of thalidomide (Thalomid) for ENL. Data are mainly derived from small randomized trials or retrospective studies conducted by the U.S. Public Health Service. These data consistently report generally successful treatment of the cutaneous manifestations of moderate to severe ENL.
- Thalidomide (Thalomid) is not indicated as monotherapy for ENL treatment in the presence of moderate to severe neuritis. Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering should be maintained on the minimum dose necessary to control the reaction. Tapering off the medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.
- Dosing with thalidomide (Thalomid) in ENL should usually continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks.
- In patients with moderate to severe neuritis associated with a severe erythema nodosum leprosum reaction, corticosteroids may be started concomitantly with thalidomide (Thalomid). Steroid usage can be tapered and discontinued when the neuritis has improved.

Investigational or Not Medically Necessary Uses

I. Kaposi sarcoma
   A. A preliminary study of thalidomide (Thalomid) has shown some activity in patients with AIDS-related KS; however, further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.
   B. Pomalidomide (Pomalyst) was studied in one ongoing, open-label, single center, single arm, Phase 1/2 trial with 28 patients with KS. There were 18 HIV-positive patients and 10 HIV-negative patients included in the trial. The HIV-positive patients continued on HAART. The primary efficacy outcome was ORR. The ORR was 71% (95% CI 51, 87) for all patients with 12 HIV-positive patients and 8 HIV-negative patients having a response. The duration of response was 12.5 months (95% CI 6.5, 24.9) for HIV-positive patients and 10.5 months (95% CI 3.9, 24.2) for HIV-negative patients. NCCN guidelines recommend pomalidomide (Pomalyst) as the preferred subsequent systemic therapy for relapsed/refractory therapy after first-line systemic options liposomal doxorubicin or paclitaxel; however, this is based on preliminary evidence from an early-phase, single center, open-label trial. Further evaluation in larger, well-controlled studies are needed to support the use of pomalidomide (Pomalyst) in the setting of KS.

II. Behçet syndrome
   A. The efficacy of thalidomide monotherapy for mucocutaneous manifestations of Behçet syndrome was evaluated in 96 patients compared to placebo. Only a minority of thalidomide (Thalomid)-treated patients responded to treatment, and some symptoms worsened. Furthermore, 7% of thalidomide-treated patients developed peripheral neuropathy.
   B. The use of thalidomide (Thalomid) for Behçet syndrome has fallen out of favor due to lack of proven efficacy and significant risk of neuropathy and teratogenicity.

III. Chronic lymphocytic leukemia (CLL)
   A. Lenalidomide (Revlimid) was studied in patients with previously treated CLL in a randomized, double-blind, placebo-controlled, Phase 3 trial (CONTINUUM). Patients included in the trial had been treated with two lines of therapy with at least a partial response after second-line therapy, had received a purine analogue, bendamustine, anti-CD20 antibody, chlorambucil, or alemtuzumab as first-line or second-line treatment; and had an Eastern Cooperative Oncology Group performance score of 0–2. Co-primary endpoints were PFS and OS; the primary endpoint was later changed to OS after the data cutoff for analysis. With a median follow-up of 31.5 months, there was no significant difference in OS between the lenalidomide (Revlimid) and the placebo groups (median 70·4 months, 95% CI 57·5–not estimable [NE] vs NE, 95% CI 62·8–NE; hazard ratio [HR] 0·96, 95% CI 0·63–1·48; p=0·86).

IV. Diffuse large B-cell lymphoma (DLBCL)
   A. NCCN guidelines list lenalidomide (Revlimid) maintenance for patients 60-80 years of age as a Category 2B recommendation. This is based off the results of an open-label, single-arm, Phase 2 trial in 48 adults with de novo DLBCL. Further evaluation in higher quality trials is needed to support its use.

B. In the relapsed setting, lenalidomide (Revlimid) was studied in small, Phase 2, open-label trials consisting of low-quality evidence. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.

V. Multiple myeloma, as part of quadruple ("quad") regimen
   A. Although triplet regimens remain the standard of care for MM, there is growing interest in quad regimens which may include the addition of monoclonal antibodies [e.g. daratumumab (Darzalex), elotuzumab (Empliciti)] to standard triplet backbone regimens. The current evidence available to support this use is limited to case series or small trials. Larger studies evaluating the safety and efficacy of these regimens are underway.

VI. Non-Hodgkin's lymphoma (NHL)
   A. Lenalidomide (Revlimid) was evaluated in patients with relapsed or refractory aggressive NHL, in an open-label, Phase 2 trial (n=49). Treatment with lenalidomide (Revlimid) led to an ORR of 35% and a median PFS of 4 months. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.

VII. Myelofibrosis
   A. Lenalidomide (Revlimid) was evaluated in a small, open-label, Phase 2 trial in combination with prednisone that reported a treatment response in 10 of 42 subjects, with 37 patients reporting a grade 3 or 4 toxicity. In an analysis of three consecutive Phase 2 trials of patients with myelofibrosis (n=125), single agent lenalidomide (Revlimid) and lenalidomide (Revlimid) plus prednisone produced higher response rates than thalidomide (Thalomid), though not statistically significant (p=0.06). Further studies are warranted. An additional trial by Daver et al. that evaluated lenalidomide (Revlimid) in combination with ruxolitinib (Jakafi) was terminated early due to failure to meet the predetermined efficacy rules for treatment success.
   B. Pomalidomide (Pomalyst) has been evaluated as a treatment option for MF-associated anemia. Results from two small randomized studies produced conflicting results.
   C. Enrollment in a clinical trial should be considered for all patients with myelofibrosis-associated anemia.

VIII. POEMS syndrome
   A. Regimens used as systemic therapy for POEMS syndrome with widespread osteosclerotic lesions or bone marrow involvement are modelled after those used in other conditions, such as MM. There are limited data to guide choice in therapy.
   B. Case reports have demonstrated clinical improvement after treatment with lenalidomide (Revlimid) with or without dexamethasone. Two small, uncontrolled studies reported responses in over 70% with 60 to 75% progression free at three years.
   C. Thalidomide (Thalomid) has also shown activity but is associated with a less favorable side effect profile.
   D. Larger, well-controlled trials are needed to confirm the safety and efficacy of these agents for POEMS syndrome.

IX. Systemic light chain amyloidosis (AL)
   A. There is insufficient evidence to support the use of lenalidomide (Revlimid) or pomalidomide (Pomalyst) for the management of AL. Both medications are listed in NCCN guidelines among several other treatment options; however, the optimal treatment of the

underlying plasma cell disorder has not been identified. Treatment of AL should be in the context of a clinical trial when possible.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new indication for Kaposi Sarcoma for Pomalyst as experimental and investigational	06/2020
• For multiple myeloma indications, updated language to clarify use as either monotherapy, or with dexamethasone as part of a double-drug or triple-drug regimen • Added CLL to the not medically necessary section • Added the following experimental/investigational indications: - As part of a quadruple regimen for MM - Systemic light chain amyloidosis - POEMS - Behçet syndrome	04/2020
Added pomalidomide (Pomalyst) and thalidomide (Thalomid) agents to policy; removed black box warnings and precautions readily available in compendia; removed laboratory criteria.	12/2019
Converted lenalidomide (Revlimid) to policy format. Added new indication of follicular lymphoma and marginal zone lymphoma. Allowed coverage as monotherapy in multiple myeloma maintenance following autologous hematopoietic stem cell transplant. Allowed a route to coverage in myelodysplastic syndromes without a deletion 5q abnormality following phase III trial data.	08/2019
Excluded package insert/monitoring question and removed renewal question regarding regular hematological laboratory tests, extended initial approval from 3 months to 6 months.	01/2018

Previous reviews	09/2012, 10/2012, 10/2014, 09/2015, 01/2016
Policy created	08/2012

Policy Type: PA/SP Pharmacy Coverage Policy: 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 inhibiting the binding 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

Product Name	Dosage Form	Indication	Quantity Limit
lenvatinib (Lenvima)	4 mg tablets	Unresectable Liver Carcinoma; Advanced Renal Cell Carcinoma; Locally Recurrent or Metastatic Progressive Thyroid Cancer; Metastatic Endometrial Carcinoma	90 tablets/30 days
	10 mg tablets		60 tablets/30 days
pazopanib (Votrient)	200 mg tablets	Advanced Renal Cell Carcinoma; Advanced Soft Tissue Sarcoma	120 tablets/30 days
sorafenib (Nexavar)	200 mg tablets	Unresectable Liver Carcinoma; Advanced Renal Cell Carcinoma; Locally Recurrent or Metastatic Progressive Thyroid Cancer	120 tablets/30 days

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 medication will be used as monotherapy unless outlined below [e.g. lenvatinib (Lenvima) in combination with everolimus (Afinitor) for Renal Cell Carcinoma]; **AND**

D. 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**

E. 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 pazopanib (Votrient) OR sorafenib (Nexavar); **OR**
   iii. The request is for lenvatinib (Lenvima); **AND**
      a. The member has had disease progression on, or intolerance to, **one** anti-angiogenic therapy unless all are contraindicated (e.g. sunitinib [Sutent], pazopanib [Votrient], axitinib [Inlyta], bevacizumab [Avastin]); **AND**
      b. Lenvatinib (Lenvima) will be used in combination with everolimus (Afinitor); **OR**
2. **Hepatocellular Carcinoma (HCC)**; **AND**
   i. The member has unresectable, advanced (stage III) or metastatic (stage IV) disease; **AND**
   ii. The request is for sorafenib (Nexavar); **OR**
   iii. The request is for lenvatinib (Lenvima); **AND**
      a. The request is for first-line systemic therapy (i.e. previously untreated with systemic chemotherapy); **OR**
3. **Thyroid Carcinoma; AND**
   i. The member has recurrent or metastatic (stage IV) disease; **AND**
   ii. The member has one of the following subtypes of differentiated thyroid carcinoma:
      a. Papillary thyroid carcinoma; **OR**
      b. Follicular thyroid carcinoma; **OR**
      c. Hurthle cell thyroid carcinoma; **AND**
   iii. The disease is refractory to radioactive iodine treatment (RAI)**; AND**
   iv. The request is for lenvatinib (Lenvima); **OR**
   v. The request is for sorafenib (Nexavar); **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 member has had disease progression on at least one anthracycline-based chemotherapy regimen unless all are contraindicated (e.g. doxorubicin, epirubicin, ifosfamide)
5. **Metastatic Endometrial Carcinoma; AND**

i. 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
   B. Sorafenib (Nexavar) for the treatment of desmoid tumors (aggressive fibromatosis)

III. Lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar) are considered investigational when used for all other conditions, including but not limited to:
   A. Gastrointestinal Stromal Tumor
   B. Adipocytic Sarcoma/Liposarcoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan 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. Disease response to treatment defined by stabilization of disease or decrease in tumor size or spread.

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 listed under this policy have received FDA-approval for patients 18 years and older. Efficacy and safety of these agents has 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, except for lenvatinib in combination with everolimus for the treatment of renal cell carcinoma.
IV. 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 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 one 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).

V. Lenvatinib (Lenvima) was studied in combination with everolimus (Afinitor) 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).

VI. Pazopanib (Votrient) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial with 435 patients with locally advanced and/or metastatic RCC who had received no prior therapy or one prior cytokine-based systemic therapy. The primary endpoint was PFS. Pazopanib (Votrient) had a PFS of 9.2 months compared to 4.2 months for placebo, with a HR of 0.46 (95% CI 0.34, 0.62).

VII. It is notable that NCCN guidelines recommend pazopanib (Votrient) as a preferred first-line therapy for clear cell histology stage IV renal cell carcinoma with a category 1 recommendation. Lenvatinib (Lenvima) in combination with everolimus (Afinitor), and sorafenib (Nexavar) are other recommended regimens for subsequent therapy with Category 1 and 2B recommendations, respectively. NCCN no longer recommends sorafenib (Nexavar) as a first-line treatment due to multiple alternative options and lack of current clinical use as a first-line treatment. Meta-analysis of clinical trials involving head-to-head comparison between multi-TKI shows that newer multi-TKI have a better efficacy profile compared to sorafenib (Nexavar). Additionally, clinical trials 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.

VIII. 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 overall survival (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).

IX. 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).

X. NCCN guidelines recommend sorafenib (Nexavar) and lenvatinib (Lenvima) as preferred regimens for first-line therapy as category 1 recommendations in patients with a Child-Pugh Class A score. Both therapies are also listed as subsequent therapy with category 2A recommendations. NCCN guidelines note that sorafenib (Nexavar) can 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 of either after progression of 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 on 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.

XI. 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).

XII. 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).

XIII. 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.

XIV. 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.

XV. For lenvatinib (Lenvima), 68% of patients required dose reductions, and 18% discontinued therapy due to AEs. Sorafenib (Nexavar) had a 32% discontinuation rate due to AEs, and in another study, there were 66% of patients requiring a dose interruption, and 64% required a dose reduction. For pazopanib (Votrient), 42% of patients required a dose interruption, and 36% of patients required a dose reduction.

XVI. Lenvatinib (Lenvima) was studied in combination with pembrolizumab (Keytruda) in an ongoing single-arm, open-label, Phase 1b/2 trial in 108 patients with metastatic endometrial carcinoma that had progressed on one prior systemic therapy. Participants in this trial had unresectable advanced endometrial cancer which was not microsatellite instability high (MSI-H) or mismatch- pair deficient (dMMR). The primary efficacy outcome was overall response rate (ORR) at week 24. The ORR at week 24 was 38.3% (95% CI 29%, 49%). Of the responders to therapy there were 32 patients (69%) with a duration of response greater than six months. This indication was approved under

accelerated approval based on the interim data for tumor response rate. Continued approval for this indication may be contingent upon verification of clinical benefit upon confirmatory clinical trials. Additionally, this is an ongoing clinical trial and data has not reached maturity. As of October 2020, the results for 13% participants were available. Quality of evidence is considered low due to open-label single arm study design and lack of measurable survival outcomes; however Washington State Health Care Authority allows use of combination pembrolizumab (Keytruda) and lenvatinib (Lenvima) for the indication of metastatic endometrial carcinoma.

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.
      ii. 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 noy be conclusive.
   C. Sorafenib (Nexavar) in combination with erlotinib for Hepatocellular Carcinoma
      i. Sorafenib (Nexavar) in combination with erlotinib, was studied in a randomized, placebo-controlled, Phase 3 trial in 720 patients with advanced HCC. Results found that the combination did not significantly improve survival relative to sorafenib (Nexavar) in combination with placebo. The combination had a significantly lower disease control rate (p=0.021) and a shorter treatment duration of 86 days compared to 123 days for sorafenib/erlotinib and sorafenib/placebo, respectively.

medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

References

1. Lenvima [Prescribing Information]. Woodcliff Lake, NJ: Eisai, Inc. February 2020.
2. Votrient [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals. May 2017.
3. Nexavar [Prescribing Information]. Whippany, NJ: Bayer Healthcare Pharmaceuticals, Inc. March 2020.
4. Makker V, Rasco D et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicenter, open-label, single-arm, phase 2 trial. Lancet Oncol. 2019 May;20(5):711-718.
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7. Olivier Mir MD et al. PAZOGIST trial, Lancet Oncology; 2016; 17 (55) 632-641.
8. National Comprehensive Cancer Network. NCCN Guidelines: Soft Tissue Sarcoma. Version 2.2020. Updated May 28, 2020.
9. National Comprehensive Cancer Network. NCCN Guidelines: Kidney Cancer. Version 1.2021. Updated July 15, 2020.
10. National Comprehensive Cancer Network. NCCN Guidelines: Hepatobiliary Cancers. Version 5.2020. Updated August 4, 2020.
11. National Comprehensive Cancer Network. NCCN Guidelines: Thyroid Carcinoma. Version 2.2020. Updated July 15, 2020.
12. National Comprehensive Cancer Network. NCCN Guidelines: Uterine Neoplasms. Version 2.2020. Updated July 24, 2020.
13. Gounder MM, Mahoney MR, et al. Sorafenib for Advanced and Refractory Desmoid Tumors. N Engl J Med. 2018 Dec 20;379(25):2417-2428.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added clinical trial data for sorafenib (Nexavar) in the setting of desmoid tumors to the supporting evidence (investigational and not medically necessary uses: C.ii)	04/2021
Updated allowance for treatment of endometrial carcinoma with Lenvima in combination with Keytruda per Uniform Medical Plan request	03/2021
Updated supporting evidence for investigational indication of endometrial carcinoma for lenvatinib (Lenvima)	12/2020
Transitioned criteria to policy format and merged into one policy; Updated criteria to include lenvatinib (Lenvima) requires failure of at least one anti-angiogenic therapy and combination therapy of lenvatinib (Lenvima) with everolimus (Afinitor); Updated disease staging requirements for most indications; Updated information on endometrial cancer for lenvatinib (Lenvima); and Updated supporting evidence section to align with policy changes	10/2020
Previous reviews • Lenvima: Updated indication to include advanced renal cell carcinoma (2017), updated indication to include unresectable hepatocellular carcinoma (2018) • Votrient: Updated to reflect FDA approved indications and quantity limits (2016) • Nexavar: Updated to reflect FDA approved indications (2016)	10/2018, 06/2017, 03/2016, 03/2016
Criteria created • Lenvima: 2015 • Votrient: 2012 • Nexavar: 2012	03/2015 02/2012 03/2012

letermovir (Prevymis™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP130

Description

Letermovir (Prevymis) is an orally administered antiviral agent that inhibits cytomegalovirus (CMV) deoxyribonucleic acid (DNA) terminase complex which helps prevent CMV infection in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

Length of Authorization

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

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
letermovir (Prevymis)	240 mg tablet	Prophylaxis for CMV Infection	30 tablets/30 days
	480 mg tablet		

Initial Evaluation

I. Letermovir (Prevymis) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist, hematologist, infectious disease, or transplant specialist; **AND**
   C. Member will be using letermovir (Prevymis) for the prevention of CMV infection or disease; **AND**
   D. 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

1. Prevymis [Prescribing Information]. Whitehouse Station, NJ: MERCK & CO, Inc. November 2017.
2. Chen K, Cheng MP, Hammond SP, et al. Antiviral Prophylaxis for Cytomegalovirus Infection in Allogeneic Hematopoietic Cell Transplantation. Blood Adv. 2018 Aug 28; 2(16): 2159–2175. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6113617/

3. UpToDate, Inc. Prevention of viral infections in hematopoietic cell transplant recipients. UpToDate [database online]. Waltham, MA. Last updated April 27, 2020. Available at: http://www.uptodate.com/home/index.html.

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed requirement of valacyclovir or ganciclovir trial given reduced efficacy and/or safety in comparison to letermovir	10/2020
Policy created	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP044

Description

Levodopa (Inbrija) is an orally inhaled metabolic precursor to dopamine used to relieve symptoms of Parkinson's disease.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
levodopa (Inbrija)	42 mg capsules	Parkinson's Disease	120 capsules/30 days*

*Maximally allowed does upon clinical review for medical necessity: 300 capsules/30 days

Initial Evaluation

I. Levodopa (Inbrija) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in consultation with, a neurologist; **AND**
   B. Not used in combination with apomorphine (Apokyn, Kynmobi); **AND**
   C. Documentation that member does **not** have a diagnosis of chronic respiratory disease (e.g. COPD, asthma, etc.); **AND**
   D. A diagnosis of **Parkinson's Disease (PD)** when the following are met:
      1. Documentation that the member has moderate to severe Parkinson's disease symptoms; **AND**
      2. Is currently on an oral levodopa regimen at least 3 times a day for a minimum of 2 weeks prior to starting levodopa (Inbrija); **AND**
      3. Documentation that the member has a decrease in wearing off symptoms in response to the member's usual morning dose of levodopa; **AND**
      4. Prescriber attest that member will be using levodopa (Inbrija) in combination with carbidopa/levodopa; **AND**
      5. The quantity requested is 120 capsules per 30 days; **OR**
         i. Documentation of medical necessity for dose escalation; **AND**
         ii. Attestation that the member has been taught how to prepare and use the inhaler system appropriately; **AND**
         iii. Attestation that the member is able to administer the full dose of levodopa (Inbrija); **AND**
      6. Treatment with the following has been ineffective, contraindicated or not tolerated:
         i. Carbidopa/levodopa IR up to five times a day OR carbidopa/levodopa XR; **AND**

ii. ONE of the following:
   a. Dopamine agonist (e.g. pramipexole, ropinirole, rotigotine)
   b. monoamine oxide –B (MAO-B) inhibitor (e.g. selegiline, rasagiline, safinamide)
   c. Catechol-O-methyl transferase (COMT) inhibitors (e.g. entacapone, tolcapone).

II. Levodopa (Inbrija) is considered investigational when used for all other conditions, including but not limited to:
   A. Mild Parkinson's disease symptoms
   B. Parkinson's disease WITHOUT documentation of motor fluctuations, "wearing off" phenomenon

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescriber attests that member will be using levodopa (Inbrija) in combination with carbidopa/levodopa ; **AND**
IV. Documentation that member has a reduction in wearing off period from baseline

Supporting Evidence

I. Moderate to severe Parkinson's disease symptoms were defined in the pivotal SPAM^{SM}-PD trial as a modified Hoehn and Yahr (H&Y) rating 22 of stages 1-3 in the ON state and recognizable, predictable OFF episodes totaling ≥2 hours per day (excluding early-morning OFF time).
II. A UPDRS Part III score of ≥ 25% after the patient's usual morning dose of levodopa reflects that the patient's wearing off motor symptoms are responsive to levodopa treatment.
III. Patients who were taking apomorphine (Apokyn) were excluded from the SPAM^{SM}-PD trial
IV. Due to the safety concerns, patients with chronic respiratory disease are excluded from the SPAM^{SM}-PD trial.
V. Levodopa (Inbrija) has only been shown to be effective in combination with carbidopa/levodopa.
VI. According to the American Family Physician diagnosis and treatment guideline for Parkinson's disease, the treatment algorithm for motor complication is:
   - Fractionate carbidopa/levodopa therapy five times a day and consider adding a dopamine agonist, MAO-B inhibitor, OR COMT inhibitor.
VII. Levodopa (Inbrija) has not been studied in patients with mild Parkinson's disease or Parkinson 's disease without motor fluctuations; therefore, it would be considered investigational when Inbrija is requested in those settings.

References

1. Inbrija [Prescribing Information]. Acorda Therapeutics: Ardsley, NY. December 2018.
2. LeWitt P, Hauser RA, Pahwa R, et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Neurol. 2019 Feb;18(2):145-154. doi: 10.1016/S1474-4422(18)30405-8.
3. UpToDate, Inc. Motor fluctuations and dyskinesia in Parkinson disease. UpToDate [Online Database]. Waltham, MA. Last updated July 12, 2018. Available from: http://uptodate.com/home/index.html. Accessed February 11, 2019.
4. Rao S., M.D., Hofmann L., M.D., and Shakil A., M.D. Parkinson's Disease: Diagnosis and Treatment. University of Texas Southwestern Medical School at Dallas Family Medicine Residency Program, Dallas, Texas. Am Fam Physician. 2006 Dec 15;74(12):2046-2054.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated formatting of QL table, improved clarity of policy requirement around previous agents trialed, added renewal requirement of continuing carbidopa/levodopa, and removed renewal requirement of 'absence of unacceptable toxicities.' Addition of new standard renewal language noting previous approvals and member is not continuing via samples.	04/2021
Policy Created	05/2019

lofexidine (Lucemyra™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP195

Description

Lofexidine (Lucemyra) is an orally administered alpha-2 adrenergic agonist.

Length of Authorization

- Initial: 14 days
- Renewal: cannot be renewed

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lofexidine (Lucemyra)	0.18 mg tablets	Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults	224 tablets/14 days

Initial Evaluation

I. Lofexidine (Lucemyra) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Member will NOT be transitioned to buprenorphine or methadone; **AND**
   C. Member will initiate therapy with naltrexone (Vivitrol) **prior** to lofexidine (Lucemyra) course completion; **AND**
   D. Total duration of therapy will not exceed 14 days; **AND**
   E. A diagnosis of **treatment for opioid use disorder needing withdrawal from opioid use** when the following are met:
      1. History of use with clonidine; **AND**
      2. History of use with tizanidine; **OR**
      3. Documentation of clinical rationale for why tizanidine AND clonidine is not medically appropriate

II. Lofexidine (Lucemyra) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Treatment transition to buprenorphine or methadone
   B. Treatment duration longer than 14 days

III. Lofexidine (Lucemyra) is considered investigational when used for all other conditions, including but not limited to:
   A. Use for marijuana dependence
   B. Use for heroin dependence

C. Acute opioid withdrawal symptoms

Supporting Evidence

I. A retrospective clinical review by Gregory and colleagues reviewed the use of a three-drug regimen including tizanidine, gabapentin, and hydroxyzine for the mitigation of withdrawal symptoms in 84 patients. Primary outcomes were completion of a medically supervised withdrawal and initiation of injectable extended release (ER) naltrexone treatment. Results showed that 94% of patients completed the medically supervised withdrawal phase, and 89% successfully transitioned to ER naltrexone.

II. Use of lofexidine (Lucemyra), in combination with an opioid agonist or partial agonist, for the treatment of opioid withdrawal symptoms increases the risk of QT interval and/or reduces the efficacy of either therapy. Combination use is considered not medically necessary.

Investigational or Not Medically Necessary Uses

I. Lofexidine (Lucemyra) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Use for marijuana dependence
   B. Use for heroin dependence
   C. Acute opioid withdrawal symptoms

References

1. Lucemyra [Prescribing Information]. Louisville, KY: US WorldMeds, LLC. November 2019.
2. Gregory Rudolf, Jim Walsh, Abigail Plawman, Paul Gianutsos, William Alto, Lloyd Mancl & Vania Rudolf (2018) A novel non-opioid protocol for medically supervised opioid withdrawal and transition to antagonist treatment, The American Journal of Drug and Alcohol Abuse, 44:3, 302-309.

Policy Implementation/Update:

Action and Summary of Changes	Date
Transitioned to policy format	10/2020
Previous Reviews	07/2018

lomitapide (Juxtapid®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP131

Description

Lomitapide (Juxtapid) is a microsomal triglyceride transfer protein inhibitor used to reduce low density lipoprotein-cholesterol (LDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lomitapide (Juxtapid)	5 mg capsules	Homozygous familial hypercholesterolemia (HoFH)	30 capsules /30 days
	10 mg capsules		
	20 mg capsules		
	30 mg capsules		
	40 mg capsules		
	60 mg capsules		

Initial Evaluation

I. Lomitapide (Juxtapid) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist, endocrinologist or lipid specialist; **AND**
   C. Member has a diagnosis of **homozygous familial hypercholesterolemia (HoFH)** as confirmed by one of the following:
      1. Genetic confirmation of two mutant alleles at the LDLR, Apo-B, PCSK9, or ARH adaptor protein 1/LDLRAP1 gene locus; **OR**
      2. Untreated LDL-C >500 mg/dL; **OR**
      3. **T**reated LDL-C ≥ 300 mg/dL with <u>one</u> of the following:
         i. Cutaneous or tendon xanthoma before ten years of age; **OR**
         ii. History of heterozygous familial hypercholesterolemia (HeFH) in both parents; **AND**
   D. Member will be on concurrent treatment with a high dose statin **<u>plus</u>** another lipid lowering therapy (e.g. ezetimibe, fibrate, nicotinic acid, LDL-apheresis) unless all are contraindicated, or not tolerated; **AND**
   E. Treatment with a PCSK-9 inhibitor [e.g. alirocumab (Praluent), evolocumab (Repatha)] has been ineffective, contraindicated, or not tolerated; **AND**

II. Lomitapide (Juxtapid) is considered investigational when used in combination with a PCSK9 inhibitor, and for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Absence of unacceptable toxicity from the medication. Examples of unacceptable toxicity may include, but are not limited to: elevations in transaminases (i.e. ALT, AST), hepatic steatosis with or without concomitant increases in transaminases; **AND**
IV. Member continues to receive other lipid-lowering therapy (e.g. statin, ezetimibe); **AND**
V. Clinical documentation (e.g. chart notes, laboratory values) confirming reduction of LDL-C while on therapy; **AND**
VI. Medication will not be used in combination with a PCSK9 inhibitor

Supporting Evidence

I. Lomitapide (Juxtapid) is indicated for the treatment of HoFH, a genetic disease marked by very high LDL-C levels.
II. The diagnosis of HoFH is made with genetic testing or clinical criteria.
    - A causative mutation in the LDLR, APOB, or PCSK9 gene(s) confirms a HoFH diagnosis.
    - Criteria for a clinical diagnosis according, to the Simon Broome Register Group, include untreated LDL-C >500 mg/dL, treated LDL-C ≥300 mg/dL, cutaneous or tendon xanthoma before age 10 years, or elevated LDL-C levels consistent with heterozygous FH in both parents.
III. All patients in the pivotal clinical trial for lomitapide (Juxtapid) met diagnostic criteria for HoFH based either on clinical criteria or on documented mutation(s) in both alleles of the LDL receptor or of genes known to affect LDL receptor function.
IV. The safety and efficacy of lomitapide (Juxtapid) for HoFH was evaluated in an open-label, Phase 3, non-randomized, dose-escalating study. The study included 29 adult patients with HoFH where the majority of patients received concurrent high-dose statin and more than half underwent regular apheresis. After 26 weeks of treatment the LDL-C was reduced by about 50% from baseline (336 to 166 mg/dL).
V. The safety and efficacy of lomitapide (Juxtapid) has not been established in pediatric patients.
VI. The effect of lomitapide (Juxtapid) on cardiovascular morbidity and mortality has not been determined.
VII. Due to the risk of hepatotoxicity, lomitapide (Juxtapid) has a REMS program to ensure safe and appropriate use, thereby limiting distribution to only certified healthcare providers and pharmacies. The requirements of the program include: limiting use to patients with a clinical or laboratory diagnosis of HoFH, excluding pregnancy and those with significant hepatic impairment (Child-Pugh B or C). Additional, elements of the program emphasize close

monitoring of hepatic function and patient education regarding a low-fat diet. Further information is available at www.JUXTAPIDREMSProgram.com.

VIII. Besides lomitapide (Juxtapid), other treatment options for HoFH include evolocumab (Repatha), LDL-apheresis, and standard lipid-lowering agents (e.g. statins, ezetimibe); however, treatment with these agents should be an adjunct to diet and exercise.

Investigational or Not Medically Necessary Uses

I. The benefit of lomitapide (Juxtapid) for indications outside of HoFH have not been established and may not outweigh the rare, but serious adverse events. The FDA approved labeling for lomitapide (Juxtapid) specifically states that it should not be used in patients with hypercholesterolemia who do not have HoFH due to the lack of safety and efficacy outside of this setting.

II. The safety and efficacy of these agents have not been established in combination with PCSK9 inhibitors.

References

1. Juxtapid [Prescribing Information]. Cambridge, MA: Aegerion Pharmaceuticals; August 2017
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3. FDA Approved Risk Evaluation and Mitigation Strategies (REMS): lomitapide (Juxtapid). From: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=IndvRemsDetails.page&REMS=25
4. Rosenson, RS. Familial hypercholesterolemia in adults: Overview. In; UpToDate. Saperia, GM (Ed), UpToDate, Waltham, MA, 2019
5. Rosenson, RS. Treatment of drug-resistant hypercholesterolemia. In: UpToDate, Saperia, GM (Ed), UpToDate, Waltham, MA, 2019

Policy Implementation/Update:

Date Created	May 2013
Date Effective	May 2013
Last Updated	December 2019
Last Reviewed	11/2015, 12/2019

Action and Summary of Changes	Date
• Transitioned to policy format • Removed mipomersen (Kynamro) from policy due to discontinuation status as of 5/31/2018 • Added requirement for specialty prescriber • Added minimum age requirement • Added details regarding confirmation of a diagnosis of HoFH • Clarified that use must be concurrent with standard lipid-lowering agents • Indicated that combination of lomitapide (Juxtapid) with PCSK9 inhibitors or use for hypercholesterolemia without HoFH is considered investigational	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP227

Description

Lonafarnib (Zokinvy) is a farnesyltransferase inhibitor.

Length of Authorization

- Initial: Four months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lonafarnib (Zokinvy)	50 mg capsules	Hutchinson-Gilford Progeria Syndrome (HGPS); processing-deficient Progeroid Laminopathies (PL)	**Initial:** Maximum 230mg/m^2/day **Renewal:** Maximum 300mg/m^2/day
	75 mg capsules		

Initial Evaluation

I. Lonafarnib (Zokinvy) may be considered medically necessary when the following criteria are met:
   A. Member is one year of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pediatrician or specialist in progeroid syndromes, genetics, or metabolic disorders; **AND**
   C. Documentation of members body surface area (BSA); **AND**
   D. Member has a BSA of 0.39m^2 or greater; **AND**
   E. Provider attestation the member's cardiovascular status will be monitored [e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography]; **AND**
   F. A diagnosis of one of the following:
      1. **Hutchinson-Gilford Progeria Syndrome (HGPS); AND**
         i. Member has genetic test confirmation of a lamin A gene mutation; **OR**
      2. **Processing-deficient Progeroid Laminopathies (PL); AND**
         i. Member has genetic test confirmation of:
            a. Heterozygous LMNA mutation with progerin-like protein accumulation; **OR**
            b. Homozygous or compound heterozygous ZMPSTE24 mutations.

II. Lonafarnib (Zokinvy) is considered <u>experimental and investigational</u> when criteria above are not met and/or when used for:

A. Processing-proficient Progeroid Laminopathies
B. Other than above mentioned Progeroid Syndromes
   i. Wiedemann-Rautenstrauch syndrome
   ii. Werner syndrome
   iii. Bloom syndrome
   iv. Rothmund-Thomson syndrome
   v. Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy
   vi. Fanconi anaemia
   vii. Seckel syndrome
   viii. Ataxia telangiectasia
   ix. Dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, a pediatrician or specialist in progeroid syndromes, genetics or metabolic disorders; **AND**
IV. Documentation of members body surface area (BSA) measured in the past three months; **AND**
V. Provider attests the member has exhibited improvement or stability of disease symptoms [e.g., cardiovascular status (e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography), bone mineral density].

Supporting Evidence

I. The safety and efficacy of lonafarnib (Zokinvy) has not been studied in pediatric patients less than 12 months of age. The activity of cytochrome P450 (CYP)3A4 and CYP3A5 is low in newborns, approximately 5% to 15% of that of an adult and only achieves full activity at six months of age. Considering these enzymes play a key role in the metabolism of lonafarnib (Zokinvy), it is expected that the clearance would be reduced and there is an increased risk of commonly observed treatment emergent adverse events (TEAEs).
II. The safety and efficacy of lonafarnib (Zokinvy) has only been studied in patients with the body surface area (BSA) ranging from 0.38 m^2 to 0.75 m^2. Due to the lack of clinical trial data on safety and efficacy, and unknown dosage strength, it is not indicated in patients with the BSA less than 0.39m^2.
III. Hutchinson-Gilford Progeria Syndrome (HPS) and processing-deficient PLs are rare and fatal genetic diseases. Considering the complexity of the disease state it is necessary for lonafarnib (Zokinvy) to be prescribed by or in consultation with a specialist in progeroid syndromes, genetics, or metabolic disorders.
IV. Patients with HGPS and processing-deficient PLs experience hypertension, strokes, angina, enlarged heart, and heart failure. Progressive atherosclerosis is common, generally leading to

death from myocardial infarction or stroke at the age of approximately 15 years. It is crucial to monitor the cardiovascular status [e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography]. In a study that sought to better understand cardiovascular disease associated with HGPS, elevated PWVcf, increased intima-media and adventitia echodensity, abnormal ABI, and increased ICA mean flow velocity were identified as pervasive disease features in HGPS. Researchers noted that non-invasive measures including PWVcf, carotid wall echodensity and ICA flow velocity offer quantitative insights into accelerated vasculopathy with HGPS and may therefore, provide indicators of disease progression or remission with therapies.

V. The safety and efficacy of lonafarnib (Zokinvy) have been studied in a observational cohort survival study, which retrospectively compared survival data from two, open-label, single-arm, Phase 2 trials (Study 1 and Study 2) in 62 patients to those from a natural history cohort in 62 patients with HGPS.
    - The primary efficacy outcome was all-cause mortality. Among the 62 patients in the treatment group four died (6.3%) and among the 62 patients in the matched untreated group 17 died (27%). None of these deaths were considered by investigators to be treatment related.
    - Through the first three years of follow up, the mean lifespan of HGPS patients treated with lonafarnib increased by three months, and increased by two and a half years through the last follow-up time (11 years) compared to untreated patients.
    - Study 1 included 28 patients (26 with classic HGPS, one with non-classic HGPS, and one with processing-deficient PL with an LMNA heterozygous mutation). Treatment was initiated with 115mg/m^2 twice daily and after four months of treatment patients who were tolerating treatment had a dose increase to 150 mg/m^2 twice daily.
        - The primary efficacy endpoint of the achievement of at least a 50% increase in the annual rate of weight gain over the rate documented at study entry by the study team, was met by eleven of 28 patients (39.3%).
        - The secondary outcome was change in carotid artery ultrasonography and corrected PWVcf. Echodensity of the carotid artery intima media (10th and 50th percentile), adventitia deep near wall (10th and 50th percentile), and adventitia luminal near wall (50th percentile) all decreased statistically significantly from baseline to end of therapy (all $p<0.05$). PWVcf improved with a median percent decrease from baseline of 15.3% (range: -43.6%, 34.1%; $p=0.0028$).
    - Study 2 consisted of two phases. In the first phase patients received lonafarnib (Zokinvy) in conjunction with zoledronic acid and pravastatin for five years. In the second phase patients received lonafarnib (Zokinvy) at a dose of 150mg/m^2 twice daily for three years.
        - The study enrolled 26 patients from Study 1 and 13 treatment naïve patients.
        - The primary efficacy endpoint of weight gain (at least 10% increase in the annual rate) or echodensity was met by 22 (71%) of patients.
    - The most common adverse reactions (≥25%) in the clinical trials were vomiting, diarrhea, infection, nausea, decreased appetite, fatigue, upper respiratory tract infection, abdominal pain, musculoskeletal pain, electrolyte abnormalities, decreased weight, headache, myelosuppression, increased aspartate aminotransferase, decreased blood bicarbonate, cough, hypertension, and increased alanine aminotransferase

VI. Progeroid laminopathies (PLs) are due to various mutations either in the LMNA gene and/or the ZMPSTE24 gene. The processing-deficient PLs are specifically due to heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations. These conditions are more rare than HGPS, and were underrepresented in the clinical trials.

Investigational or Not Medically Necessary Uses

I. Lonafarnib (Zokinvy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Progeroid syndromes (Wiedemann-Rautenstrauch syndrome, Werner syndrome, Bloom syndrome, Rothmund-Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy, Fanconi anaemia, Seckel syndrome, Ataxia telangiectasia, Dyskeratosis congenita and Hoyeraal-Hreidarsson syndrome) are a group of very rare genetic disorders that are characterized by clinical features that mimic physiological ageing, such as hair loss, short stature, skin tightness, cardiovascular diseases and osteoporosis. But considering the mechanism of action, lonafarnib (Zokinvy) would not be effective in these populations.
   B. Processing-proficient Progeroid Laminopathies – considering the pathophysiology of the disease state and the mechanism of action, lonafarnib (Zokinvy) would not be effective in these populations.

References

1. Zokinvy [Prescribing Information]. Eiger BioPharmaceuticals: Palo Alto, CA. November 2020.
2. Leslie B Gordon, MD, PhD, et.al. Hutchinson-Gilford Progeria Syndrome. GeneReviews. 2003.
3. Gordon LB, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci U S A. 2012;109(41):16666-16671. doi:10.1073/pnas.1202529109
4. Gordon LB, et al. Clinical Trial of the Protein Farnesylation Inhibitors Lonafarnib, Pravastatin, and Zoledronic Acid in Children With Hutchinson-Gilford Progeria Syndrome. Circulation. 2016;134(2):114-125. doi:10.1161/CIRCULATIONAHA.116.022188
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP219

Split Fill Management*

Description

Mannitol (Bronchitol) is an orally administered sugar alcohol inhalation powder.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
mannitol (Bronchitol)	40 mg capsules	Cystic Fibrosis	560 capsules/28 days

Initial Evaluation

I. **Mannitol (Bronchitol)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   C. A diagnosis of **Cystic Fibrosis** when the following are met:
      1. Provider attestation member has passed mannitol (Bronchitol) tolerance test; **AND**
      2. Treatment with hypertonic saline has been ineffective, contraindicated, or not tolerated

II. Mannitol (Bronchitol) is considered investigational when used for all other conditions, including but not limited to:
   A. Bronchiectasis
   B. Parkinson's Disease
   C. Chronic Obstructive Pulmonary Disease (COPD)

Renewal Evaluation

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

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

III. Member has exhibited improvement or stability of disease symptoms [e.g., improvement in FEV1, decrease in pulmonary exacerbations, decrease in hospitalization rate, improved quality of life].

Supporting Evidence

I. FDA approval for mannitol (Bronchitol) is based on three international, Phase 3, randomized, double blind, 26-week trials [CF301 (n=324), CF302 (n=318), CF303 (n=423)] which evaluated mannitol (Bronchitol) compared to subtherapeutic mannitol (control) in CF.
   - CF301 and CF302 included patients six years of age and older.
   - CF303 included adult patients only.

II. Trials CF301 and CF303 met their primary outcome of a change in FEV1 over 26 weeks. However, none of the trials met statistically significant differences in pulmonary exacerbation rates nor in quality of life improvements.
   - CF301 Treatment difference: 92.9 mL (95% CI: Not Reported; P <0.001)
   - CF303 Treatment difference: 54 mL (95% CI: 8-100; P= 0.02)

III. Patients in the three clinical trials were able to continue use of dornase alfa (Pulmozyme); however, use of hypertonic saline was not permitted. To date, no studies have been conducted using mannitol (Bronchitol) concomitantly with hypertonic saline and there are no head-to-head trials comparing the two therapies. Safety and efficacy of concomitant use of mannitol (Bronchitol) and hypertonic saline has not been established.

IV. Although mannitol (Bronchitol) was evaluated in two trials that included pediatric patients (CF301 and CF302), safety and efficacy in this population remains uncertain. The manufacturer submitted data from pediatric trials CF301 and CF302 to the FDA in 2012 seeking approval in patients six years of age and older. The FDA issued a complete response letter due to inadequate efficacy as trial CF302 did not meet its primary endpoint, coupled with an increased risk of hemoptysis, especially in the pediatric population. The FDA then recommended a third study be completed to show efficacy evidence in adult patients and confirm an acceptable safety profile. Additionally, per the package insert, mannitol (Bronchitol) is not indicated for use in children and adolescents. The safety and effectiveness of mannitol (Bronchitol) has not been established in pediatric patients for cystic fibrosis. Patients aged six to 17 years were included in two 26-week, double-blind clinical trials (Trials CF301 and CF302). In these trials, 154 patients under 18 years of age received mannitol (Bronchitol) and 105 patients received control (50 mg inhaled mannitol). Hemoptysis was reported in 12 of 154 (7.8%) patients who received mannitol (Bronchitol) and in 2 of 105 (1.9%) patients who received control.

V. Guidelines recommend chronic use of hypertonic saline in CF patients regardless of lung disease severity (*Grade B, moderate recommendation*). Dornase alfa (Pulmozyme) is also recommended as maintenance therapy for all levels of lung disease severity (*Grade B, moderate recommendation*), with a strong recommendation (*Grade A)* in those with moderate to severe disease. Guidelines have not been updated to include mannitol (Bronchitol) in the treatment CF.

VI. Given current guideline recommendations for use of hypertonic saline to improve lung function and quality of life and reduce exacerbations, coupled with lack of head-to-head trials comparing mannitol (Bronchitol) to hypertonic saline and lack of statistically significant differences in pulmonary exacerbation rates nor in quality of life improvements with mannitol (Bronchitol) use

in CF301, CF302, or CF303 studies, use of hypertonic saline prior to mannitol (Bronchitol) is required.

Investigational or Not Medically Necessary Uses

I. Mannitol (Bronchitol) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Bronchiectasis
      i. A Phase 3 trial (NCT00669331) evaluating mannitol (Bronchitol) to control (50 mg mannitol) found use of mannitol (Bronchitol) in patients with clinically significant bronchiectasis did not significantly reduce exacerbation rates. Further evaluation is needed to confirm use of mannitol (Bronchitol) in this population.
   B. Parkinson's Disease
      i. As of December 2020, trials are currently recruiting in this setting.
   C. COPD
      i. Clinical trials evaluating mannitol (Bronchitol) in COPD were withdrawn due to recruitment failures.

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

References

1. Bronchitol [Prescribing Information]. Chiesi USA, Inc.: Cary, NC. October 2020.
2. Bilton D, Robinson P, Cooper P, et al. Inhaled dry powder mannitol in cystic fibrosis: an efficacy and safety study. Eur Respir J. 2011;38(5):1071-1080.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2021

Policy Type: PA Pharmacy Coverage Policy: UMP232

Description

Mecamylamine (Vecamyl) is an orally administered sympathetic ganglionic blocker, which blocks cholinergic stimuli at nicotinic receptors leading to blood vessels dilation and reduction in blood pressure.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Mecamylamine (Vecamyl)	2.5 mg tablet	Moderately severe to severe hypertension	300 tablets/30 days
		Uncomplicated malignant hypertension	

Initial Evaluation

I. Mecamylamine (Vecamyl) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist; **AND**
   C. A diagnosis of **Moderately severe to severe hypertension OR Uncomplicated malignant hypertension** when the following are met:
      1. Treatment with at least one agent from FIVE of the following classes of antihypertensive agents has been ineffective or not tolerated (Note, if a class of agents is contraindicated, a trial and failure of at least five agents or combinations thereof from the remaining groups is required):
         i. Thiazide diuretics (e.g. hydrochlorothiazide)
         ii. Angiotensin-converting enzyme inhibitors (e.g. lisinopril, captopril, benazepril)
         iii. Angiotensin II receptor antagonists (e.g. losartan, valsartan)
         iv. Beta blockers (e.g. metoprolol)
         v. Calcium channel blockers (e.g. amlodipine, diltiazem)
         vi. Direct renin inhibitors (e.g. aliskiren)
         vii. Other (e.g. clonidine, hydralazine, doxazosin) **AND**

2. Treatment with at least one parenteral antihypertensive agent (e.g. IV nitroprusside, nicardipine, clevidipine, labetalol) has been ineffective, contraindicated, or not tolerated.

II. Mecamylamine (Vecamyl) is considered investigational when used for all other conditions, including but not limited to:
   A. Major depressive disorder (MDD)
   B. Giles de la Tourette's syndrome
   C. Hyperreflexia
   D. Nicotine dependence

Renewal Evaluation

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

Supporting Evidence

I. Mecamylamine (Vecamyl) is a nicotinic parasympathetic ganglionic blocker, which prevents stimulation of postsynaptic receptors by acetylcholine released from presynaptic nerve endings. The hypotensive effect of mecamylamine (Vecamyl) is attributed to reduction in sympathetic tone, vasodilation, and reduced cardiac output. It is considered a nonselective antagonist that easily passes through the blood-brain barrier, and thus, having the potential to affect nicotinic acetylcholine receptors in the central nervous system.
II. Mecamylamine (Vecamyl) is FDA approved for use in patients 18 years of age and older. Efficacy and safety of this drug are not established in the pediatric population.
III. Mecamylamine (Vecamyl) should be given with great discretion, if at all, when renal insufficiency is manifested by a rising or elevated BUN. The drug is contraindicated in uremia. Patients receiving antibiotics and sulfonamides should generally not be treated with ganglion blockers. Other contraindications are glaucoma, organic pyloric stenosis, or hypersensitivity to the product.
IV. The package insert for mecamylamine (Vecamyl) does not include any clinical trials as it was approved using an abbreviated new drug application (ANDA) of the innovator product, mecamylamine (Inversine). Approved on March 1, 1956, Inversine was available prior to the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, which led to inclusion of Inversine as an approved DESI drug; however, the distribution of Inversine was discontinued in 2009.

V. An observational clinical study (N=17) in 1957 examined the effects of mecamylamine monotherapy for blood pressure reduction from baseline (>150/100 mm Hg). Each patient was initiated on mecamylamine 2.5mg twice daily before undergoing a set dose titration. Treatment response was defined as a decrease in mean blood pressure by at least 20 mm Hg or a reduction of blood pressure to the normotensive level (defined by the investigators as less than 150/100 mm Hg). Response rate to mecamylamine was reported to be 52% at average 34 mg/day dose, while the other half of subject population (non-responders) had no blood pressure reductions despite doubling the average dose.

VI. Mecamylamine (Vecamyl) is not an acceptable alternative agent to consider for supplemental use after first-line antihypertensive agents have failed to provide adequate response. More predictably effective agents with proven effects on morbidity and mortality and with safer side effect profiles have replaced mecamylamine for use in both essential and accelerated hypertension.

VII. It should be noted that parenteral antihypertensives (e.g. IV nitroprusside, nicardipine, clevipine, labetalol etc.) are most often used in the initial treatment of malignant hypertension due to their faster onset of action. Trial of a parenteral antihypertensive agent is warranted before consideration of mecamylamine (Vecamyl) as the next therapeutic agent.

VIII. The Clinical Practice Guidelines from the American College of Cardiology/American Heart Association Task Force (2017) do not include ganglionic blockers (e.g. mecamylamine (Vecamyl)) as a recommended primary or secondary treatment option. The Evidence-Based Guideline for the Management of High Blood Pressure in Adults from the panel members of the eighth joint national committee (2014) advise selection among four specific medication classes (thiazide type diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers) as initial treatment and inclusion of other classes (e.g. beta blockers, direct renin inhibitors, alpha1 blockers, centrally acting drugs and direct vasodialator) as secondary choices in treatment.

Investigational or Not Medically Necessary Uses

I. Major depressive disorder (MDD)
   A. The principal focus of research on mecamylamine largely involves its potent blockade of nicotinic receptors in central nervous system at doses that do not have a significant effect on parasympathetic function (2.5-10 mg/day). Recently mecamylamine was studied via two short-term, phase III clinical trials, as an add-on treatment to existing antidepressant agents. These trials did not show significant difference in treatment groups compared to a placebo.

II. Giles de la Tourette's syndrome and Hyperreflexia
   A. Use of mecamylamine for the treatment of Giles de la Tourette's syndrome and hyperreflexia has been studied in retrospective case studies and the quality of evidence in these settings is considered low.

III. Nicotine dependence
   A. A randomized, double-blind, placebo controlled clinical trial (N=48) assessed efficacy of mecamylamine in combination with transdermal nicotine patches as compared to placebo in combination with nicotine patch. Although this study reported greater abstinence rates

in treatment group at week 7 (50% versus 16%), the trial was not adequately powered to analyze effect size and the primary outcome assessment was based on patient self-reporting. Additionally, all subjects received transdermal nicotine, which confounded the outcomes assessment. Mecamylamine has not been FDA-approved in this setting.

References

1. Vecamyl [Prescribing Information]. Fort Collins, CO: Manchester Pharmaceuticals; July 2015.
2. Shytle RD, Penny, E, et. al. Mecamylamine (Inversine): an old antihypertensive with new research directions. Journal of Human Hypertension. 2002; (16): 453-457.
3. The Death of TC-5214. Kefauver-Harris Amendments Revolutionized Drug Development. Updated on October 10, 2012. Available at http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856.
4. Moyer, John; Heider, Charles; Dennis, Edward. Mecamylamine (Inversine) in the treatment of hypertension. JAMA. 1957;164(17):1879-1886.
5. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. JACC,. 2018; 71, e127-248.

Policy Implementation/Update:

Action and Summary of Changes	Date
Transition of old criteria document to the policy format; added requirement of drug being prescribed by a specialist; removed criteria for validation of contraindications before treatment start; added E/I uses; added supporting evidence	05/2021
Criteria created	09/2013

Policy Type: PA/SP Pharmacy Coverage Policy: UMP133

Description

Mecasermin (Increlex) is an injection that is indicated for the treatment of growth failure in children with severe primary insulin-like growth factor (IGF-1) deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
mecasermin (Increlex)	40 mg/4 mL multiple dose vial	Severe primary insulin-like growth factor (IGF-1) deficiency; Growth hormone (GH) gene deletion with neutralizing antibodies to GH	7.2 mg/kg/30 days

Initial Evaluation

I. Mecasermin (Increlex) may be considered medically necessary when the following criteria below are met:
   A. Member is a between 2-18 years of age; **AND**
   B. Medication is prescribed by, or in consultation with, a pediatric endocrinologist or a pediatric nephrologist; **AND**
   C. Member has evidence of non-closure of the epiphyseal plate confirmed by radiograph; **AND**
   D. A diagnosis of one of the following:
      1. **Severe primary insulin-like growth factor (IGF-1) deficiency**
         i. Member meets <u>ALL</u> of the following:
            a. Height standard deviation score ≤ -3.0; **AND**
            b. Basal IGF-1 standard deviation score ≤ -3.0; **AND**
            c. Normal or elevated growth hormone (GH) level, [serum growth hormone level of ≥ 10 ngm/mL to at least two stimuli (insulin, levodopa, arginine, clonidine, or glucagon)]; **OR**
      2. **Growth hormone (GH) gene deletion**
         i. Member has developed neutralizing antibodies to GH; **AND**
         ii. Member has normal thyroid function (TSH in the range of 0.5-6 uIU/mL); **AND**

iii. Member is not malnourished (BMI < 18 kg/m^2); **AND**
iv. Member does not have active or suspected neoplasia (e.g. cancer)

II. Mecasermin (Increlex) is considered investigational when used for all other conditions, including but not limited to:
   A. Secondary forms of IGF-1 deficiency such as:
      1. GH deficiency
      2. Malnutrition
      3. Hypothyroidism
      4. Chronic treatment with pharmacologic doses of anti-inflammatory steroids

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
II. Member has shown a response in the first 6 months of the IGF-1 therapy (e.g. increase in height, increase in height velocity); **AND**
III. Member has evidence of non-closure of the epiphyseal plate, confirmed by radiograph

Supporting Evidence

I. Mecasermin (Increlex) is for the long-term treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency (primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Severe primary IGFD is defined by:
   - Height standard deviation score ≤ -3.0
   - Basal IGF-1 standard deviation score ≤ -3.0
   - Normal or elevated GH
II. Insulin-like growth factor (IGF-1) is the principal hormonal mediator of statural growth. Under normal circumstances, growth hormone (GH) binds to its receptor in the liver and other tissues, and stimulates the synthesis/secretion of IGF-1.
   - In target tissues, the type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signaling, which stimulates multiple processes leading to statural growth.
   - The metabolic actions of IGF-1 are, in part, directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues.
III. Severe primary IGF-1 deficiency includes members with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient; therefore, they cannot be expected to respond adequately to exogenous GH treatment.
IV. Mecasermin (Increlex) is not a substitute to growth hormone (GH) for approved GH indication.
V. Mecasermin (Increlex) is not indicated for use after epiphyseal closure.

Investigational Use

I. Mecasermin (Increlex) is not intended for use in members with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

References

1. Increlex [package insert].Cambridge, MA: Ipsen Biopharmaceuticals, Inc;2019.
2. UpToDate, Inc. Growth hormone insensitivity syndromes. UpToDate [database online]. Waltham, MA. Updated March 8, 2019. Available at: http://www.uptodate.com/home/index.html. Accessed November 9, 2019.

Policy Implementation/Update:

Date Created	September 2008
Date Effective	October 2008
Last Updated	November 2019
Last Reviewed	12/2008, 11/2019

Action and Summary of Changes	Date
Criteria updated to new policy format. Specific changes include: removal of bone age requirement (If male, bone age is less than 16 years of age; or if female, bone age is less than 14 years of age) and update on child 2 years of age or older.	11/2019

mechlorethamine (Valchlor®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP134

Description

Mechlorethamine (Valchlor) is a topical nitrogen analog of sulfur mustard and is a biologic alkylating agent.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

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

Initial Evaluation

I. Mechlorethamine (Valchlor) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an oncologist or dermatologist; **AND**
   C. Will not be used in combination with bexarotene (Targretin); **AND**
   D. A diagnosis of **cutaneous T-cell lymphoma** when the following are met:
      1. The disease is stage IA or IB (i.e., limited, localized); **AND**
      2. The member is relapsed, refractory, or intolerant to at least one other skin-directed therapy (e.g., corticosteroids, phototherapy, imiquimod, topical retinoids, carmustine, local radiation).

II. Mechlorethamine (Valchlor) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Contact dermatitis
   B. Non-Hodgkin lymphoma
   C. Lichen planopilaris

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
IV. Member has exhibited response to therapy such as improvement in CAILS score, decrease in affected surface area, or decrease in plaque/scale elevation or severity.

Supporting Evidence

I. Mechlorethamine (Valchlor) gel was assessed in a randomized, observer-blinded, active-controlled (versus compounded mechlorethamine ointment), non-inferiority clinical trial of subjects with stage IA, IB, and II A mycosis fungoides-type cutaneous T-cell lymphoma. Subjects had received at least one prior skin-directed therapy, including the following: topical corticosteroids, phototherapy, bexarotene (Targretin) gel, topical nitrogen mustard. The median number of prior therapies was two. Mechlorethamine (Valchlor) was applied topically on a daily basis for 12 months. Subjects were evaluated for a response on a monthly basis for the first six months and then every two months for the last six months using the Composite Assessment of Index Lesion Severity (CAILS) score. This score is obtained by adding the severity score of each of the following categories for up to five index lesions: erythema, scaling, plaque elevation, and surface area. Response was defined by a 50% or greater reduction in baseline score. A complete response was defined as achieving a score of 0. Subjects were also evaluated using the Severity Weighted Assessment Tool (SWAT). The SWAT score is derived by measuring each involved area as a percentage of total body surface area (% BSA) and multiplying it by a severity weighting factor. Response was defined as a 50% or greater reduction in baseline SWAT score. Sixty percent of subjects achieved a response in CAILS score versus 48% with the comparator arm. For the SWAT score, 50% in the mechlorethamine (Valchlor) arm met criteria for response versus 46% of the comparator arm. Mechlorethamine (Valchlor) statistical non-inferiority was met.
II. The mean average daily use in the trial was 1-2 tubes per month. The cost of one tube of mechlorethamine (Valchlor) is $4,000-$5,000 per month; thus for a quantity exception to be considered, clinical review of body surface area affected, application amount, frequency, adherence, etc. is warranted.

Investigational or Not Medically Necessary Uses

I. Mechlorethamine (Valchlor) has not been sufficiently evaluated for safety and/or efficacy in the following settings:
   A. Contact dermatitis
   B. Non-Hodgkin lymphoma
   C. Lichen planopilaris

References

1. Valchlor [Prescribing Information]. Malvern, PA: Ceptaris Therapeutics, Inc. August 2013.
2. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol. 2013;149(1):25-32.

Policy Implementation/Update:

Date Created	January 2014
Date Effective	March 2014
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format. Criteria updated to allow for oncologist prescribing. Renewal criteria changed to require specialist prescriber and specified parameters for improvement.	11/2019

Policy Type: QE Pharmacy Coverage Policy: UMP233

Description

All medications covered by this policy work to induce catharsis by the osmotic effects of the unabsorbed sulfate salts and polyethylene glycol (PEG) in the GI tract. Specifically, sulfate salts provide sulfate anions, which are poorly absorbed, and PEG, which is primarily unabsorbed, causes water to be retained in the GI tract resulting in watery diarrhea.

Length of Authorization

- Initial: One time with each request*

  **Can be approved multiple times, as requested by provider, if policy is met*
- Renewal: See "Initial" Authorization

Medications Included in this Policy

Product Name	Dosage Form	Indication
All therapies with the FDA approval for use in colonoscopy preparation	Multiple	Colonoscopy preparation

Initial Evaluation

I. **Colonoscopy preparation medications** may be considered medically necessary when the following criteria are met:
   A. Medication requested is being used as bowel preparation for colorectal cancer screening

II. Colonoscopy preparation medications are <u>excluded</u> 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 (<u>non-OTC</u>) are covered at a zero-cost share for up to 2 fills per year for members between the ages of 50-75 years with a valid prescription. The purpose of this policy is to review requests exceeding 2 fills per year to ensure use in preparation for a colonoscopy before allowing payment at a zero-cost share.

References

1. United States Department of Labor. FAQ About Affordable Care Act Implementation (Part 31). April 20, 2016. Accessed via https://www.dol.gov/ebsa/faqs/faq-aca31.html on July 30, 2016.
2. Facts & Comparisons. Bowel Evacuants. Accessed via http://online.factsandcomparisons.com/MonoDisp.aspx?monoid=fandc-hcp10331&book=DFC on July 30, 2016.

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria transitioned to policy format	05/2021
Criteria created	07/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP046

Description

Mepolizumab (Nucala) is a subcutaneously administered monoclonal antibody (IgG1 Kappa) that antagonizes interleukin-5 (IL-5).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
mepolizumab (Nucala)	100 mg/mL syringe, 100 mg/mL autoinjector	Asthma (severe)	1 syringe/autoinjector/28 days
		Eosinophilic granulomatosis with polyangiitis	3 syringes/autoinjectors/28 days
		Hypereosinophilic Syndrome	3 syringes/autoinjectors/28 days

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 <u>ALL</u> of the following:

a. History or presence of asthma; **AND**

b. Blood eosinophil level 10% or an absolute eosinophil count >1000 cells/mm3; **AND**

c. TWO or more of the following:

i. Histopathologic evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration or eosinophil rich granulomatous inflammation

ii. Neuropathy

iii. Pulmonary infiltrates

iv. Sinonasal abnormalities

v. Cardiomyopathy

vi. Glomerulonephritis

vii. Alveolar hemorrhage

viii. Palpable purpura

ix. Antineutrophil Cytoplasmic Antibody (ANCA) positivity; **AND**

iii. Member must have blood eosinophils ≥150 cells/µL within 6 weeks of dosing; **AND**

iv. Member has been on stable doses of concomitant oral corticosteroid therapy for at least 4 weeks (i.e., prednisone or prednisolone at a dose of 7.5 mg/day); **AND**

v. Physician has assessed baseline disease severity utilizing an objective measure/tool (e.g., Birmingham Vasculitis Activity Score [BVAS], history

of asthma symptoms and/or exacerbations duration of remission or rate of relapses, etc.); **OR**

3. **Hypereosinophilic Syndrome (HES); AND**
   i. Member is 12 years of age or older; **AND**
   ii. Provider attests to ALL of the following:
      a. Member has been diagnosed with HES for at least 6 months prior to starting treatment; **AND**
      b. Member is confirmed to have F1P1L1-PDGFRα kinase-negative disease; **AND**
      c. Member does NOT have non-hematologic secondary HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy); **AND**
      d. Background HES therapy 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.

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

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:
   - **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**

- **Eosinophilic Granulomatosis with Polyangiitis; AND**
  i. 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**
- **Hypereosinophilic Syndrome; AND**
  i. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in HES flares, improved fatigue, reduced oral corticosteroid requirements, decreased eosinophil levels)

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 <u>severe eosinophilic asthma</u> were evaluated in 3 randomized, placebo controlled, multicenter trials of 24 to 52 weeks in duration. The <u>primary outcome</u> 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.

- <u>Trial inclusion criteria</u> required patients to have a history of 2 or more exacerbations requiring systemic corticosteroids in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without oral corticosteroids (OCS). Patients were required to have at least 1 of the following 4 prespecified criteria in the previous 12 months: blood eosinophil count ≥300 cells/mcL, sputum eosinophil

count ≥3%, exhaled nitric oxide concentration ≥50 ppb, or deterioration of asthma control after ≤25% reduction in regular maintenance ICS/OCS.

IV. The FDA approval of mepolizumab (Nucala) in the setting of eosinophilic granulomatosis with polyangiitis was evaluated in a multicenter, double-blind, parallel-group, phase 3 trial. The two primary end points were the accrued weeks of remission over a 52-week period, according to categorical quantification, and the proportion of participants in remission at both week 36 and week 48. In the mepolizumab treatment arm, there was significantly more accrued weeks of remission than placebo (28% vs. 3% of the participants had ≥24 weeks of accrued remission; odds ratio, 5.91; 95% confidence interval [CI], 2.68 to 13.03; P<0.001) and a higher percentage of participants in remission at both week 36 and week 48 (32% vs. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; P<0.001). The members that were enrolled in this trial were at least 18 years of age.

V. The FDA approval of mepolizumab (Nucala) in the setting of hypereosinophil 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 or add-on tiotropium, or add-on LTRA. Other controller options for Step 5 include add-on anti-IL5, or add-on low dose OCS, though guidelines note to consider side effects.

Investigational or Not Medically Necessary Uses

I. Mepolizumab (Nucala) has not been adequately studied for the following conditions and does not have established safety and efficacy in these populations:
    A. Non-severe, non-eosinophilic phenotype asthma

i. Mepolizumab (Nucala) has not been studied in members with non-severe, non-eosinophilic phenotype asthma; therefore, it would be considered investigational when Nucala is requested in that setting.

B. GPA (Wegener's granulomatosis) with polyangiitis and MPA (microscopic polyangiitis)
   i. Both GPA and MPA diagnoses were excluded in the phase 3 trial (A Study to Investigate Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis).

C. HES (hypereosinophilic syndrome) with F1P1L1-PDGFRα kinase-positive disease
   i. Mepolizumab (Nucala) has not been studied in members with F1P1L1-PDGFRα kinase-positive disease; therefore, it would be considered investigational when Nucala is requested in this setting.

References

1. Nucala [Prescribing Information]. Philadelphia, PA: GlaxoSmithKline LLC. Updated Sept 2020. Accessed Jan 2021.
2. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab Treatment in Members with Severe Eosinophilic Asthma. N Engl J Med 2014; 371:1198-1207. DOI: 10.1056/NEJMoa1403290.
3. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. N Engl J Med 2017; 376:1921-1932. DOI: 10.1056/NEJMoa1702079.
4. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2020 Update. Available from: http://www.ginasthma.org. Accessed January 2021.
5. Roufosse F, Kahn JE, Rothenberg ME, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2020;146(6):1397-1405. DOI: 10.1016/j.jaci.2020.08.037.

Policy Implementation/Update:

Action and Summary of Changes	Date
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 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.	03/2021
Policy updated to reflect the newly approved age expansion for SEA from members 12 years and older to 6 years or older. Also added leukotriene modifiers as an example of a controller medication per GINA guidelines. To the EGPA section, examples of an objective measure/tool were added to align with renewal criteria and changed classification criteria for eosinophils to > 10% per ACR classification.	10/2019
New Policy	06/2019

Policy Type: PA Pharmacy Coverage Policy: UMP205

Description

Metoclopramide (Gimoti) is nasally administered dopamine (D2) antagonist.

Length of Authorization

- Initial: Three months
- Renewal: Three months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
metoclopramide (Gimoti)	15 mg intranasal spray	Acute and recurrent diabetic gastroparesis	10 ml/28 days

Initial Evaluation

I. Metoclopramide (Gimoti) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is diagnosed with diabetic gastroparesis; **AND**
   C. Treatment with oral metoclopramide has been ineffective, contraindicated (e.g., member has inability to swallow), or not tolerated

II. Metoclopramide (Gimoti) is considered investigational when used for all other conditions, including but not limited to:
   A. Gastroparesis in nondiabetic patients
   B. Nausea and/or vomiting
   C. Chemotherapy-induced nausea and vomiting, prophylaxis
   D. Dyspepsia
   E. Migraine

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited initial improvement of disease symptoms [e.g., reduction in nausea, abdominal pain, bloating, or improvement in early satiety early satiety] **AND**

IV. Provider attests that member continues to have symptoms and benefit of repeated therapy outweighs the risks

Supporting Evidence

I. Per the American College of Gastroenterology, initial recommended pharmacological approaches to treatment should include prokinetic therapy with oral metoclopramide (cited as the first line agent).
II. The effectiveness of metoclopramide (Gimoti) has been established based on studies of oral metoclopramide.
III. Per FDA label, the use of metoclopramide (all dosage forms and routes of administration) for longer than 12 weeks should be avoided due to risk of developing tardive dyskinesia with long-term use.
IV. Per FDA label, metoclopramide (Gimoti) is not recommended as initial therapy in patients 65 years and older. Geriatric patients receiving an alternative metoclopramide product at a stable dosage of 10 mg four times daily can be switched to metoclopramide (Gimoti).
V. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for using metoclopramide (Gimoti) for indications other than for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis.
VI. Metoclopramide (Gimoti) was studied in three multicenter, randomized clinical trials. There is variance in the dose and outcomes studied, but clinically significant results defined by improvement in symptom severity from moderate to mild were seen in all clinical trials.
VII. Individual clinical trials of metoclopramide (Gimoti) are considered low quality due to open-label trial design, small sample sizes, and applicability concerns given underrepresentation of type 1 diabetic patients; however, the overall quality of the evidence is considered moderate at this time due to collection of data available through metoclopramide trials and metoclopramide (Gimoti) trials.
VIII. The safety profile of metoclopramide (Gimoti) is similar to that of metoclopramide tablets.

Investigational or Not Medically Necessary Uses

I. Metoclopramide (Gimoti) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Nondiabetic gastroparesis
   B. Nausea and/or vomiting
   C. Chemotherapy-induced nausea and vomiting, prophylaxis
   D. Dyspepsia
   E. Migraine

References

1. Gimoti [Prescribing Information]. Solana Beach, California: Evoke Pharma. June 2020.
2. Camilleri M, Parkman HP. Clinical Guideline: Management of Gastroparesis. Am J Gastroenterol. 2013. 108(1):18-38.
3. Bharucha, Adil E. "Epidemiology and natural history of gastroparesis." Gastroenterology clinics of North America vol. 44,1 (2015): 9-19.

4. Parkman HP, Carlson MR, Gonyer D. Metoclopramide Nasal Spray Reduces Symptoms of Gastroparesis in Women, but not Men, With Diabetes: Results of a Phase 2B Randomized Study. Clin Gastroenterol Hepatol. 2015;13(7):1256-1263.e1.
5. Parkman HP, Carlson MR, Gonyer D. Metoclopramide nasal spray is effective in symptoms of gastroparesis in diabetics compared to conventional oral tablet. Neurogastroenterol Motil. 2014;26(4):521-528. doi:10.1111/nmo.12296
6. McCallum RW, Fass R, Bhandari BR. Symptom severity influences drug efficacy in women with diabetic gastroparesis: results of a phase 3 study with metoclopramide nasal spray. Gastroenterology. 2017;152(5):S1313.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

metreleptin (Myalept®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP093

Description

Metreleptin (Myalept) is a leptin analog that binds to and activates the human leptin receptor as replacement therapy to treat generalized lipodystrophy due to congenital or acquired generalized lipodystrophy.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

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

Initial Evaluation

I. Metreleptin (Myalept) may be considered medically necessary when the following criteria below are met:
   A. Member is one year of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. A diagnosis of **Congenital Lipodystrophy OR Acquired Generalize Lipodystrophy** when the following are met:
      1. Provider attests that the fasting leptin concentration at baseline is below the normal range; **AND**
      2. Member has a diagnosis of type 2 diabetes mellitus (T2DM) or insulin resistance; **AND**
      3. Member has a persistent hemoglobin A1c (HbA1c) > 7% despite dietary intervention and medication management (e.g., metformin) for T2DM; **AND**
      4. Member has a diagnosis of hypertriglyceridemia; **AND**
      5. Member has persistent triglyceride levels > 250 mg/dL despite dietary intervention and medication management for hypertriglyceridemia (e.g., fibrates, omega-3 fatty acids); **AND**
      6. Member does not have any hematologic abnormalities (e.g., leukopenia, neutropenia, bone marrow abnormalities, lymphadenopathy).

II. Metreleptin (Myalept) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:

A. Partial lipodystrophy
B. Localized lipodystrophy
C. Liver disease (e.g., nonalcoholic steatohepatitis [NASH])
D. Human Immunodeficiency Virus (HIV) – related lipodystrophy
E. Metabolic disease (e.g., T2DM, hypertriglyceridemia)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
II. The member is not continuing therapy based off established therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for continuation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms as defined by, a reduction from baseline for **one** of the following parameters:
   A. HbA1c
   B. Fasting glucose
   C. Triglycerides; **AND**
IV. Member does not have any hematologic abnormalities (e.g., leukopenia, neutropenia, bone marrow abnormalities, lymphadenopathy).

Supporting Evidence

I. Although the guideline states that there is no age limit for initiation of metreleptin (Myalept), and there were reported case studies where children as young as six months have been treated, the actual pediatric inclusion population in the FDA approval of metreleptin (Myalept) was 1 to 17 years of age.
II. According to the guideline (The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline), there is no defined serum leptin levels that have established to rule out the diagnosis of lipodystrophy. Therefore, specific lab values may not be very informative for the diagnosis of congenital or acquired generalized lipodystrophy.
III. Members with congenital or acquired generalized lipodystrophy and T2DM, metformin is a first-line agent for diabetes and insulin resistance, along with, other considerations for antihyperglycemia agents: insulin is effective for hyperglycemia, and thiazolidinediones, which should be used with caution in generalized lipodystrophy as their efficacy has not been established in that setting.
IV. Members with congenital or acquired generalized lipodystrophy and hypertriglyceridemia, fibrates and/or long-chain omega-3 fatty acids should be used for hypertriglyceridemia.
V. As part of the metreleptin (Myalept) Risk Evaluation and Mitigation Strategy (REMS) program, provider will need to evaluate members with acquired generalized lipodystrophy for significant hematologic abnormalities due to the reported risk of T-cell lymphoma in that population.

Investigational or Not Medically Necessary Uses

I. There is limited evidence to suggest the safety and efficacy of metreleptin (Myalept) outside of the FDA-approved indications of congenital or acquired generalized lipodystrophy. Additionally, the following indications listed below were denoted to have a "limitation of use" in the metreleptin (Myalept) package insert.
   A. Partial lipodystrophy
   B. Liver disease (e.g., nonalcoholic steatohepatitis [NASH])
   C. Human Immunodeficiency Virus (HIV) – related lipodystrophy
   D. Metabolic disease (e.g., T2DM, hypertriglyceridemia)

References

1. Myalept [Prescribing Information]. Cambridge, MA: Aegerion Pharmaceuticals, Inc. August 2015.
2. Brown RJ, Araujo-Vilar D, Cheung PT, et al. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. The Journal of Clinical Endocrinology & Metabolism, Volume 101, Issue 12, 1 December 2016, Pages 4500–4511. Available at: https://doi.org/10.1210/jc.2016-2466

Policy Implementation/Update:

Date Created	September 2014
Date Effective	September 2014
Last Updated	October 2019
Last Reviewed	10/2019

Action and Summary of Changes	**Date**
Criteria transitioned into policy with the following updates: addition of supporting evidence, addition of investigational section along with supporting evidence, inserted lab values for type 2 diabetes and hypertriglyceridemia, added sample language to the renewal section, and assess for stability parameters upon renewal.	10/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP201

Description

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

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
metyrosine (generic Demser)	250 mg capsule	pheochromocytoma	480 capsules/30 days
metyrosine (Demser)			

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 <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Velocardiofacial syndrome-associated psychosis
   B. Bipolar disorder
   C. Schizophrenia
   D. Gilles de la Tourette's syndrome

E. Sarcoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member requires long-term pharmacologic treatment following surgery or has malignant pheochromocytoma; **AND**
IV. Treatment with the following has been ineffective, contraindicated, or not tolerated:
   A. A selective alpha blocker (e.g., doxazosin, terazosin or prazosin); **AND**
   B. Generic phenoxybenzamine; **AND**
V. Member has exhibited improvement or stability of disease symptoms [e.g., hypertension, diaphoresis, headache, palpitations, tachycardia, syncope, anxiety] while on therapy

Supporting Evidence

I. Pheochromocytoma is a rare neuroendocrine tumor that hypersecrete one or more catecholamines (epinephrine, norepinephrine, and dopamine) and ff left untreated, cardiovascular morbidity and mortality are high. Once diagnosed, patients should undergo surgical resection of the pheochromocytoma following appropriate medical preparation. Preop medications are used for volume expansion and to control hypertension and preventing a hypertensive crisis during surgery. Patients with undiagnosed pheochromocytomas who undergo surgery for other reasons (and therefore have not undergone preoperative medical therapy), have an increased surgical mortality rate due to lethal hypertensive crises, malignant arrhythmias, and multiorgan failure. No randomized, controlled trials have compared the different approaches, and there is no universally accepted method of preparation for surgery in patients with pheochromocytoma.
II. Guidelines recommend preoperative combined alpha and beta blockade to prevent perioperative cardiovascular complications. Both selective (e.g. phenoxybenzamine) and non-selective (e.g. doxazosin, terazosin, prazosin) alpha-blockers have been used, there is insufficient evidence to recommend one over the other. After adequate alpha blockade has been achieved, beta blockade is initiated, which typically occurs two to three days preoperatively. Metyrosine can then be considered in patients who cannot be treated with the typical combined alpha and beta blockade protocol because of intolerance or cardiopulmonary reasons. Preoperative medical treatment is recommended for 7 to 14 days to allow adequate time to normalize blood pressure and heart rate.
III. Metyrosine (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

1. Demser [package insert]. Bridgewater, NJ. Valeant Pharmaceuticals International, Inc. December 2017
2. Uptodate. Treatment of pheochromocytoma in adults. Updated 11/25/2019
3. Uptodate. Paraganglioma and pheochromocytoma: Management of malignant disease. Updated 09/12/2019
4. Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915-1942.
5. PDQ® Adult Treatment Editorial Board. PDQ Pheochromocytoma and Paraganglioma Treatment. Bethesda, MD: National Cancer Institute. Updated 10/16/2020. Available at: https://www.cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq. [PMID: 26389312]
6. Metyrosine. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: http://www.micromedexsolutions.com.
7. Carandang CG, Scholten MC. Metyrosine in psychosis associated with 22q11.2 deletion syndrome: case report. J Child Adolesc Psychopharmacol. 2007;17(1):115-120.
8. Bausch Health Americas, Inc. Metyrosine (Demser®) for the Treatment of Psychotic Disorders in Patients with Velocardiofacial Syndrome. Available from: http://www.clinicaltrials.gov/ct2/show/NCT01127503. NLM identifier: NCT01127503.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP094

Description

Midostaurin (Rydapt) is an orally administered tyrosine kinase inhibitor (TKI) targeting FLT3 and KIT D816V receptors to induce cell apoptosis.

Length of Authorization

- Initial: Six months
- Renewal:
    - i. AML: Cannot be renewed
    - ii. Systemic mast cell disease: 12 months

Quantity limits

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

Initial Evaluation

I. Midostaurin (Rydapt) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. A diagnosis of one of the following:
      1. **Acute myeloid leukemia (AML)**; **AND**
         i. The member has FLT3 mutation-positive AML; **AND**
         ii. Will be used in combination with standard cytarabine and daunorubicin induction AND cytarabine consolidate therapy; **AND**
         iii. Will not be used with any other oncolytic therapy outside of cytarabine and daunorubicin; **AND**
         iv. The member has received no prior therapy for AML; **OR**

2. **Systemic mast cell disease**; **AND**
    i. Systemic mast cell disease is characterized by one of the following: aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL); **AND**
    ii. Midostaurin (Rydapt) will not be used in combination with any other oncolytic medication.

II. Midostaurin (Rydapt) is considered investigational when used for all other conditions, including but not limited to:
    A. Pediatric leukemia
    B. Rectal cancer
    C. Acute myeloid leukemia in absence of FLT3 mutation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Midostaurin (Rydapt) is prescribed by, or in consultation with an oncologist; **AND**
    A. For **acute myeloid leukemia**:
        a. No renewal, one 6-month (initial) approval per lifetime.
    B. For **systemic mast cell disease**;
        a. Midostaurin (Rydapt) will not be used in combination with any other oncolytic medication; **AND**
        b. Clinical documentation of response to treatment, such as stabilization or improvement of disease, and absence of unacceptable toxicity from the medication.

Supporting Evidence

I. Midostaurin (Rydapt) was evaluated in three trials. Trial 1: in combination with chemotherapy in a randomized, double-blind, placebo-controlled trial in adults with FLT3-mutated AML. Subjects received 50 mg twice daily on days 8-21 for up to two cycles, followed by up to 12 months of midostaurin (Rydapt) therapy. Although evaluated for up to one year of therapy, the FDA-approval for midostaurin (Rydapt) indicates combination therapy with cytarabine and daunorubicin for two cycles of induction and four cycles of consolidation - for a complete total of six 28-day cycles. The primary outcome was overall survival (OS) which was statistically in favor of midostaurin (Rydapt) [HR 0.77; 95% CI 0.63-0.95, p=0.016]; however, OS data plateaued before reaching the median. Median survival could not be reliably estimated.
II. Midostaurin (Rydapt) has not been sufficiently evaluated for safety and/or efficacy in combination with any other oncolytic medication outside of cytarabine and daunorubicin in the setting of AML.

III. In Trial 2, midostaurin (Rydapt) was evaluated in a single-arm, open-label trial in ASM, SM-AHN, and MCL, collectively referred to as advanced SM. The trial included 116 adult subjects that had relapsed or progressed on or after 0-2 prior therapies. The primary outcome was complete remission (CR) plus incomplete remission (ICR) by six cycles via the Valent criteria for ASM and SM-AHN, with twenty-one percent of subjects meeting the primary endpoint (16-38%, depending on the specific type of SM). The median duration of CR+ICR was not reached at time of evaluation, and the median time to CR+ICR was 0.5 months.

IV. Trial 3 was a single-arm, open-label trial of 26 subjects with advanced SM. By Valent criteria, 10 achieved a response by two cycles that was sustained for at least eight weeks.

V. Midostaurin (Rydapt) is available in 25 mg capsules to be given as 50 mg twice daily on days 8-21 of each 28-day cycle for a total of six cycles in AML or, given as 100 mg twice daily continuously for SM.

Investigational or Not Medically Necessary Uses

I. The safety and efficacy of midostaurin (Rydapt) has not been sufficiently established in the following settings:
   A. Pediatric leukemia
   B. Rectal cancer
   C. Acute myeloid leukemia in absence of FLT3 mutation

References

1. Rydapt [Prescribing Information]. East Hanover, NJ. Novartis Pharmaceuticals Corporation. 2017.
2. Gotlib J., Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med. 2016. June 30;374(26): 2530-2541.
3. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 2.2020. Updated September 2019. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx
4. Stone RM, Mandrekar SJ, Sandfor BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017. Aug 3;377(5): 454-464.

Policy Implementation/Update:

Date Created	July 2017
Date Effective	August 2017
Last Updated	November 2019
Last Reviewed	November 2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy. Age requirement added. Clarification of appropriate line of therapy required for approval. Renewal allowance removed for AML and extended to six months for SM.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: 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

Product Name	Dosage Form	Indication	Quantity Limit
mifepristone (Korlym)	300 mg tablets	Hyperglycemia secondary to hypercortisolism in Cushing's syndrome	120 tablets/30 days

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

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 (Korylm) 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

1. Korlym [Prescribing Information]. Menlo Park, CA: Corcept Therapeutic, Inc. May 2017.
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Policy Implementation/Update:

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

Policy Type: PA/SP Pharmacy Coverage Policy: UMP096

Description

Migalastat (Galafold) is a pharmacologic chaperone that binds to and stabilizes specific mutant forms of alfa-galactosidase, thereby facilitating proper trafficking of the enzyme to lysosomes and increasing enzyme activity

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
migalastat (Galafold)	123 mg capsule	Fabry disease	15 capsules/30 days

Initial Evaluation

I. Migalastat (Galafold) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an endocrinologist or a specialist in genetics; **AND**
   C. Medication will not be used in combination with Enzyme Replacement Therapy (ERT); **AND**
   D. A diagnosis of **Fabry disease** when the following are met:
      1. Documentation of a confirmed diagnosis with mutation of alpha-galactosidase A (alpha-Gal A) gene; **AND**
      2. Documentation that member has a mutation in the gene encoding galactosidase alpha gene (GLA) resulting in a mutant protein that would respond to migalastat (Galafold) (i.e. member has an **amenable** GLA variant); **AND**
      3. Documentation of the member's baseline value of GL-3 inclusions per kidney interstitial capillary; **AND**
      4. Member does not have an eGFR <30 mL/minute/1.73 m2 OR ESRD requiring dialysis; **AND**
      5. Member is ERT-naïve and is not a candidate for ERT (due to contraindication, etc.); **OR**
      6. Member is ERT-experienced and not able to continue ERT therapy

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
II. Member has received a previous prior authorization approval for this agent; **AND**
III. Member does not have an eGFR <30 mL/minute/1.73 m2 OR ESRD requiring dialysis; **AND**
IV. Evidence of disease response with treatment as defined by a 50% reduction in GL-3 inclusions per kidney interstitial capillary compared to pre-treatment baseline; **AND**
V. Documentation by chart notes of disease stability or improvement in clinical symptoms

Supporting Evidence

I. Safety and efficacy of migalastat (Galafold) has not been established in pediatric patients.
II. Eligible patients in the pivotal study (Study 011) had either never received ERT or had not received ERT for at least 6 months. Efficacy and safety of migalastat (Galafold) in combination with ERT is currently in early clinical trial stages.
III. Migalastat is only suitable for people with specific amenable mutations. Only mutations for which migalastat produced substantial increases in enzyme activity were judged amenable. Migalastat does not work in people with non-amenable mutations. Patients with non-amenable GLA variants within the clinical study had no change from baseline in the primary endpoint of number of GL-3 inclusions per kidney interstitial capillary. Per the package insert, consultation with a clinical genetics professional is strongly recommended in cases where the amenable GLA variant is of uncertain clinical significance or may be benign (not causing Fabry disease). Refer to the table in the package insert listing specific GLA gene variants that are amenable to treatment with migalastat (Galafold) or listed within the following search tool found at: http://www.fabrygenevariantsearch.com. Additionally, Fabrazyme (ERT) can be used in all variants of Fabry disease for the treatment of both adults and children. Migalastat (Galafold) is only indicated in the subset of adult patients with a confirmed amenable GLA mutation.
IV. The primary endpoint in Galafold trials was the percentage of patients who had a response (≥50% reduction in the number of globotriaosylceramide inclusions per kidney interstitial capillary) at 6 months. Baseline values are needed as this was the outcome measured used in clinical trials to assess treatment effect.
V. Use of migalastat (Galafold) is not recommended in patients with severe renal impairment (eGFR <30 mL/minute/1.73 m2) or with ESRD requiring dialysis, these patients were excluded from clinical trials.
VI. Migalastat (Galafold) has not been demonstrated in clinical trials to have a clinically meaningful benefit in patients with Fabry disease relative to placebo. While one trial concluded it has "comparable" effects on renal function relative to ERT, "comparable" was not well defined and ERT also has limited evidence for efficacy in Fabry disease. The pivotal trial for migalastat (Galafold) failed to meet its primary endpoint and its outcome measure is of unknown significance as the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established. Though ERT therapy also assessed GL-3 inclusion reduction and provides low quality evidence, Fabrazyme is not specific to amendable variants and can be used in all variants of Fabry disease for the treatment of both adults and children.

References

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7. ClinicalTrials.gov. Study of the Effects of Oral AT1001 (Migalastat Hydrochloride) in Patients With Fabry Disease. Available from: https://clinicaltrials.gov/ct2/show/NCT00925301. Accessed September 26, 2018.
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9. Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. J Med Genet. 2017;54(4):288-296.

Policy Implementation/Update:

Date Created	September 2018
Date Effective	November 2018
Last Updated	November 2019
Last Reviewed	09/2019

Action and Summary of Changes	**Date**
Specified mutation needed to have a genetically confirmed diagnosis. Added requirement for agent to be prescribed by or in consultation with an endocrinologist or a specialist in genetics.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP135

Description

Miglustat (Zavesca) and eliglustat (Cerdelga) are orally administered glucosylceramide synthase inhibitors.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

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

Initial Evaluation

I. Miglustat (Zavesca) or eliglustat (Cerdelga) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with a provider that specializes in the treatment of Gaucher disease (e.g., endocrinologist, geneticist, hematologist, etc.); **AND**
   C. Will not be used in combination with other medications used to treat type 1 Gaucher disease [e.g., imiglucerase (Cerezyme), taliglucerase (Elelyso), velaglucerase (Vpriv), other agents listed in this policy, etc.]; **AND**
   D. A diagnosis of **type 1 Gaucher disease** when the following are met:
      1. Diagnosis is confirmed by **one** of the following:
         i. Deficiency of glucocerebrosidase (acid β-glucosidase) enzyme activity in peripheral blood leukocytes or cultured fibroblasts; **OR**
         ii. Genetic testing confirming mutation in glucocerebrosidase (*GBA*) gene; **AND**

2. The request is for generic miglustat or brand miglustat (Zavesca); **AND**
    i. Treatment with **ONE** enzyme replacement therapy (ERT) [e.g., imiglucerase (Cerezyme), taliglucerase (Elelyso), velaglucerase (Vpriv)] has been ineffective, contraindicated, or not tolerated; **AND**
    ii. If the request is for brand miglustat (Zavesca), the member has an intolerance or contraindication to generic miglustat; **OR**
3. The request is for eliglustat (Cerdelga); **AND**
    i. The member has undergone CYP2D6 genotyping by an FDA-cleared test and is classified as one of the following: [Note: eliglustat (Cerdelga) is not indicated for ultra-rapid metabolizers]
        a. Poor Metabolizer (PM); **OR**
        b. Intermediate Metabolizer (IM); **OR**
        c. Extensive Metabolizer

II. Miglustat (Zavesca) and/or eliglustat (Cerdelga) are considered investigational when used for all other conditions, including but not limited to:
    A. Type 3 Gaucher disease
    B. Gangliosidases (GM1 and GM2)
    C. Cystic Fibrosis
    D. Pompe Disease
    E. HIV Infection
    F. Niemann-Pick Disease
    G. Tay-Sachs Disease
    H. Sandhoff Disease

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Miglustat (Zavesca) or eliglustat (Cerdelga) will not be used in combination with other medications used for the treatment of type 1 Gaucher disease (i.e. will be used as monotherapy); **AND**
IV. Member has exhibited improvement or stability of disease manifestations [e.g., improvements in mean liver volume and/or spleen volumes, changes in hemoglobin levels and platelet count, etc.] and/or symptoms [e.g., fatigue, bleeding episodes, bruising, bone pain, etc.]

Supporting Evidence

I. Miglustat (Zavesca) obtained FDA approval for treatment of type 1 Gaucher disease in 2003 based on the result of two open-label, uncontrolled studies and one randomized, open-label, active-controlled study. In the uncontrolled open-label trials, patients experienced a significant mean reduction in liver and spleen volume from baseline and non-significant change in platelet counts and hemoglobin concentration. These results were maintained or further decreased during the extension period of both trials. In the randomized, active-controlled study, patients were randomized to receive miglustat (Zavesca) alone, imiglucerase (Cerezyme) alone, or miglustat (Zavesca) in combination with imiglucerase (Cerezyme). There were no significant differences between the groups for mean absolute changes in liver and spleen volume and hemoglobin concentration. However, there was a significant reduction in platelet counts between the miglustat (Zavesca) and imiglucerase (Cerezyme) monotherapy groups. During the open-label extension period, all patients were transitioned to miglustat (Zavesca) monotherapy and no significant changes liver volume, spleen volume, or hemoglobin concentration were observed.

II. Eliglustat (Cerdelga) obtained FDA approval for treatment of type 1 Gaucher disease under priority review in 2014 based on the results of one randomized, double-blind, placebo-controlled study in treatment naïve patients and one randomized, open-label, active-controlled, non-inferiority study in patients transitioning from enzyme replacement therapy.

III. A randomized, double-blind, placebo-controlled trial investigated eliglustat (Cerdelga) against placebo in type 1 Gaucher disease treatment naive patients. The results showed a statistically significant improvement in percentage change in spleen volume and liver volume, absolute change in hemoglobin level, and percentage change in platelet count from baseline to nine months compared to placebo. During the open label extension phase, improvements in spleen and liver volume, hemoglobin level, and platelet count continued through the two-year trial duration and through four years in a separate uncontrolled trial.

IV. A randomized, open-label, active-controlled, non-inferiority study evaluated eliglustat (Cerdelga) versus imiglucerase in patients who were previously treated with enzyme replacement therapy. The primary composite endpoint required stability in all four component domains (hemoglobin level, platelet count, liver volume and spleen volume) based on changes between baseline and 12 months according to pre-specified thresholds of change. Eliglustat (Cerdelga) met the criteria to be declared non-inferior to imiglucerase in maintaining patient stability. During the open-label extension phase, patients continued to show stability, as previously defined in the initial 12 months of the trial, at two years of treatment.

V. Patients enrolled in the studies for miglustat (Zavesca) and eliglustat (Cerdelga) were 18 and older. The safety and/or efficacy of use in pediatric and adolescent patients has not been evaluated.

VI. Miglustat (Zavesca) and eliglustat (Cerdelga) have largely been studied as monotherapy, with the exception of one treatment arm in a single study involving miglustat (Zavesca). Long-term safety and efficacy of either agent used in combination with enzyme replacement therapy, or other agents used to treat type 1 Gaucher disease has not been evaluated.

VII. Gaucher disease is a rare autosomal recessive lysosomal storage disorder (LCD) that is caused by mutations in the glucocerebrosidase enzyme (*GBA*) and/or deficiency of the enzyme glucocerebrosidase. Diagnosis of Gaucher disease type 1 should be confirmed by a physician

specializing in the treatment of Gaucher disease via blood tests to confirm deficiency of the glucocerebrosidase enzyme (acid β-glucosidase) in peripheral leukocytes or cultured fibroblasts or genetic testing to confirm mutation in *GBA* prior. Treatment is not necessary for all patients with Gaucher disease type 1, as some patients are asymptomatic. However, treatment is generally lifelong for symptomatic patients once treatment is initiated.

VIII. According to recent guidelines, treatment with enzyme replacement therapy (ERT) remains first-line treatment for type 1 Gaucher disease and is delivered intravenously. Miglustat (Zavesca) is a second line oral treatment indicated when ERT is no longer accepted by the patient or cannot be tolerated. Eliglustat (Cerdelga) may be used as a first-line treatment alternative to ERT.

IX. Miglustat (Zavesca) is commonly discontinued due to adverse effects including diarrhea (observed in over 85% of patients during clinical trials), weight loss (~65%), tremor and peripheral neuropathy. Eliglustat (Cerdelga) is generally better tolerated with the most common adverse events comprising of arthralgia (45%), back pain (12%), fatigue (14%) and headache (13 to 40%).

X. Miglustat (Zavesca) is contraindicated in women who are or may become pregnant. Providers should discuss the risks of teratogenicity when administered to women of reproductive potential.

XI. Eliglustat (Cerdelga) was found to be heavily affected by a patient's CYP2D6 metabolizer status and therefore requires CYP2D6 genotyping before prescribing. Recommended dosing differs between poor metabolizers and intermediate/extensive metabolizers. Eliglustat (Cerdelga) is not recommended for ultra-rapid metabolizers due to difficulty obtaining reliable blood levels of the drug. Concurrent use of strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, quinidine, etc.) is not recommended and these agents should be discontinued prior to initiating therapy with eliglustat (Cerdelga).

Investigational or Not Medically Necessary Uses

I. Miglustat (Zavesca) and/or eliglustat (Cerdelga) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Type 3 Gaucher disease
   B. Gangliosidases (GM1 and GM2)
   C. Cystic Fibrosis
   D. Pompe Disease
   E. HIV Infection
   F. Niemann-Pick Disease
   G. Tay-Sachs Disease
   H. Sandhoff Disease

References

1. Stirnemann J, Belmatoug N, Camou F, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. *Int. J. Mol. Sci.* 2017, 18, 441; doi: 10.3390/ijms18020441
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3. Wang RY, Bodamer OA, et al. Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals. ACMG Standards and Guidelines. *Genetics in Medicine*. 2011 May; 13(5).
4. Miglustat [Prescribing Information]. Actelion Pharmaceuticals US, Inc.: South San Francisco, CA. November 2017.
5. Eliglustat [Prescribing Information]. Genzyme Ireland, Ltd.: Waterford, Ireland. August 2018.

Policy Implementation/Update:

Action and Summary of Changes	Date
Transitioned criteria to new policy format and combined previous miglustat and eliglustat criteria into one policy and added the following requirements: age 18 and older, prescribed by or in consultation with specialist, used as monotherapy and diagnosis confirmed by genetic and/or blood testing	11/2020
Miglustat (Zavesca) criteria created	05/2018
Eliglustat (Cerdelga) criteria created	11/2014

Policy Type: QE Pharmacy Coverage Policy: UMP160

Description

Migraine abortive therapies, or acute treatments, include triptans, CGRP antagonists, and lasmiditan (Reyvow) which is a selective serotonin agonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Product Name	Dosage Form	Quantity Limit	Quantity Exception
almotriptan	6.25 mg tablet	9 tablets/30 days	20 tablets/30 days
	12.5 mg tablet	12 tablets/30 days	20 tablets/30 days
almotriptan (Axert)	12.5 mg tablet	12 tablets/30 days	20 tablets/30 days
eletriptan	20 mg tablet	9 tablets/30 days	20 tablets/30 days
	40 mg tablet		
eletriptan (Relpax)	20 mg tablet	9 tablets/30 days	20 tablets/30 days
	40 mg tablet		
frovatriptan	2.5 mg tablet	10 tablets/30 days	30 tablets/30 days
frovatriptan (Frova)	2.5 mg tablet	10 tablets/30 days	30 tablets/30 days
naratriptan	1 mg tablet	9 tablets/30 days	20 tablets/30 days
	2.5 mg tablet		
naratriptan (Amerge)	1 mg tablet	9 tablets/30 days	20 tablets/30 days
	2.5 mg tablet		
rizatriptan	5 mg tablet	12 tablets/30 days	30 tablets/30 days
	5 mg ODT		
	10 mg tablet		
	10 mg ODT		
rizatriptan (Maxalt)	5 mg tablet	12 tablets/30 days	30 tablets/30 days
	10 mg tablet		
rizatriptan (Maxalt-MLT)	10 mg tablet	12 tablets/30 days	30 tablets/30 days
sumatriptan (oral)	25 mg tablet	9 tablets/30 days	20 tablets/30 days
	50 mg tablet		
	100 mg tablet		
sumatriptan (Imitrex) (oral)	25 mg tablet	9 tablets/30 days	20 tablets/30 days
	50 mg tablet		
	100 mg tablet		
sumatriptan/ naproxen (oral)	85-500 mg tablet	9 tablets/30 days	20 tablets/30 days
sumatriptan/	85-500 mg tablet	9 tablets/30 days	20 tablets/30 days

naproxen (Treximet) (oral)			
sumatriptan (nasal)	5 mg spray	6 doses (1 box)/30 days	18 doses (3 boxes)/30 days
	20 mg spray		
sumatriptan (Imitrex) (nasal)	5 mg spray	6 doses (1 box)/30 days	18 doses (3 boxes)/30 days
	20 mg spray		
sumatriptan (Onzetra Xsail) (nasal)	11 mg powder	8 doses (1 kit/16 nosepieces)/30 days	16 doses (2 kits/32 nosepieces)/30 days
sumatriptan (Tosymra) (nasal)	10 mg spray	6 doses (1 box)/30 days	18 doses (3 boxes)/30 days
sumatriptan (SQ)	4 mg/0.5 mL	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
	6 mg/0.5mL		
sumatriptan (Imitrex) (SQ)	4 mg/0.5 mL Kit	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
	6 mg/0.5 mL solution		
sumatriptan (Imitrex Statdose) (SQ)	4 mg/0.5 mL solution	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
	6 mg/0.5 mL refill		
	6mg/0.5 ML system		
sumatriptan (Zembrace Symtouch) (SQ)	3 mg/0.5 mL solution	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
zolmitriptan (oral)	2.5 mg tablet	9 tablets/30 days	20 tablets/30 days
	5 mg tablet		
	2.5 mg ODT		
	5 mg ODT		
zolmitriptan (Zomig/ZMT) (oral)	2.5 mg tablet	9 tablets/30 days	20 tablets/30 days
	5mg tablet		
	2.5 mg ODT		
	5 mg ODT		
zolmitriptan (Zomig) (nasal)	2.5 mg spray	6 doses/30 days	18 doses (3 boxes)/30 days
	5 mg spray		
lasmiditan (Reyvow)	50 mg tablet	4 tablets/30 days	8 tablets/30 days
	100 mg tablet	8 tablets/30 days	16 tablets/30 days
ubrogepant (Ubrelvy)	50 mg tablet	8 tablets/30 days	16 tablets/30 days
	100 mg tablet	16 tablets/30 days	32 tablets/30 days

Initial Evaluation

I. A quantity exception may be considered medically necessary when the following criteria below are met:
   A. Member has tried and failed prophylactic therapy with at least <u>one</u> agent listed in <u>EACH</u> of the <u>three groups</u> (these specific agents required). Please note, if a group is contraindicated, a trial and failure of three remaining agent is required:
      1. Group 1: propranolol, metoprolol, atenolol, timolol, nadolol
      2. Group 2: amitriptyline, venlafaxine
      3. Group 3: topiramate, sodium valproate, divalproex sodium; **AND**

B. The member has tried each of the prophylactic therapies for at least three months, or did not tolerate therapy with an adequate trial; **AND**
C. Provider attestation that medication overuse headache has been ruled out as the cause or contributor to the member's migraines.

II. Triptans, lasmiditan (Reyvow), and ubrogepant (Ubrelvy) are considered investigational when used for all other conditions, including but not limited to:
A. Migraine prophylaxis

Renewal Evaluation

I. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in migraine symptom severity, duration, etc.) with the quantity previously allowed; **AND**
II. Provider attestation that the member is being monitored for medication overuse headache and the requested therapy is not causing or adding to medication overuse headache; **AND**
III. Provider attestation that the member is still in need of the quantity being requested and the member stockpiling is not occurring.

Supporting Evidence

I. This policy aims to ensure appropriate use of prescription abortive migraine therapies, limit overuse, occurrence of rebound headache, and direct members to migraine prevention therapy when appropriate.
II. Triptans have an established safety and efficacy profile for the abortive treatment of migraine; however, overuse of these therapies may result in exacerbation of migraine (i.e., medication overuse headache). Medication overuse headache (MOH) may occur with other therapies for abortive migraine treatment including, but not limited to: acetaminophen, NSAIDS, opioids, and ergot derivatives. After lifestyle modifications, non-pharmacologic therapies, and avoidance of triggers have been employed, pharmacologic therapy may be necessary. Triptans are the mainstay of therapy and are recommended as first-line treatment by governing bodies and treatment guidelines such as American Academy of Neurology, American Family Physician, and American Headache Society. Avoidance of MOH may be employed by using triptans less than two days per week on average, and package inserts for many triptan therapies recommend using less than 10 days per month. Prior to use of this frequency of triptans, prophylactic therapy for prevention of migraine may be warranted. Triptans are not indicated for the continual prophylactic treatment of migraine.
III. As of March 2020, MOH had not been noted for CGRP-antagonists or ubrogepant (Ubrelvy); however, long term safety data in treating more than 15 or eight migraines per month, respectively, has not been evaluated. These therapies are not indicated for prevention of migraine. For ubrogepant (Ubrelvy) the daily maximum dose is 200 mg.
IV. Lasmiditan (Reyvow) has warnings for MOH in the prescribing information. The label indicates treatment of more than four migraine days per months has not been evaluated and treating 10

or more migraines per month with this or other abortive migraine therapies may contribute to worsening of migraines. The daily maximum dose is 200 mg per day.

V. The agents listed in the policy are recommended by guidelines with Level A and B recommendations (i.e., efficacious or probably efficacious). There is no available evidence, or evidence to suggest against, use of any other agent not in the list above (e.g., gabapentin, nortriptyline, calcium channel blockers, SSRIs). These agents should not be considered for an adequate trial of prophylactic therapy given the negative or no evidence.

VI. Guidelines label a "treatment success" with prophylactic therapy as a 50% reduction in migraine after three months. Additionally, some agents take one-to-three months to show efficacy. If the prophylactic therapy has not been trialed for three months, the trial is not considered adequate for prophylactic efficacy; however, many migraine sufferers are unable to tolerate the recommended prophylactic therapies.

VII. The quantity limits are based on maximum daily dose, as recommended per the FDA, as well as treating with migraine therapies ten or less days per month, package size considerations as well as safety of therapies contained in this policy.

Investigational or Not Medically Necessary Uses

I. Triptans, lasmiditan (Reyvow), and ubrogepant (Ubrelvy) have not been FDA-approved, or sufficiently studied for safety and efficacy for migraine prophylaxis.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Removed Nurtec from current policy as this was moved to Aimovig, Emgality, Ajovy/CGRP policy instead	04/2021
Corrected quantity limit for Nurtec to reflect manufacturer guidance and allowance of 8/30 or 16/30	07/2020
New FDA-approved migraine therapies added to policy: lasmiditan (Reyvow), ubrogepant (Ubrelvy), rimegepant (Nurtec ODT).	04/2020

Prior authorization criteria transitioned to policy format. Addition of requirement to rule out medication overuse headache, inclusion of new agents and removal of obsolete products.	12/2019
Update to delete step therapy questions to align with current processes, created tables for QLL, changed question on prophylactic therapy options to fit with current evidence and guidelines, added duration of therapy question to ensure appropriate trial of prophylactic therapy, updated agent chart.	05/2018
Updated with clinical note regarding pediatric strength of Treximet.	10/2016
Updated with Onzentra Xsail.	05/2016
Reviewed and Updated: validated and updated product availability and quantity limit lists. Criteria updated to include trial of three therapeutic categories, removal of questions on daily triptan use and specialty provider.	01/2016
Previous Reviews	08/2014, 01/2013, 08/2012, 04/2012
Policy created	09/2011

miltefeosine (Impavido®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP097

Description

Miltefosine (Impavido) is an orally administered antileishmanial medication that induces apoptosis-like cell death and stops the growth of specific *Leishmania* species.

Length of Authorization

- Initial: 28 days
- Renewal: No renewal

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
miltefosine (Impavido)	50 mg capsules	Visceral leishmaniasis Cutaneous leishmaniasis Mucosal leishmaniasis	30 to 44 kg: 56 capsules/28 days OR ≥ 45 kg: 84 capsules/28ays

Initial Evaluation

I. Miltefosine (Impavido) may be considered medically necessary when the following criteria below are met:
   A. Member is 12 years of age or older; **AND**
   B. Member weighs at least 30 kg (66 lbs); **AND**
   C. Medication is prescribed by, or in consultation with an infectious disease specialist; **AND**
   D. A diagnosis of one of the following:
      1. Visceral leishmaniasis due to *Leishmania donovani*; **OR**
      2. Cutaneous leishmaniasis due to the following: *Leishmania braziliensis, Leishmania guyanensis,* or *Leishmania panamensis*; **OR**
      3. Mucosal leishmaniasis due to *Leishmania braziliensis*; **AND**
   E. Laboratory confirmation of leishmaniasis species were identified following **ONE** of the recommended tests provided by the Centers for Disease Control and Prevention (CDC) listed here:
      1. Stained slides (using tissue from biopsy specimens, impression smears or dermal scrapings)
      2. Culture medium
      3. Polymerase chain reaction (PCR)
      4. Serologic testing (e.g., rK39 Rapid Test); **AND**
   F. For the diagnosis of visceral leishmaniasis, treatment with liposomal amphotericin B (Ambisome) has been ineffective, contraindicated, or not tolerated.

II. Miltefosine (Impavido) is considered not medically necessary when criteria above are not met and/or when used for:
   A. The treatment of leishmaniasis outside of the visceral/cutaneous/mucosal settings, and not due to the species associated with visceral/cutaneous/mucosal leishmaniasis.

Supporting Evidence

I. Miltefosine (Impavido) is FDA-approved in the adolescents and adults ≥ 12 years and older weighing ≥ 30 kg (66lbs).
II. For the treatment of visceral leishmaniasis, the safety and efficacy was studied in one randomized, open-label, active-controlled (amphotericin B) trial in Bihar, India. The final cure rates for miltefosine (Impavido) and amphotericin B were 94% and 97%, respectively. Final cure was defined as initial cure at end of therapy plus absence of signs and symptoms of visceral leishmaniasis at six months follow up.
III. For the treatment of cutaneous leishmaniasis, the safety and efficacy was studied in a placebo controlled study in Colombia, Guatemala and Brazil. The finally cure rates at 95% CI with P-value <0.0001 were reported:
   A. Colombia: 82% miltefosine (Impavido) vs 30% placebo
   B. Guatemala: 48% miltefosine (Impavido) vs 20% placebo
   C. Brazil: 76.3% miltefosine (Impavido), placebo was not reported.
IV. For the treatment of mucosal leishmaniasis, the safety and efficacy was studied in a single-arm study in Bolivia that included 79 patients. At the end of therapy, reported at 12 months, 49 patients (62%) had complete resolution of edema, erythema, infiltration, and erosion from the involved mucosal sites.
V. The CDC has specific guidelines for leishmaniasis confirmation test. They can be found here: https://www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_diagnosis_guide_leishmaniasis_2016.pdf.

Investigational or Not Medically Necessary Uses

I. The treatment of leishmaniasis outside of the visceral/cutaneous/mucosal settings, and not due to the species associated with visceral/cutaneous/mucosal leishmaniasis.
   A. There is limited evidence to suggest the safety and efficacy of miltefosine (Impavido) outside of the FDA approved leishmaniasis settings and the specific species accordingly.

References

1. Impavido [Prescribing Information]. Wilmington, DE: Paladin Therapeutics, Inc. March 2014.
2. Centers for Disease Control and Prevention. Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Disease Society (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). October 2018. Available at: https://www.cdc.gov/parasites/leishmaniasis/health_professionals/index.html#dx

Policy Implementation/Update:

Date Created	April 2016
Date Effective	August 2016
Last Updated	October 2019
Last Reviewed	4/2016, 10/2019

Action and Summary of Changes	Date
Transitioned criteria into policy with the following additions: supporting evidence, investigational section and CDC diagnostic recommendations.	10/2019

Multiple Sclerosis

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP047

Description

Medications included in this policy are subcutaneous and oral disease modifying therapies for the treatment of multiple sclerosis.

Length of Authorization

Cladribine (Mavenclad) only

- Initial: 12 months
- Renewal: Two months, maximum of one renewal per lifetime

All other agents

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
cladribine (Mavenclad)	10 mg tablets (box of 4 tablets)	Relapsing forms of multiple sclerosis (MS)	1 box (4 tablets)/26 days*
	10 mg tablets (box of 5 tablets)		1 box (5 tablets)/26 days*
	10 mg tablets (box of 6 tablets)		1 box (6 tablets)/26 days*
	10 mg tablets (box of 7 tablets)		1 box (7 tablets)/26 days*
	10 mg tablets (box of 8 tablets)		1 box (8 tablets)/26 days*
	10 mg tablets (box of 9 tablets)		1 box (9 tablets)/26 days*
	10 mg tablets (box of 10 tablets)		1 box (10 tablets)/26 days*
daclizumab (Zinbryta)	150mg/mL single-dose PFS±		1 syringe/28 days
dimethyl fumarate (Tecfidera, dimethyl fumarate)	30 day starter pack		1 starter pack/30 days (60 capsules/30 days)
	120 mg capsule		60 capsules/30 days
	240 mg capsule		60 capsules/30 days
monomethyl fumarate (Bafiertam)	95 mg capsule		120 capsules/30 days
diroximel fumarate (Vumerity)	231 mg capsule		120 capsules/30 days

fingolimod (Gilenya)	0.25 mg capsule		30 capsules/30 days
	0.5 mg capsule		30 capsules/30 days
glatiramer acetate (Copaxone, Glatopa, glatiramer acetate)	20 mg/mL single dose PFS		30 syringes per/30 days
glatiramer acetate (Copaxone, Glatopa, glatiramer acetate)	40 mg/mL single dose PFS		12 syringes/28 days
interferon beta-1a (Avonex)	30 mcg/0.5mL PFS		4 syringes (1 kit)/28 days
	30 mcg/0.5mL pen		4 pens/28 days
interferon beta-1a (Plegridy)	Starter Pack – (Pen Injector or PFS)		1 starter pack/28 days
	125 mcg/0.5mL (Pen Injector or PFS)		2 pens (or PFS)/28 days
interferon beta-1a (Rebif)	22 mcg/0.5mL (Auto-injector or PFS)		12 syringes/28 days
	44 mcg/0.5mL (Auto-injector or PFS)		12 syringes/28 days
	Titration Pack (PFS or Solution)		1 pack (12 syringes)/28 days
interferon beta-1b (Betaseron)	0.3 mg powder for reconstitution		14 syringes/28 days
interferon beta-1b (Extavia)	0.3 mg powder for reconstitution		15 syringes/30 days
ofatumumab (Kesimpta)	20 mg/0.4mL Auto-injector		Initial: 3 pens/28 days
			Maintenance: 1 pen/28 days
ozanimod (Zeposia)	0.23 mg capsules		4 tablets/4 days
	0.46 mg capsules		3 tablets/3 days
	0.92 mg capsules		30 tablets/30 days
ponesimod (Ponvory)	2-10 mg starter pack		**Initial:** 14 tablets/14 days **Maintenance:** 30 tablets/30 days
	20 mg tablet		
siponimod (Mayzent)	0.25 mg starter pack		12 tablets/5 days
	0.25 mg tablets		112 tablets/28 days
	2 mg tablets		30 tablets/30 days
teriflunomide (Aubagio)	7 mg tablets		28 tablets/28 days
	14 mg tablets		28 tablets/28 days

*Maximum of 2 boxes/331 days

‡PFS: Prefilled Syringe

Initial Evaluation

Interferon beta-1a (Avonex), generic dimethyl fumarate, fingolimod (Gilenya), glatiramer acetate (Glatopa), and generic glatiramer acetate 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), ponesimod, and teriflunomide (Aubagio)** 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 <u>two</u> of the following have been ineffective, contraindicated or not tolerated: interferon beta-1a (Avonex), generic dimethyl fumarate, fingolimod (Gilenya), or generic glatiramer acetate/Glatopa

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 <u>allergy</u> to the generic equivalent [i.e. skin rashes (particularly hives), itching, respiratory compilations and angioedema] that required medical intervention to prevent impairment or damage; **OR**

3. The prescriber is requesting the brand name drug due to a documented intolerance to the generic equivalent which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. More than one generic equivalent has been tried, or there is only one generic equivalent for the prescribed brand drug; **AND**

D. For Brand Tecfidera: Documentation of treatment with all three (1, 2 and 3) 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; **OR**

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

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 <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
    A. Primary Progressive MS (PPMS)

Renewal Evaluation

I. 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**

II. If the request is for Brand Tecfidera:
    A. In the absence of a drug shortage, coverage of multi-source brand Tecfidera is to be considered medically necessary when the prescriber is requesting the multi-source brand drug due to a documented adverse reaction to the generic equivalent; **AND**
    B. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**

a. The prescriber must document one or more of the following, indicating that the reaction:
    i. Was life-threatening; **OR**
    ii. Required hospitalization; **OR**
    iii. Required intervention to prevent impairment or damage; **OR**
b. The prescriber is requesting the brand name drug due to a documented allergy to the generic equivalent [i.e. skin rashes (particularly hives), itching, respiratory compilations and angioedema] that required medical intervention to prevent impairment or damage; **OR**
c. The prescriber is requesting the brand name drug due to a documented intolerance to the generic equivalent which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
    i. More than one generic equivalent has been tried, or there is only one generic equivalent for the prescribed brand drug; **OR**

III. If the request is for siponimod (Mayzent) and treatment has been interrupted for four or more consecutive daily doses, a re-titration starter package is covered by the manufacturer

Supporting Evidence

I. **Siponimod (Mayzent):** Per the package label, if treatment with siponimod (Mayzent) is interrupted for FOUR or more consecutive daily doses after completion of initial titration, treatment should be reinitiated with Day 1 of the titration regimen, including first-dose monitoring when appropriate. Siponimod (Mayzent) manufacturer, Novartis, confirmed 5-day titration packs/starter pack will be shipped from HomeScripts mail order pharmacy at no charge to commercial plans. Even in cases where the member needs to re-titrate the starter pack is covered by Novartis via HomeScripts.

II. American Academy of Neurology (AAN) guidelines recommend clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity, guidelines do not contain treatment sequencing recommendations.

III. AAN guidelines recommend clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience one or more relapses, two or more unequivocally new MRI-detected lesions, or increased disability on examination over a one-year period of using a DMT.

IV. DMTs take a variable amount of time to become clinically active, and new lesion formation may occur after initiation but before the time of full efficacy, confounding interpretation of follow-up MRI scans. Consequently, many clinicians obtain new baseline MRI three to six months after initiating DMTs to monitor from a treated baseline. The optimal interval for ongoing monitoring is uncertain, as short-term stability as evidenced by clinical and MRI criteria may not consistently predict long-term stability.

V. Per Lublin, et al. 2014, disease activity is determined by clinical relapses assessed at least annually and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions).

VI. The FDA Summary Review for Regulatory Action on the NDA for siponimod (Mayzent) states the following: In the active secondary progressive phase of the disease, patients can accrue disability both from acute relapses and from the progressive component of the disease. Active secondary progressive disease and relapsing-remitting disease overlap in evolution. Categorization as secondary progressive disease is based on clinical judgment; there are no clinical findings or biomarkers that meaningfully define or predict the phenotypes of relapsing forms of MS. A continued progression of disability with no concurrent inflammatory activity and no clinical relapses is described a non-active secondary progressive MS. Importantly, to support an indication for the treatment of secondary progressive MS (as distinct from active secondary progressive MS), it is critical that efficacy be established in patients who have non-active secondary progressive MS (SPMS), and that the drug effect be clearly distinguished from an effect on inflammatory demyelination and clinical relapses that are present in patients with active SPMS (a relapsing form of MS). Multiple drugs have been approved for the treatment of relapsing forms of MS. Conversely, there is a significant unmet medical need for the treatment of non-active SPMS…… The indication supported by the submitted data is therefore for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. It must be emphasized that thirteen different therapies have been approved to treat relapsing forms of multiple sclerosis, and that the population for which siponimod will be indicated is the same as for those drugs. The siponimod labeling will be the first explicitly describing that relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, but all sponsors of the drugs approved for the treatment of relapsing forms of multiple sclerosis will be requested to update their indication statements to conform with this contemporary nomenclature.

VII. In the United States, the Office of Generic Drugs at the Food and Drug Administration (FDA) follows a rigorous review process to make sure that, compared to the brand name (or innovator) medications, the proposed generic medications:

- Contain the same active/key ingredient
- Have the same strength
- Use the same dosage form (for instance, a table, capsule, or liquid) and
- Use the same route of administration (for instance, oral, topical, or injectable)

VIII. The FDA's review process also ensures that generic medications perform the same way in the human body and have the same intended use as the name brand medication. Healthcare professionals and consumers can be assured that FDA-approved generic drug products have met the same rigid manufacturing standards as the innovator drug. In addition, FDA inspects facilities to make certain the generic manufacturing, packaging, and testing sites pass the same quality standards as those of brand-name drugs.

- Thus, when an adverse reaction or allergy occurs to any medication (brand or generic), it is important to report to MedWatch.
- In order to keep effective medical products available on the market, the FDA relies on the voluntary reporting of these events. This information is used to maintain safety surveillance and to monitor if modifications in use or design of the product are warranted to increase patient safety.

IX. It can be difficult to distinguish an allergy from a distinct adverse event related to the generic, therefore any event thought to be related to the medication should be reported to MedWatch.

- As defined by the American Academy of Allergy, Asthma, and Immunology, an allergic reaction occurs when the immune system overreacts to a substance, triggering an allergic reaction. Sensitivities to drugs may produce similar symptoms, but do not involve the immune system. Only 5-20% of adverse reactions to drugs are considered true allergic reactions. The chances of developing an allergy are higher when you take the medication frequently or when it is rubbed on the skin or given by injection, rather than taken by mouth. The most frequent types of allergic symptoms to medications include skin rashes (particularly hives), itching, respiratory complications and angioedema. The most severe form of immediate allergic reactions is anaphylaxis, and symptoms include hives, facial or throat swelling, wheezing, light-headedness, vomiting and shock.

X. Tools used in diagnosis of MS:

MS with a relapsing-remitting course	
• Based upon two separate areas of damage occurred at different points in time (dissemination in time). Unless contraindicated, MRI should be obtained.	
Dissemination in <u>time</u> (Development/appearance of new CNS lesions over time)	Dissemination in <u>space</u> (Development of lesions in distinct anatomical locations within the CNS)

• ≥ 2 clinical attacks; OR
• 1 clinical attack AND one of the following:
  ○ MRI indicating simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI compared to baseline scan
  ○ CSF-specific oligoclonal bands
	• ≥ 2 lesions; OR
	• 1 lesion AND one of the following:
	  ○ Clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location
	  ○ MRI indicating ≥ 1 T2-hyperintense lesions characteristic of MS in ≥ 2 of 4 areas of the CNS (periventricular, cortical or juxtacortical, infratentorial, or spinal cord)

Secondary progressive MS course	
• MS course characterized by steadily increasing objectively documented neurological disability independent of relapses. Fluctuations, periods of stability, and superimposed relapses might occur. Secondary progressive multiple sclerosis, is further distinguished as a progressive course following an initial relapsing-remitting course. • Diagnosed retrospectively based on previous year's history.	

Investigational Uses or Not Medically Necessary Uses

I. Primary Progressive MS

A. All agents included in this policy have not been evaluated in or have not been found to have a positive effect on progression in the setting of PPMS.

References

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22. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83(3):278-86.
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25. ofatumumab (Kesimpta) [Prescribing Information]. East Hanover, NJ; Novartis. August 2020.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Update to initial requests for brand Tecfidera or brand Copaxone to require trial of Avonex, Gilenya, and glatiramer acetate (Glatopa)/generic glatiramer acetate for brand Tecfidera requests; and trial of Avonex, Gilenya, and generic dimethyl fumarate for brand Copaxone requests	05/2021
Adding loading dose to QL table for kesimpta	02/2021

Addition of brand Copaxone into policy aligning with requirements for brand Tecfidera requiring medical necessity for brand over generic.	12/2020
Addition of ofatumumab (Kesimpta) and ponesimod to policy within non-preferred position. Addition of brand Tecfidera criteria requiring medical necessity for brand over generic.	11/2020
Updated preferred products to specify generic dimethyl fumarate upon new generic availability (effective 10/2020). Removed criteria specific to branded Copaxone. Addition of monomethyl fumarate (Bafiertam) to policy within non-preferred position.	09/2020
Updated to include ozanimod (Zeposia) as a non-preferred product	04/2020
Updated fingolimod (Gilenya) as a preferred product effective 4/1/2020 per WA PDL update	03/2020
Updated to add non-preferred Vumerity	11/2019
Updated to include box around preferred agents not requiring prior authorization	10/2019
Updated to new policy format. Added newly approved drugs Mayzent and Mavencald. Added question requiring diagnosis confirmed and documented by laboratory report (e.g., MRI).	08/2019
Policy created from criteria	11/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP077

Split Fill Management*

Description

Neratinib (Nerlynx) is an orally administered Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 and 4 (HER2, HER4) irreversible inhibitor.

Length of Authorization

- Initial:
  - i. Early stage breast cancer: 12 months
  - ii. Metastatic breast cancer: Six months
- Renewal:
  - i. Early stage breast cancer: Cannot be renewed
  - ii. Metastatic breast cancer: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
neratinib (Nerlynx)	40 mg tablets	Breast cancer, early stage, HER2-positive, following trastuzumab	180 tablets/30 days
		Breast cancer, advanced or metastatic HER2-positive	

Initial Evaluation

I. Neratinib (Nerlynx) may be considered medically necessary when the following criteria are met:
   A. Member is a female 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Neratinib (Nerlynx) will **not** be used in combination with another oncology therapy unless outlined below (e.g. in combination with capecitabine in metastatic disease); **AND**
   D. The member has **not** previously progressed on, or after, treatment with another tyrosine kinase inhibitor (e.g., lapatinib [Tykerb], tucatinib [Tukysa]); **AND**
   E. A diagnosis of one of the following:
      1. **Early stage (I-III) breast cancer**; **AND**
         i. Documentation is provided showing the disease is HER2-positive AND hormone receptor (HR)-positive; **AND**
         ii. The member has received adjuvant trastuzumab-based therapy (e.g., Herceptin, Trazimera, Kanjinti, etc.) within the past 12 months; **OR**
      2. **Advanced or metastatic breast cancer; AND**
         i. Documentation is provided showing the disease is HER2-positive; **AND**

ii. Member has received ≥2 prior anti-HER2-based regimens [e.g., trastuzumab (Herceptin), pertuzumab (Perjeta), trastuzumab emtansine (Kadcyla; TDM-1)] in the metastatic setting; **AND**

iii. Will be used in combination with capecitabine

II. Neratinib (Nerlynx) is considered not medically necessary when criteria above are not met and/or when used for:

A. Early stage breast cancer in members that have not received trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.) in the past 12 months
B. Early stage breast cancer that is not HR-positive
C. Early stage breast cancer in combination with trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.)

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

A. Triple negative breast cancer
B. Breast cancer that is HER-2 negative
C. Non-small cell lung cancer
D. Colorectal cancer
E. Head and neck cancer
F. Ovarian, endometrial, uterine cancer
G. Bladder or rectal cancer
H. Early stage breast cancer for greater than one year
I. Solid tumors, other than breast cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, an oncologist; **AND**
IV. A diagnosis of **advanced or metastatic breast cancer; AND**
- Will be used in combination with capecitabine; **AND**
- Will not be used with any other oncology therapy outside of capecitabine; **AND**
- Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

I. Neratinib (Nerlynx) was evaluated for safety and efficacy in the ExteNET trial; a randomized, double-blind, placebo-controlled trial in women who had been previously treated with trastuzumab therapy and had HER2-positive breast cancer.

II. Subjects included had early stage (I-III) disease and had completed trastuzumab within the past two years; however, the majority of subjects had received trastuzumab within the past year (81%). Notably, results were statistically significant in those that received trastuzumab within the past year and were not for those that had received treatment 1-2 years prior. The primary outcome was invasive disease-free survival (iDFS) defined as time between date of randomization to first occurrence of invasive recurrence. Results for the iDFS at 24 months was 94.2% for neratinib (Nerlynx) compared to 91.9% for placebo (HR 0.66 [0.49-0.90], p=0.008). Subgroup analyses showed a statistically significant result for those with HR-positive disease but did not for HR-negative disease. Additionally, results favored neratinib (Nerlynx) in those that used therapy after trastuzumab; however, were not significant for those concurrently receiving trastuzumab.

III. Neratinib (Nerlynx) has only been evaluated for safety and efficacy for up to one year of therapy in early stage disease; matching the prescribing information, which notes continuous dosing for one year in this setting.

IV. Neratinib (Nerlynx) was evaluated for safety and efficacy in the advanced or metastatic population in the NALA trial; a randomized, open label, trial evaluating neratinib (Nerlynx) plus capecitabine compared to lapatinib (Tykerb). Patients included in the trial had metastatic HER2-postive breast cancer and had received 2 or more prior anti-HER2 regimens [e.g., trastuzumab (Herceptin), pertuzumab (Perjeta), trastuzumab emtansine (Kadcyla; TDM-1)] in the metastatic setting. Median progression free survival (PFS) was 5.6 months with neratinib (Nerlynx) plus capecitabine and 5.5 months with lapatinib plus capecitabine (HR, 0.76; 95% [CI], 0.63 to 0.93; P=0.0059). Overall survival was 21.0 months with the neratinib (Nerlynx) arm and 18.7 months with the lapatinib arm; however, the between group difference was not statistically significant (HR, 0.88; 95% CI, 0.72 to 1.07; P=0.2086).

V. Patients in the NALA trial were excluded if they were previously treated with capecitabine, neratinib, lapatinib, or any other HER2 directed tyrosine kinase inhibitor. At this time, there is a lack of scientific evaluation for safety and efficacy of neratinib (Nerlynx) following progression on, or after, another tyrosine kinase inhibitor.

VI. In the NALA trial, 59% of patients were hormone receptor positive (HR+) and 41% were hormone receptor negative (HR-). Thus, coverage of neratinib (Nerlynx) is available regardless of hormone receptor status.

VII. ER testing should be used to determine if a patient is a candidate for endocrine therapies. Per NCCN guidelines, women with Stage IV or recurrent disease characterized by tumors that are HR-positive, HER2-positive tumors have the option of receiving HER2-directed therapy as a component of their treatment plan. Options include, treatment with a HER2-targeted therapy plus chemotherapy or endocrine therapy alone or in combination with HER2-targeted therapy. Endocrine therapy alone or in combination with HER2- targeted therapy is a less toxic approach compared with HER2-targeted therapy combined with chemotherapy. Premenopausal women treated with HER2-targeted therapy and endocrine therapy should receive ovarian suppression or ablation.

Investigational or Not Medically Necessary Uses

I. In the early stage breast cancer pivotal trial, ExteNET, subgroup analyses showed non statistically significant results for neratinib (Nerlynx) in the following populations:
   A. Breast cancer in members that have not received trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.) in the past 12 months
   B. Breast cancer that is not HR-positive
   C. Breast cancer in combination with trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.)

II. Neratinib (Nerlynx) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. Triple negative breast cancer
   B. Breast cancer that is HER-2 negative
   C. Non-small cell lung cancer
   D. Colorectal cancer
   E. Head and neck cancer
   F. Ovarian, endometrial, uterine cancer
   G. Bladder or rectal cancer
   H. Breast cancer for greater than one year
   I. Solid tumors, other than breast cancer

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

References

1. NCCN Clinical Practice Guideline in Oncology: Breast Cancer. Version 4.2020. National Comprehensive Cancer Network. Available at https://www.nccn.org/professionals/ physician_gls/pdf/breast.pdf. Updated May 8, 2020.
2. Nerlynx [Prescribing Information]. Los Angeles, CA. Puma Biotechnology, Inc. February 2020.
3. Chan PA, Delaloge S., Holmes FA. , et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2016;17(3): 367-377.
4. Puma Biotechnology, Inc. A study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ metastatic breast cancer who have received two or more prior HER2 directed regimens in the metastatic setting (NALA). Available from: http://www.clinicaltrials.gov/ct2/show/NCT01808573. NLM identifier: NCT01808573.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new indication for advanced or metastatic breast cancer. Addition of split fill management.	07/2020
Criteria transitioned to policy, with updates to newest format: inclusion of specialty provider, clarification on concurrent therapies, age requirement.	10/2019
Criteria created	09/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP136

Split Fill Management*

Description

Nilotinib (Tasigna) is a Bcr-Abl kinase inhibitor that binds to, and stabilizes, the inactive conformation of the kinase domain of the Abl protein.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
nilotinib (Tasigna)	50 mg capsules	Newly diagnosed OR resistant/intolerant Ph+ CML in chronic phase	112 capsules/28 days
	150 mg capsules	Newly diagnosed Ph+ CML in chronic phase	112 capsules/28 days
	200 mg capsules	Resistant or intolerant Ph+ CML Gastrointestinal Stromal Tumors (GIST)	112 capsules/28 days

Initial Evaluation

I. Nilotinib (Tasigna) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. Medication will <u>not</u> 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 <u>chronic</u> 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 <u>chronic</u> phase Ph+ or BCR-ABL1 mutation positive CML; **AND**
            a. Member is one year of age or older; **AND**
            b. Treatment with a tyrosine kinase inhibitor [e.g. imatinib (Gleevec)] has been ineffective, contraindicated, or not tolerated; **OR**

2. **Gastrointestinal Stromal Tumors (GIST)**; **AND**
    i. Treatment with ALL the following have been ineffective, contraindicated, or not tolerated:
        a. imatinib (Gleevec)
        b. sunitinib (Sutent)
        c. regorafenib (Stivarga)

II. Nilotinib (Tasigna) is considered investigational when used for all other conditions, including but not limited to:
    A. CML without Philadelphia chromosome
    B. CML in the blast phase

Renewal Evaluation

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

Supporting Evidence

I. Nilotinib (Tasigna) is FDA-approved for treatment of adult and pediatric patients greater than one year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase and is a NCCN Category 1.
II. Nilotinib (Tasigna) for the treatment Ph+ CML resistant to prior therapy is only FDA-approved for use in the pediatric population in patients with chronic phase Ph+CML.
III. Nilotinib (Tasigna) is FDA-approved for use in adult patients with chronic phase and accelerated phase Ph+ CML resistant to, or intolerant of, prior therapy that included imatinib.
IV. Payment considerations for nilotinib for the treatment of Gastrointestinal Stromal tumors is reserved for members who have tried and failed imatinib (Gleevec) and sunitinib (Sutent) for the treatment of GIST. This recommendation is reflective of NCCN guidelines. Much of the data comes from phase II studies and retrospective analyses involving a small number of patients. In a randomized phase 3 study of nilotinib as 3rd line therapy and best supportive care (with or without a TKI) in patients with GIST resistant to imatinib and sunitinib (n=248) the PFS on nilotinib (Tasigna) was not found to be superior to best supportive care (109 days vs 111 days; P=0.56). Additionally, regorafenib has FDA approval and NCCN category 1 designation for GIST in patients previously treated with imatinib and sunitinib.

Investigational or Not Medically Necessary Uses

I. Nilotinib (Tasigna) has not been sufficiently evaluated in the following settings. Limited evidence may be available;, however, safety and efficacy have not been established for:
   A. CML without Philadelphia chromosome
   B. CML in the blast phase

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

References

1. Tasigna [Prescribing Information]. East Hanover, NJ: Novartis; September 2019.
2. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia – v.2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.
3. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma – v.3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf.

Policy Implementation/Update:

Date Created	February 2012
Date Effective	August 2010
Last Updated	December 2019
Last Reviewed	03/2012, 07/2012, 08/2012, 01/2013, 05/2018, 12/2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format. Expanded renewal duration from 6 months to 12 months for all indications. Required agent be used as monotherapy and not in combination with other oncolytics.	12/2019
Added new indication in pediatric patients one year of age or older with Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase (Ph+ CML-CP). Allowed for approval in the second line CML setting after being treated with a TKI (other than imatinib). For GIST off-label use, added a requirement to try/fail regorafenib as well as the existing agents (imatinib and sunitinib).	05/2018

nilutamide (Nilandron®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP199

Description

Nilutamide (Nilandron) is an orally active first-generation nonsteroidal antiandrogen agent, which blocks effects of testosterone at the androgen receptor level, preventing androgen response.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Nilutamide (Nilandron)*	150 mg tablet	Metastatic prostate cancer	**Initial**: 60 tablets/ 30 days for one month **Maintenance**: 30 tablets/ 30 days

*Generic nilutamide is a formulary agent and does not require prior authorization

Initial Evaluation

I. Nilutamide (Nilandron) may be considered medically necessary when following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
   C. A diagnosis of **metastatic prostate cancer**; **AND**
   D. Treatment with generic nilutamide has been ineffective, contraindicated or not tolerated

II. Nilutamide (Nilandron) is considered <u>investigational</u> 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, and oncologist or urologist.

IV. Coverage of brand name nilutamide (Nilandron) requires failure, intolerance or contraindication to generic nilutamide. Nilutamide is the AB-rated generic to nilutamide (Nilandron), and is deemed to be bioequivalent to the brand formulation; however, is a more cost-effective option.

References

1. Nilandron (nilutamide) [prescribing information]. St. Michael, Barbados: Concordia Pharmaceuticals; received May 2017.
2. Orange Book: approved drug products with therapeutic equivalence evaluations. U.S. Food & Drug Administration. Accessed October 2020. Available at: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	10/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP138

Split Fill Management* [applies to nintedanib (Ofev) only]

Description

Nintedanib (Ofev) is an orally administered tyrosine kinase inhibitor.
Pirfenidone (Esbriet) is an orally administered pyridine that is thought to exert antifibrotic properties by decreasing fibroblast proliferation and the production of fibrosis associated proteins and cytokines.

Length of Authorization

- Initial:
  - Esbriet: 12 months
  - Ofev: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
nintedanib (Ofev)	100 mg capsules	Idiopathic pulmonary fibrosis (IPF); Systemic sclerosis-associated interstitial lung disease (SSc-ILD); Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype	60 capsules/30 days
	150 mg capsules		
pirfenidone (Esbriet)	267 mg capsules or tablets	Idiopathic Pulmonary Fibrosis (IPF)	207 capsules or tablets/ 30 days
	801 mg tablets		90 tablets/30 days

Initial Evaluation

I. Nintedanib (Ofev) and prifenidone (Esbriet) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   C. Nintedanib (Ofev) and prifenidone (Esbriet) will not be used in combination with each other; **AND**
   D. Provider attests the member is currently abstaining from <u>any form of smoking</u>; **AND**

E. Documentation of baseline assessment [forced vital capacity (%FVC) **OR** carbon monoxide diffusing capacity (DLCO) **OR** six-minute walking distance (6MWD)]; **AND**
F. A diagnosis of one of the following:
    1. **Idiopathic pulmonary fibrosis (IPF); AND**
        i. Member has a usual interstitial pneumonia pattern (UIP) confirmed by a high resolution computed tomographic (HRCT) scan or surgical lung biopsy; **OR**
    2. **Systemic sclerosis-associated interstitial lung disease (SSc-ILD); AND**
        i. Request is for nintedanib (Ofev); **AND**
        ii. The diagnosis confirmed by a high resolution computed tomographic (HRCT) scan; **OR**
    3. **Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype; AND**
        i. Request is for nintedanib (Ofev); **AND**
        ii. Member has fibrotic features in lungs confirmed by a high resolution computed tomographic (HRCT) scan; **AND**
        iii. Member has clinical signs of progression (eg. decline in %FVC with worsening respiratory symptoms **or** increasing extent of fibrotic changes on chest imaging)

II. Nintedanib (Ofev) and prifenidone (Esbriet) are considered 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

Renewal Evaluation

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

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

III. Provider attests that member has exhibited improvement or stability of disease symptoms (e.g., increase in forced vital capacity (%FVC), carbon monoxide diffusing capacity (DLCO), or six-minute walking distance (6MWD) from baseline); **AND**

IV. Nintedanib (Ofev) and prifenidone (Esbriet) will not be used in combination with each other; **AND**

V. Provider attests that member is currently abstaining from any form of smoking; **AND**

VI. If for the diagnosis of **Systemic sclerosis-associated interstitial lung disease (SSc-ILD) or Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype:**

   A. Request is for nintedanib (Ofev)

Supporting Evidence

I. Nintedanib (Ofev) inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). It binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signaling 13 cascades.

II. Idiopathic pulmonary fibrosis (IPF) is an idiopathic chronic fibrosing interstitial pneumonia with a histopathologic or radiographic pattern of usual interstitial pneumonia (UIP).

III. High resolution computed tomography (HRCT) should be obtained in all patients suspected of having IPF. When the results of the HRCT cannot allow the clinician to make a confident diagnosis of IPF, surgical lung biopsy may be warranted. However, the decision requires assessment of the benefits of having a definitive diagnosis relative to the risks of the surgical procedure.

IV. For the treatment of IPF, nintedanib (Ofev) was studied in 1,066 patients with IPF in two Phase 3 trials (INPULSIS-1 and INPULSIS-2). These were randomized, double-blind, placebo-controlled studies comparing treatment with nintedanib (Ofev) 150 mg twice daily to placebo for 52 weeks.

- The primary outcome: The adjusted annual rate of change in FVC (in mL):
  i. INPULSIS-1: -114.7 mL per year in the nintedanib (Ofev) group and -239.9 mL per year in the placebo group over week 52 (absolute difference of 125.2 mL, 95% CI: 77.7, 172.8; *p*<0.001)
  ii. INPULSIS-2: -113.6 mL per year in the nintedanib (Ofev) group and -207.3 mL per year in the placebo group over week 52 (absolute difference of 93.7 mL, 95% CI: 44.8, 142.7; *p*<0.001)
- The secondary lung function outcomes:

	INPULSIS-1			**INPULSIS-2**		
End Points	**Nintedanib (N=307)**	**Placebo (N=204)**	**95% CI; *P* value**	**Nintedanib (N=327)**	**Placebo (N-217)**	**95% CI; *P* value**
Adjusted absolute mean change from baseline in FVC (mL)	-95.1	-205.0	109.9 (71.3, 148.6; *P*<0.001)	-95.3	-205.0	109.8 (70.9, 148.6; *P*<0.001)
Adjusted absolute mean change from baseline in FVC (% predicted)	-2.8%	-6.0%	3.2% (2.1, 4.3; *P*<0.001)	-3.1%	-6.2%	3.1% (1.9, 4.3; *P*<0.001)

FVC response at week 52 (%): FVC decline ≤ 5%	52.8%	38.2%	1.85% (1.28, 2.66; *p*=0.001)	53.2%	39.3%	1.79% (1.23, 2.55; *p*=0.001)
FVC response at week 52 (%): FVC decline ≤ 10%	70.6%	56.9%	1.91% (1.32, 2.79; *P*<0.001)	69.6%	63.9%	1.29% (0.89, 1.86; *p*=0.18)

V. The presence of SSc-ILD is defined by the identification of fibrotic features on HRCT scan. Surgical lung biopsy is seldom performed in SSc patients, unless the HRCT pattern is atypical, there is suspicion of a different diagnosis, or there is a complication such as cancer.

VI. Pulmonary function tests (PFT) in patients with SSc-ILD demonstrate a restrictive pattern, with FVC and diffusion capacity of the lung for carbon monoxide (DLCO). DLCO is a measure of the conductance of gas transfer from inspired gas to the red blood cells. A low DLCO combined with reduced lung volumes suggests interstitial lung disease (ILD).

VII. For systemic sclerosis-associated interstitial lung disease (SSc-ILD), nintedanib (Ofev) was studied in a Phase 3, randomized, double-blind, placebo-controlled trial (N=576) (SENSCIS trial). Patients received either nintedanib (Ofev) 150 mg twice daily (N=228) or placebo (N=288) for at least 52 weeks.

- The primary outcome: The adjusted annual rate of change in FVC (in mL): -52.4 mL per year in the nintedanib (Ofev) group and -93.3 mL per year in the placebo group over week 52 (absolute difference of 40.9 mL, 95% CI: 2.9, 79.0; *p*=0.04).

VIII. Safety and efficacy of nintedanib (Ofev) have not been established in pediatric patients.

IX. The safety and efficacy of pirfenidone (Esbriet) was studied in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in patients (40 to 80 years of age) with idiopathic pulmonary fibrosis (IPF) and a %FVC of at least 50%.

A. Study One: 52-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=278) versus placebo (n=277). The primary efficacy outcome for the change in %FVC at week 52 demonstrated a statistically significant treatment effect with pirfenidone (Esbriet) when compared to placebo.

B. Study Two: 72-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=174) or pirfenidone (Esbriet) 1197 mg/day (n=87) to placebo (n=174). The primary efficacy outcome for the change in %FVC at week 72 demonstrated a statistically significant treatment effect with pirfenidone (Esbriet) when compared to placebo.

C. Study Three: 72-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=171) to placebo (n=173). In this study, there was no statistically significant difference at week 72 for the change in %FVC from baseline when compared to placebo.

X. The exact etiology of IPF is not known, but the associated risk factors include cigarette smoking, viral infection, environmental pollutants, chronic aspiration, genetic predisposition, and drugs.

XI. According to the American Thoracic Society guidelines, the diagnosis of IPF requires:

A. Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).

B. The presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy.

C. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.

XII. The clinical efficacy of nitendanib (Ofev) has been studied in patients with chronic fibrosing ILDs with a progressive phenotype in a randomized, double-blind, placebo-controlled phase 3 trial (Study 5). A total of 663 patients were randomized in a 1:1 ratio to receive either nitendanib (Ofev) 150 mg twice daily or matching placebo for at least 52 weeks. Randomization was stratified based on high resolution computed tomography (HRCT) fibrotic pattern.
   A. The primary endpoint was the annual rate of decline in FVC (in mL) over 52 weeks. There was a statistically significant reduction by 107 mL in patients receiving OFEV compared to patients receiving placebo.

XIII. High-resolution computed tomography (HRCT) of the chest is mandatory in order to assess if ILD is present and, if so, to begin the differential diagnosis.

XIV. Progression of fibrosing ILDs is reflected in an increase in fibrosis evident on a computed tomography scan, a decline in FVC and gas exchange (DLCO), worsening of symptoms and exercise capacity (6MWD), and deterioration in health-related quality of life.
   A. There is no standardized definition of PF-ILD that clinicians and researchers have agreed upon. Several criteria have been used to define progression in patients with IPF, with most of these based on an absolute or relative decline in FVC and diffusing capacity of the lung for DLCO of greater than or equal to 5–10% or greater than or equal to 10–15%, a decline in 6MWD > 50 m, or worsening dyspnea and quality of life scores. FVC is a reliable, valid, and responsive measure of clinical status in patients, and a decline of 2-6%, although small, represents a clinically important difference. FVC is used as a surrogate marker of disease severity and progression. DLCO is considered a standard predictor of survival. The distance walked in the 6MWT is used in a variety of pulmonary diseases and is predictive of mortality.

Investigational or Not Medically Necessary Uses

I. There is currently no evidence to suggest safety and/or efficacy with nitendanib (Ofev) or pirfenidone (Esbriet), when used for the treatment of bronchiolitis obliterans syndrome (BOS), lymphangioleiomyomatosis (LAM), non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), esophagogastric cancer, thyroid cancer, breast cancer, ovarian cancer, or pancreatic cancer. Further there is no evidence to support the use of nitendanib (Ofev) in combination with pirfenidone (Esbriet).

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

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
• Added nintedanib (Ofev) to the Moda Split Fill program • Added criteria for nintedanib (Ofev) new indication Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype [request is for nintedanib (Ofev) and member has greater than 10% fibrotic features confirmed by a high resolution computed tomographic (HRCT) scan and clinical signs of progression (eg. decline in %FVC with worsening of respiratory symptoms, **or** increasing extent of fibrotic changes on chest imaging)]. • Added criteria for baseline assessment [eg. forced vital capacity (%FVC) or carbon monoxide diffusing capacity (DLCO) or six minute walking distance (6MWD)]	06/2020
Criteria updated to new policy format. Specific changes include: Updated idiopathic pulmonary fibrosis (IPF) initial evaluation. Combined policies with pirfenidone (Esbriet) for the indication of idiopathic pulmonary fibrosis (IPF). Added new indication of systemic sclerosis-associated interstitial lung disease (SSc-ILD), SSc-ILD initial evaluation, investigational use, and renewal evaluation. Added new supporting evidences and references.	12/2019
Policy created	10/2014

Policy Type: PA/SP Pharmacy Coverage Policy: UMP139

Split Fill Management*

Description

Niraparib (Zejula) is an orally administered poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the treatment, or maintenance therapy, of ovarian, fallopian tube, or primary peritoneal cancer.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
niraparib (Zejula)	100 mg capsules	Treatment for: advanced ovarian, fallopian tube, or primary peritoneal cancer Maintenance for: recurrent or advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer	90 capsules/30 days

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., t*BRCAm)*; **OR**

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 thrity-three patients, who were in complete or partial response to first-line platinum-based chemotherapy, were randomized 2:1 to niraparib (Zejula) or matched placebo. Patients with and without homologous recombination deficiency (HRD, e.g. gBRCA*m*) were included. At the end of treatment period, niraparib (Zejula) treatment

arm showed a statistically significant improvement in median progression free survival (PFS) as compared to placebo arm.

A. Homologous recombination deficiency (HRD; e.g. gBRCA*m*) cohort: median PFS was 21.9 months in niraparib (Zejula) arm and 10.4 months in placebo arm (hazard ratio 0.43; 95% CI, 0.31 to 0.59; P<0.001)
B. Overall population (without HRD; gBRCA*m*) cohort: median PFS was 13.8 months in niraparib (Zejula) arm and 8.2 months in placebo arm (HR 0.62; 95% CI, 0.5 to 0.76; *p*<0.001).

None of the treated patients had a history of taking bevacizumab (Avastin). Therefore, efficacy and safety of niraparib (Zejula) after first-line therapy with bevacizumab (Avastin), or in combination with, bevacizumab (Avastin) is not supported.

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

1. Zejula [Prescribing Information]. Research Triangle Park, NC: GlaxoSmithKline LLC, 04/2020.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new indication and supporting evidence for first-line maintenance therapy in women with advanced ovarian cancer; Updated policy format to categorize recommendation for niraparib (Zejula) based treatment OR maintenance therapy; added split fill management	09/2020
Criteria transition into policy with the following updates made: addition of supporting evidence and investigation section, broke out the different indications (treatment versus maintenance therapy) due to the newly approved indication for late-line treatment in women with recurrent ovarian cancer, included 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.	11/2019
Criteria created	08/2017

nitisinone (Nityr™; Orfadin®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP140

Description

Nitisinone (Nityr; Orfadin) competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase (4HPPD), an enzyme present early in the tyrosine degradation pathway, thereby preventing the accumulation of toxic metabolites.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
nitisinone (nitisinone)	2 mg capsule	Hereditary tyrosinemia type 1	2 mg/kg/day
	5 mg capsule		
	10 mg capsule		
nitisinone (Nityr)	2 mg tablet		
	5 mg tablet		
	10 mg tablet		
nitisinone (Orfadin)	2 mg capsule		
	5 mg capsule		
	10 mg capsule		
	20 mg capsule		
	4 mg/mL suspension		

Initial Evaluation

I. Nitisinone (Nityr; Orfadin) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a provider who specializes in the treatment of genetic or metabolic disorders; **AND**
   B. A diagnosis of **hereditary tyrosinemia type 1 (HT-1)** when the following are met:
      1. Elevated succinylacetone (SA); **AND**
      2. Documentation of baseline plasma tyrosine level; **AND**
      3. Treatment will be used in conjunction with a diet restricted in tyrosine and phenylalanine

II. Nitisinone (Nityr; Orfadin) is considered <u>investigational</u> when used for all other conditions, including but not limited to:
   A. Alkaptonuria

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not established on therapy through the use of samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms (e.g. biochemical and/or clinical response).

Supporting Evidence

I. In patients with HT-1, tyrosine metabolism is interrupted due to a lack of the enzyme (fumarylacetoacetate hydrolase) needed in the last step of tyrosine degradation. Toxic metabolites of tyrosine, succinylacetoacetate (SAA) and succinylacetone (SA), accumulate and cause liver and kidney toxicity. Nitisinone (Nityr; Orfadin) competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase (4HPPD), an enzyme present early in the tyrosine degradation pathway, thereby preventing the build-up of the toxic metabolites SAA and SA.
II. Nitisinone (Nityr; Orfadin) must be used in conjunction with a diet restricted in tyrosine and phenylalanine to prevent further increased tyrosine levels. Dose is titrated as needed based on biochemical and/or clinical response. If the biochemical response is satisfactory, the dosage should be adjusted only according to body weight gain. Dose should not be adjusted according to tyrosine concentration.
III. Nitisinone (Nityr; Orfadin) should be started as early as possible (i.e. immediately after diagnosis of HT1 by blood or urine measurement of SA).
IV. If the biochemical parameters (except plasma SA) have not normalized within one month of starting therapy, the dose should be increased to 1.5 mg/kg/day. The dose of nitisinone should be adjusted to completely suppress excretion of SA; however, it may take as long as three months for complete suppression of SA to occur. A dose of 2 mg/kg/day may be needed, especially in infants; although, this dose should be considered maximal. Monitoring of the nitisinone blood levels is recommended for dose adjustment and also to check adherence.

Investigational or Not Medically Necessary Uses

I. Nitisinone (Nityr; Orfadin) has not been sufficiently evaluated in the following settings. Limited evidence is available; however, safety and efficacy have not been established for:
   A. Alkaptonuria

References

1. Orfadin [Prescribing Information]. Waltham, MA: Sobi, Inc; May 2019.
2. Nityr [Prescribing Information]. Cambridge, United Kingdom: Cycle Pharmaceuticals Ltd.; November 2018.
3. UpToDate, Inc. Disorders of tyrosine metabolism. UpToDate [database online]. Waltham, MA. Last updated August 08, 2019 Available at: http://www.uptodate.com/home/index.html.

Policy Implementation/Update:

Date Created	December 2019
Date Effective	December 2019
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date

obeticholic acid (Ocaliva®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP141

Description

Obeticholic acid (Ocaliva) is a Farnesoid X Receptor (FXR) agonist that works by suppressing bile acid synthesis and increasing bile acid transport out of the hepatocytes, thus reducing overall hepatic exposure to toxic levels of bile acids.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
obeticholic acid (Ocaliva)	5 mg tablets	Primary Biliary Cholangitis (PBC)	30 tablets/30 days
	10 mg tablets		

Initial Evaluation

I. Obeticholic acid (Ocaliva) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a gastroenterologist or hepatologist; **AND**
   B. A diagnosis of **Primary Biliary Cholangitis (PBC)** [i.e. primary biliary cirrhosis]; **AND**
      1. Diagnosis confirmed by **TWO** of the following:
         i. Alkalaine phosphate (e.g. ALP) level at least 1.5 times the upper limit of normal
         ii. Positive antimitochondrial antibodies (AMA) test
         iii. Histopathologic evidence (i.e. nonsuppurative cholangitis and destruction of small or medium-sized bile ducts); **AND**
      2. Treatment with ursodeoxycholic acid (e.g. Urso, Ursodiol) has been ineffective, contraindicated, or not tolerated; **AND**
         i. Inadequate response is defined as an alkaline phosphate level greater than 1.67 times the upper limit of normal after one year of treatment with ursodeoxycholic acid; **AND**
      3. Member has compensated liver disease (Child-Pugh A).

II. Obeticholic acid (Ocaliva) is considered investigational when used for all other conditions, including but not limited to:
   A. Non-alcoholic steatohepatitis (NASH)
   B. Non-alcoholic fatty liver disease (NAFLD)

C. Familial partial lipodystrophy
D. 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. Member has a diagnosis of **Primary Biliary Cholangitis (PBC)** [i.e. primary biliary cirrhosis]; **AND**
    A. Member has compensated liver disease (Child-Pugh A); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g. reduction of pruritus, reduced fatigue, or decrease in alkaline phosphate levels)

Supporting Evidence

I. Obeticholic acid (Ocaliva) is FDA-approved for the treatment of primary biliary cholangitis (PBC) when used in combination with ursodeoxycholic acid (UDCA) in adults with inadequate response to UDCA; or, as monotherapy in adults unable to tolerate UDCA.
II. Per the American Association for the Study of Liver Diseases (AASLD) guidelines, UDCA at a dose of 13 to 15 mg/kg/day is the first-line therapy for PBC.
III. Treatment response in PBC is monitored using liver biochemical values - specifically, serum ALP and total bilirubin. Improvements in liver tests are typically seen within a few weeks, with the majority of liver test improvements occurring within 6 to 9 months. About 20% of patients will have normalization of liver biochemistries after two years.
IV. Per guidelines, the benefit of obeticholic acid (Ocaliva) in patients with decompensated liver disease is unestablished. In September 2017, the FDA issued a warning regarding inappropriate dosing of obeticholic acid (Ocaliva) in patients with moderate to severe liver impairment (Child-Pugh-Turcotte B and C), which was associated with worsening PBC and death. Therefore, the use of obeticholic acid (Ocaliva) in patients with decompensated PBC is not recommended.

Investigational or Not Medically Necessary Uses

I. Obeticholic acid (Ocaliva) has not been sufficiently evaluated in the following settings:
    A. Non-alcoholic steatohepatitis (NASH)
        1. Obeticholic acid (Ocaliva) is being studied in an ongoing clinical trial that enrolled 2,480 participants. A total of 931 patients with stage F2–F3 fibrosis were included in the primary analysis [311 in the placebo group, 312 in the obeticholic acid (Ocaliva) 10 mg group, and 308 in the obeticholic acid (Ocaliva) 25 mg group]. An interim analysis was done after a minimum of 750 randomized patients with fibrosis stages F2 or F3 reached their actual or planned month-18 visit.
            - The primary endpoint of fibrosis improvement by at least one stage with no worsening of NASH was met by 37 (12%) patients in the placebo group, 55 (18%) patients in the obeticholic acid (Ocaliva) 10 mg group (p=0.045

vs placebo), and 71 (23%) patients in the obeticholic acid (Ocaliva) 25 mg group (p=0.0002 vs placebo).

- The primary endpoint of NASH resolution (based on no hepatocellular ballooning and no residual lobular inflammation) with no worsening of fibrosis **did not** meet statistical significance in the intent-to-treat population (25 [8%] patients in the placebo group vs 35 [11%] in the obeticholic acid (Ocaliva) 10 mg group [p=0·18] or 36 [12%] in the obeticholic acid (Ocaliva) 25 mg group [p=0·13]).
- Treatment-emergent adverse events occurred in 548 (83%) patients in the placebo group, 579 (89%) in the obeticholic acid (Ocaliva) 10 mg group, and 601 (91%) in the obeticholic acid (Ocaliva) 25 mg group.
- Pruritus was the most common adverse event and was seen in 123 (19%) patients in placebo group, 183 (28%) patients in the obeticholic acid (Ocaliva) 10mg group, and 336 (51%) patients in the obeticholic acid (Ocaliva) 25mg group.
- The end-of-study analysis will evaluate the effect of obeticholic acid (Ocaliva) on clinical outcomes (including progression to cirrhosis and all-cause mortality) and the long-term safety of obeticholic acid and will be completed once approximately 291 adjudicated clinical outcome events occur. Patients are expected to have a minimum follow-up time of approximately 4 years.

2. According to the practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association first line treatment for NASH is weight loss as it generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation.
3. Based on the data reviewed to date, the predicted benefit of obeticholic acid (Ocaliva) based on a surrogate histopathologic endpoint remains uncertain and does not sufficiently outweigh the potential risks for the treatment of patients with liver fibrosis due to NASH. Additional efficacy and safety data are needed to support its use in NASH.

B. Non-alcoholic fatty liver disease (NAFLD)
C. Familial partial lipodystrophy
D. Obesity

References

1. Ocaliva [Prescribing Information]. New York, NY: Intercept Pharmaceuticals, Inc. January 2018.
2. UpToDate, Inc. Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis (primary biliary cirrhosis). UpToDate [database online]. Waltham, MA. Updated February 11, 2019. Available at: http://www.uptodate.com/home/index.html.
3. UpToDate, Inc. Overview of the treatment of primary biliary cholangitis (primary biliary cirrhosis). UpToDate [database online]. Waltham, MA. Updated March 04, 2019. Available at: http://www.uptodate.com/home/index.html.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added supporting evidence for the investigational use in NASH	07/2020
Prior authorization criteria transitioned to policy format. Updated initial and renewal durations. Addition of specialist requirements. Addition of confirmed diagnosis and Child Pugh A classification. Further clarification of characteristics of inadequate response to ursodeoxycholic acid. Addition of renewal criteria.	12/2019
Policy created	06/2016

Policy Type: PA/SP Pharmacy Coverage Policy: UMP142

Description
Octreotide acetate (Sandostatin, Bynfezia Pen, Mycapssa) works by suppressing LH response to GnRH, decreasing splanchnic blood flow, and inhibiting the release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

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

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
octreotide acetate (generic, Sandostatin)	50 mcg/mL ampule, vial, syringe	Acromegaly	90 ampules, vials, syringes/30 days
		Metastatic carcinoid tumor	
		Vasoactive intestinal peptide tumor (VIPoma)	
	100 mcg/mL ampule, vial, syringe	Acromegaly	
		Metastatic carcinoid tumor	
		Vasoactive intestinal peptide tumor (VIPoma)	
	500 mcg/mL ampule, vial, syringe	Acromegaly	
		Metastatic carcinoid tumor	
		Vasoactive intestinal peptide tumor (VIPoma)	
	1000mcg/5mL (200 mcg/mL) vial	Acromegaly	9 vials/30 days
		Metastatic carcinoid tumor	23 vials/30 days
		Vasoactive intestinal peptide tumor (VIPoma)	14 vials/30 days
	5000mcg/5mL (1000 mcg/mL) vial	Acromegaly	2 vials/30 days
		Metastatic carcinoid tumor	5 vials/30 days
		Vasoactive intestinal peptide tumor (VIPoma)	3 vials/30 days
octreotide acetate (Bynfezia Pen)	7000mcg/2.8mL (2500 mcg/mL) prefilled injection pen	Acromegaly	2 pens/30 days
		Metastatic carcinoid tumor	4 pens/30 days
		Vasoactive intestinal peptide tumor (VIPoma)	2 pens/30 days
octreotide acetate (Mycapssa)	20 mg capsule	Acromegaly	112 capsules/28 days
Provider Administered Agents*			

octreotide acetate, mi-spheres (Sandostatin LAR)	10 mg vial	Acromegaly; Metastatic carcinoid tumor; Vasoactive intestinal peptide tumor (VIPoma)	N/A
	20 mg vial		
	30 mg vial		

**Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit.*

Initial Evaluation

I. **Octreotide acetate (Sandostatin, Bynfezia Pen, Mycapssa) and generic octreotide acetate** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. If requesting injectable brand octreotide acetate (Sandostatin, Bynfezia Pen): Treatment with generic octreotide has been ineffective, not tolerated, or is contraindicated; **AND**
   C. A diagnosis of one of the following:
      1. Acromegaly; AND
         i. Member has had inadequate response to, or cannot be treated with surgical resection and pituitary irradiation; **AND**
         ii. If requesting oral octreotide acetate (Mycapssa): member has a documented response and tolerability to treatment with long-acting octreotide injection (Sandostatin LAR) OR lanreotide (Somatuline Depot) injection; **AND**
            a. Provider rationale as to why continuation of therapy with long-acting octreotide injection (Sandostatin LAR) OR lanreotide (Somatuline Depot) injection is not appropriate (i.e., there is medical necessity for change outside of patient preference); **OR**
      2. **Metastatic carcinoid tumor; AND**
         i. Use is intended for the symptomatic management of severe diarrhea and/or flushing episodes; **AND**
         ii. The request is for injectable octreotide (e.g. generic octreotide acetate, Sandostatin, Bynfezia Pen); **OR**
      3. Vasoactive intestinal peptide tumors (VIPomas) [pancreatic neuroendocrine (islet cell) tumor, insulinoma, glucagonoma, somatostatinoma, and gastrinoma]; **AND**
         i. Use is intended for the symptomatic management of profuse watery diarrhea; **AND**
         ii. The request is for injectable octreotide (e.g. generic octreotide acetate, Sandostatin, Bynfezia Pen); **AND**

II. Octreotide (Sandostatin, Sandostatin LAR, Bynfezia Pen) is considered investigational when used for all other conditions.

III. Octreotide oral capsules (Mycapssa) are considered investigational when used for all other conditions, including but not limited to, metastatic carcinoid tumor and vasoactive intestinal peptide tumors (VIPomas).
   A. Octreotide capsules (Mycapssa) have only been studied and FDA-approved in the setting of long-term maintenance of acromegaly symptoms and is therefore considered

investigational when used for all other indications, including metastatic carcinoid tumors and VIPomas.

Renewal Evaluation

I. Disease response with improvement in patient's symptoms including reduction in symptomatic episodes (such as diarrhea, rapid gastric dumping, flushing), and/or stabilization of glucose levels, and/or decrease in size of tumor or tumor spread; **OR**

II. For **acromegaly** ONLY: Disease response as indicated by an improvement in signs and symptoms compared to baseline; **AND**

   1. Age-adjusted normalization of serum IGF-1; **OR**
   2. Reduction of growth hormone (GH) by random testing to < 1.0 mcg/L

Supporting Evidence

I. The 2014 Endocrine Society Practice Guidelines for Acromegaly recommend transsphenoidal surgery/surgical resection/debulking as primary therapy for Acromegaly patients, followed by radiation therapy for residual tumor mass following surgery. In patients with persistent disease following surgery, guidelines recommend use of somatostatin receptor ligands (SRLs) or pegvisomant as the initial adjuvant medical therapy.

II. Bynfezia Pen was approved via the 505 (b)(2) pathway and relies on the FDA's finding of safety and effectiveness for the previously approved drug Sandostatin (octreotide acetate injection). The FDA has found that Bynfezia Pen and Sandostatin are pharmacokinetically bioequivalent based on data from the comparative PK study submitted with the NDA. The FDA expects the benefits and risks of Bynfezia pen used at the proposed doses will be similar to the benefits and risks associated with Sandostatin for the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIPoma) secreting tumors.

III. Octreotide acetate oral capsules (Mycapssa) was approved for the treatment of Acromegaly ONLY by the FDA based on data from the randomized, double-blind, placebo controlled, phase 3 CHIASMA OPTIMAL study in Acromegaly patients who were previously treated with stable doses of long-acting SRLs (octreotide or lanreotide). The primary endpoint was the proportion of patients maintaining biochemical response, defined as IGF-1 ≤ 1.0 x ULN, studied in a population of adult patients age 18 and older who had evidence of active acromegaly disease and had an average IGF-1 of ≤ 1.0 x ULN on a stable dose of injectable octreotide or lanreotide. The primary endpoint was met, as 58% of patients receiving oral octreotide capsules maintained IGF-1 response versus the 19% receiving placebo (P=0.008). Octreotide acetate oral capsules (Mycapssa) were safe and well tolerated. No new or unexpected significant safety signals were observed during the trial. In the absence of head to head studies, long acting injectables remain the best value treatment for acromegaly and are preferred unless there is medical necessity for the oral product.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added Bynfezia Pen to policy with requirement for inadequate response to generic octreotide, unless not tolerated or contraindicated. Mycapssa capsules added in the setting of acromegaly requiring response with long acting octreotide injection or lanreotide (Somatuline Depot) injection; and requiring rationale for use of oral formulation over continuation of injectable long acting product. Removed trial and failure of bromocriptine from requirements for approval of injectable octreotide for acromegaly. Updated quantity limits of all products to align with diagnosis.	9/2020
Transitioned to policy format and updated the following: • Added age requirement of 18 years or older • For octreotide (Sandostatin), added requirement for inadequate response to generic octreotide, unless not tolerated or contraindicated • Removed octreotide (Sandostatin LAR) from the policy as it is excluded from coverage under the pharmacy benefit	12/2019
Previous review	10/2017
Criteria created	10/2016

olaparib (LYNPARZA®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP048

Description

Olaparib (Lynparza) is an orally administered poly (ADP-ribose) polymerase (PARP) enzymes inhibitor including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
olaparib (Lynparza)	100 mg tablets	Breast cancer, metastatic, HER2-negative, germline BRCA-mutated (gBRCAm); Ovarian cancer, advanced gBRCAm; Ovarian cancer, first-line maintenance therapy for gBRCAm or somatic BRCA-mutated (sBRCAm) or homologous recombination deficient-positive (HRD); Ovarian cancer, recurrent (maintenance therapy); Pancreatic cancer, first-line therapy for gBRCA-mutated, metastatic adenocarcinoma; Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated	120 tablets/30 days
	150 mg tablets		

Initial Evaluation

I. Olaparib (Lynparza) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in consultation with, a specialist in oncology; **AND**
   B. Not used in combination with other anti-cancer agents, unless otherwise outlined in the criteria below; **AND**

C. The patient has not progressed on or after prior PARP inhibitor therapy (e.g., niraparib [Zejula], rucaparib [Rubraca]); **AND**

D. A diagnosis of:

1. **Ovarian cancer, Recurrent Maintenance; AND**
   - i. Diagnosis of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer; **AND**
   - ii. Has completed at least TWO prior platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) chemotherapy regimens; **AND**
   - iii. The tumor is considered to be platinum-sensitive (i.e., the patient is responsive to their most recent platinum-based regimen, as defined by complete or partial response for more than 6 months); **AND**
   - iv. Provider attests, with supporting documentation, that member's recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) chemotherapy regimen; **OR**
2. **Ovarian cancer, First-line Maintenance; AND**
   - i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) of gBRCAm OR sBRCAm; **AND**
   - ii. Has not received bevacizumab in prior treatment; **OR**
     - **a.** Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gHRDm (homologous recombination deficient-positive mutation); **AND**
     - **b.** Member has had a positive response to prior bevacizumab treatment and bevacizumab will be continued; **AND**
   - iii. Diagnosis of advanced (stage ≥III) epithelial ovarian, fallopian tube, or primary peritoneal cancer; **AND**
   - iv. Has completed at least ONE prior platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
   - v. The tumor is considered to be platinum-sensitive (i.e., the patient is responsive to their most recent platinum-based regimen, as defined by a complete or partial response for more than 6 months); **AND**
   - vi. Provider attest with supporting documentation that member's epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) chemotherapy regimen; **OR**
3. **Ovarian cancer, Advanced; AND**
   - i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gBRCAm OR sBRCAm; **AND**
   - ii. Diagnosis of advanced (stage ≥III) epithelial ovarian, fallopian, or primary peritoneal cancer; **AND**
   - iii. Has progression of disease following THREE or more prior lines of chemotherapy; **OR**
4. **Breast cancer; AND**
   - i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gBRCAm; **AND**

ii. Diagnosis of HER2-negative, metastatic breast cancer; **AND**

iii. Has received prior treatment with both an anthracycline (e.g., doxorubicin) AND a taxane (e.g., paclitaxel) in the neoadjuvant, adjuvant, or metastatic setting; **AND**

iv. Has NOT received more than TWO prior chemotherapy regimens in the metastatic setting; **AND**

v. Has progression of disease on at least ONE prior endocrine therapy in the adjuvant or metastatic setting; **OR**

a. Endocrine therapy has been deemed inappropriate by the treating healthcare provider; **OR**

5. Pancreatic cancer, First-line Maintenance; AND

i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gBRCAm; **AND**

ii. Diagnosis of metastatic pancreatic adenocarcinoma; **AND**

iii. The member has received at least 16 weeks of continuous treatment with a platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin) that was administered as first-line therapy; **AND**

iv. Provider attests that the disease has not progressed while on first-line platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin); **OR**

6. Prostate cancer, Metastatic castration-resistant; AND

i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) alteration in at least **one** of the following HRR genes: ATM, BRCA1, BRCA2; **AND**

ii. Has progressed on prior enzalutamide or abiraterone treatment; **AND**

iii. Member has had a prior bilateral orchiectomy; **OR**

a. Used in combination with luteinizing-hormone-releasing hormone analog therapy (e.g. leuprolide (Eligard, Lupron), histrelin (Vantas))

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

A. Breast cancer without metastasis, and/or HER2-negative breast cancer, and/or breast cancer without gBRCAm

B. Pancreatic cancer without metastasis, and without gBRCAm

C. Metastatic, gBRCAm pancreatic cancer that has progressed on first line platinum-based chemotherapy

D. Metastatic, castration-resistant prostate cancer with a tumor mutation NOT listed above (including BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L)

E. Use after disease progression on or after prior PARP inhibitor therapy

F. Use in combination with other anti-cancer 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. Clinical documentation of response to treatment (e.g. stabilization of disease or decrease in tumor size/spread)

Supporting Evidence

I. In the pivotal trials for maintenance treatment of recurrent ovarian cancer and first-line maintenance therapy for ovarian cancer with gBRCAm or sBRCAm, eligible patients had completed at least ONE course of platinum-based chemotherapy.
II. In the pivotal trials for first-line maintenance therapy for ovarian cancer with gBRCAm or sBRCAm **non-eligible** patients included: patients with early stage disease (FIGO State I, IIA, IIB, or IIC) and patients with prior bevacizumab treatment.
III. Subjects were randomized to treatment allocation within eight weeks after completion of the last dose of platinum-based chemotherapy. The intent is that treatment is started within a reasonable timeframe consistent with a maintenance treatment plan (i.e., as close to 8 weeks as possible), but recognize that scheduling or other factors may impact the ability of a patient to start exactly within these first eight weeks. There can be some flexibility within reason but use clinical judgement and patient specific factors when assessing this criterion to ensure this is falling within the maintenance treatment timeframe vs subsequent therapy.
IV. In the pivotal trial for breast cancer with metastatic, HER2-negative and gBRCAm, eligible patients had received neoadjuvant, adjuvant, or treatment for metastatic disease with an anthracycline (unless it was contraindicated) and a taxane.
    - Approximately 70% of patients had received treatment in the metastatic setting; however, patients had received <u>no more than two</u> previous chemotherapy regimens for <u>metastatic</u> disease. More than two therapies in other settings (e.g., neoadjuvant, adjuvant) did not apply to this criterion.
    - Eligible patients in this trial could have hormone-receptor positive metastatic breast cancer (i.e., estrogen-receptor positive, progesterone-receptor positive, or both) or triple negative metastatic breast cancer. Patients with hormone-receptor positive disease had received at least one endocrine therapy (adjuvant therapy or therapy for metastatic disease) and had disease progression during therapy, unless they had disease for which endocrine therapy was considered to be inappropriate.
V. The pivotal trial (POLO), is a phase 3 trial that studied metastatic, gBRCAm pancreatic cancer; eligible patients had received a minimum of 16 weeks of first-line platinum based chemotherapy (cisplatin, carboplatin, or oxaliplatin) and had not progressed while on the first-line platinum based chemotherapy. The patients were randomized in a 3:2 ratio to receive maintenance olaparib (Lynparza) or placebo with the primary end point progression-free survival. The median progression-free survival was statistically significant, 7.4 months in the olaparib (Lynparza) arm

compared to 3.8 months in the placebo arm (HR 0.53 [95% CI, 0.35-0.81], p=0.0035). The interim analysis of overall survival showed no difference between the olaparib and placebo groups (median, 18.9 months vs. 18.1 months; hazard ratio for death, 0.91; 95% CI, 0.56 to 1.46; P=0.68). Additionally, quality of life was based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, there was no significant between-group differences in health-related quality of life, as indicated by the overall change from baseline in the global quality-of-life score (on a 100-point scale, with higher scores indicating better quality of life (between-group difference, −2.47 points; 95% CI, −7.27 to 2.33)).

- As it currently stands, treatment with olaparib (Lynparza) in the setting of metastatic gBRCam pancratic cancer showed no difference in overall survival (OS) and quality of life (QoL) when compared to placebo. Therefore, limited exception should be granted to those who do not meet the criteria for metastatic, gBRCAm pancreatic cancer as stated in this policy.
- The preferred systemic regimens for metastatic, gBRCAm pancreatic cancer include:
    i. FOLFIRINOX or modified FOLFIRINOX ± subsequent chemoradiation
    ii. Gemcitabine + albumin-bound paclitaxel ± subsequent chemoradiation

VI. PAOLA-1, the phase 3 trial that studied olaparib (Lynparza) as dual therapy with bevacizumab for maintenance therapy for advanced ovarian cancer, was a double-blind, randomized, placebo-controlled trial with the primary endpoint of progression free survival (PFS). The primary endpoint results of the predefined subgroups of HRD-positive, HRD-negative, or unknown found only a statistically significant difference in PFS in the HRD-positive subjects (HR: 0.33, 95% CI: 0.25, 0.45) and not the HRD-negative or unknown patients (HR: 0.92, 95% CI: 0.72, 1.17). Subjects enrolled in the trial had Stage III or IV disease and had a successful response to prior taxane-based chemotherapy.

VII. PROfound, the phase 3 trial that studied olaparib (Lynparza) in metastatic castration-resistant prostate cancer, enrolled men with homologous recombination repair (HRR) gene mutations in at least one of 15 prespecified HRR genes. Eligible patients had either a history of bilateral orchiectomy or were using luteinizing-hormone-releasing hormone analog therapy and had progressed on enzalutamide or abiraterone acetate or both, and were randomized (2:1) to receive either olaparib (Lynparza) or investigator's choice of enzalutamide or abiraterone acetate. Subjects were assigned cohorts based on HRR mutation (Cohort A: ATM, BRCA1, BRCA2; Cohort B: BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L). The primary endpoint was progression free survival (PFS) in Cohort A, and was significant between the treatment groups (HR: 0.34, 95% CI: 0.25, 0.47; p<0.001). Additionally, overall survival (OS) in Cohort A was significantly different between treatment groups (HR: 0.69, 95% CI: 0.50, 0.97; p=0.0175). PFS and OS were studied in Cohort B as exploratory endpoints and the results were not statistically significant and did not suggest improved outcomes with olaparib (Lynparza) over abiraterone or enzalutamide in those patients.

Investigational or Not Medically Necessary Uses

I. Breast cancer without metastasis, and/or HER2-negative breast cancer, and/or breast cancer without gBRCAm

A. The safety and efficacy of olaparib in the breast cancer setting has only been established in patients with metastatic, HER2-negative, and gBRCA mutation.

II. Pancreatic cancer without metastasis, and without gBRCAm

A. The safety and efficacy of olaparib in the pancreatic cancer setting has only been established in patients with metastatic disease with gBRCAm who has not progressed on the first-line platinum based chemotherapy.

III. Metastatic, gBRCAm pancreatic cancer that has progressed on first line platinum based chemotherapy

A. The safety and efficacy of olaparib in the pancreatic cancer setting has only been established in patients with metastatic disease with gBRCAm who has not progressed on the first-line platinum based chemotherapy.

IV. Use after disease progression on, or after, prior PARP inhibitor therapy

A. There is no evidence to support the use of a subsequent PARP inhibitor following progression of disease on another PARP inhibitor.

V. Metastatic castration-resistant prostate cancer with other tumor mutations (including BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L)

A. The phase 3 trial PROfound studied olaparib (Lynparza) versus enzalutamide or abiraterone in Cohort A (ATM, BRCA1, BRCA2) and Cohort B (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L). While statistically significant differences in progression free survival (PFS) and overall survival (OS) were found in treatment with olaparib (Lynparza) in Cohort A and pooled Cohort A+B, the same was not found in Cohort B alone. Exploratory endpoints found PFS in Cohort B (HR: 0.88; 95% CI: 0.58, 1.36) and OS in Cohort B (HR: 0.73; 95% CI: 0.45, 1.23) not to be statistically significant and does not indicate improved patient outcomes with use of olaparib (Lynparza) over enzalutamide or abiraterone in these patients.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Included new FDA expanded indications as first-line maintenance therapy in advanced HRD-positive ovarian cancer in combination with bevacizumab and metastatic castration-resistant prostate cancer with certain HRR mutations. Supporting evidence has been included in the policy.	10/2020
Included new FDA expanded indication as first-line maintenance therapy in pancreatic adenocarcinoma with metastasis, gBRCAm, and patients whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. The criteria for approval in the pancreatic adenocarcinoma setting is to label, and the supporting evidence has been included in this policy. Advanced ovarian cancer without gBRCAm has been removed from the investigational and experimental section since olaparib (Lynparza) is approved in ovarian cancer without gBRCAm or sBRCAm. Pancreatic cancer without gBRCAm, and pancreatic cancer that has progressed on platinum based chemotherapy have been added to the investigational and experimental section with supporting evidence. To improve clarity, for all the indications in this policy, the mutation documentation and the specific diagnoses have been separated out into individual criterion. Removal of toxicity question upon renewal as this is managed by the provider.	02/2020
Removal of DDID to reflect the most updated template version, removed the 8 weeks criterion around most recent platinum-based therapy in the setting of maintenance therapy in ovarian cancer; in place of the 8 weeks criterion, provider attestation and documentation is required instead.	12/2019
Criteria transitioned to policy format with the following additional updates: Included new FDA expanded indication as first-line maintenance therapy in ovarian cancer with gBRCAm or sBRCAm after complete or partial response to platinum-based chemotherapy. Additionally, a question was added to the renewal portion of this policy to assess for toxicity. Capsule formulation is no longer available; therefore, it has been removed from policy. Lastly, NCCN recognizes the term “deleterious” as pathogenic in the setting of gBRCAm OR sBRCAm; therefore, the policy has been updated to include the term “pathogenic” and “likely pathogenic” in parentheses next to the terms “deleterious” and “suspected deleterious” respectively.	03/2019
Criteria update: Added coverage criteria for ovarian cancer maintenance and metastatic breast cancer	02/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP143

Description

Omacetaxine mepesuccinate (Synribo) is a reversible protein synthesis inhibitor which binds to the A-site cleft of the ribosomal subunit to interfere with chain elongation and inhibit protein synthesis. It acts independently of BCR-ABL1 kinase-binding activity, and has demonstrated activity against tyrosine kinase inhibitor-resistant BCR-ABL mutations.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
omacetaxine mepesuccinate (Synribo)	3.5 mg vial	Chronic or accelerated phase CML	Initial: 28 vials/28 days Maintenance: 14 vials/28 days

Initial Evaluation

I. Omacetaxine mepesuccinate (Synribo) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
   C. A diagnosis of **chronic myelogenous leukemia (CML)** when the following are met:
      1. CML is in chronic or accelerated phase; **AND**
      2. Member has a complete blood count preformed routinely during treatment; **AND**
      3. Treatment with at least TWO of the below tyrosine kinase inhibitors (TKI) has been ineffective, contraindicated, or not tolerated:
         i. imatinib (Gleevec)
         ii. bosutinib (Bosulif)
         iii. nilotinib (Tasigna)
         iv. dasatinib (Sprycel)

II. Omacetaxine mepesuccinate (Synribo) is considered investigational when used for all other conditions.

Renewal Evaluation

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

Supporting Evidence

I. Omacetaxine mepesuccinate (Synribo) is indicated for the treatment of chronic or accelerated phase CML in patients resistant and/or intolerant to at least two tyrosine kinase inhibitors.
II. Myelosuppression with Grade 3/4 neutropenia, thrombocytopenia, and anemia commonly occur; generally reversible, although may require treatment delay and/or a reduction in the number of treatment days with future cycles. Myelosuppression may rarely be fatal. Blood counts should be monitored in induction and maintenance cycles.
III. Non-hematologic toxicities include Grade 3 or 4 hyperglycemia. Avoid use of omacetaxine mepesuccinate (Synribo) in the setting of poorly controlled diabetes.
IV. Within the pivotal trial, disease progression was defined as reduction of cells expressing Philadelphia chromosome mutation, normalization of white blood cells, or until patient is no longer achieving clinical treatment benefit.
V. Dosing with omacetaxine mepesuccinate (Synribo) in the initial phase is 1.25 mg/m2 subcutaneously twice daily for 14 consecutive days every 28 days, over a 28-day cycle. This cycle is repeated at this dosing every 28 days until patients achieve a hematologic response. Following hematologic response, the maintenance dosing regimen is initiated, which is 1.25 mg/m2 subcutaneously twice daily for 7 consecutive days every 28 days, over a 28-day cycle.

Investigational or Not Medically Necessary Uses

I. There is limited to no evidence to support the use of omacetaxine mepesuccinate (Synribo) in any other condition.

References

1. Synribo [Prescribing Information]. North Wales, PA: Teva Pharmaceuticals USA Inc; November 2019.
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Policy Implementation/Update:

Date Created	February 2013
Date Effective	February 2013
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Extend approval duration to six months for initial approvals and 12 months for renewals. Required agent be used as monotherapy and not in combination with other oncologic medications.	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP175

Description

Omalizumab (Xolair) is a subcutaneously administered monoclonal antibody that binds to IgE causing the IgE receptors to downregulate and limit the degree of release of the mediators of allergic response.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
omalizumab (Xolair)	75 mg/0.5mL prefilled syringe	Allergic asthma	1 syringe per 28 days
		Systemic mastocytosis	
		Chronic rhinosinusitis with nasal polyposis (CRSwNP)	
	150 mg/mL prefilled syringe	Allergic asthma	1 syringe per 28 days
		Chronic idiopathic urticaria (CIU)	
		Systemic mastocytosis	
		Chronic rhinosinusitis with nasal polyposis (CRSwNP)	
	150 mg vial	Allergic asthma	1 vial per 28 days
		Chronic idiopathic urticaria (CIU)	
		Systemic mastocytosis	
		Chronic rhinosinusitis with nasal polyposis (CRSwNP)	

Initial Evaluation

I. Omalizumab (Xolair) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); **AND**
   B. Must <u>not</u> be used in combination with another monoclonal antibody (e.g., benralizumab, dupilumab, mepolizumab, reslizumab, etc.); **AND**
   C. A diagnosis of one of the following:
      1. Moderate to severe persistent allergic asthma; AND
         i. Member is six years of age or older; **AND**
         ii. Member has a positive skin test or in vitro reactivity to a perennial aeroallergen; **AND**
         iii. Member <u>must</u> weigh <u>between</u> 20 kg (44 lbs.) and 150 kg (330 lbs.); **AND**

iv. Member has a serum total IgE level, measured before the start of treatment, of either:
    a. ≥ 30 IU/mL and ≤ 700 IU/mL in members age ≥ 12 years; **OR**
    b. ≥ 30 IU/mL and ≤ 1300 IU/mL in members age 6 to <12 years; **AND**

v. Member has **MODERATE** asthma as defined by one of the following:
    a. Daily symptoms
    b. Nighttime awakenings > 1x/week but not nightly
    c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs daily
    d. Some limitation to normal activities
    e. Lung function (percent predicted FEV1) >60%, but <80%
    f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to mild asthma; **OR**

vi. Member has **SEVERE** asthma as defined by one of the following:
    a. Symptoms throughout the day
    b. Nighttime awakenings, often 7x/week
    c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs several times per day
    d. Extremely limited normal activities
    e. Lung function (percent predicted FEV1) <60%
    f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**

vii. Member is currently being treated with:
    a. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
        i. One additional asthma controller medication (e.g., long-acting beta-2 agonist [LABA] {e.g., Serevent Diskus}, long-acting muscarinic antagonist [LAMA] {e.g., Spiriva Respimat}, leukotriene receptor antagonist [e.g., Singular], or theophylline); **OR**
    b. A maximally tolerated ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **OR**

2. Chronic idiopathic urticaria (CIU); **AND**

i. Member is 12 years of age or older; **AND**

ii. Underlying cause of the member's condition is NOT considered to be any other allergic condition(s) or other form(s) of urticaria; **AND**

iii. Member is avoiding triggers (e.g., NSAIDs, etc.); **AND**

iv. Documented baseline score from an objective clinical evaluation tool, such as: urticaria activity score (UAS7), angioedema activity score (AAS), Dermatology Life Quality Index (DLQI), Angioedema Quality of Life (AE-QoL), or Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL); **AND**

v. Member had an inadequate response to a minimum (1) month trial on previous therapy of a second-generation H1-antihistamine product*; **AND**

vi. Member had an inadequate response to a minimum (1) month trial on previous therapy of at least **one** of the following:
    1. Updosing/dose advancement (up to 4-fold) of a second generation H1-antihistamine*
    2. Add-on therapy with a leukotriene antagonist (e.g., montelukast, zafirlukast, etc.)
    3. Add-on therapy with another H1-antihistamine*
    4. Add-on therapy with a H2-antagonist (e.g. ranitidine, etc.)
    5. Add-on therapy with cyclosporine; **OR**

3. Systemic mastocytosis; AND

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

ii. Used for the prevention of **one** of the following:
    a. Chronic mast-cell-mediator-related cardiovascular (e.g., pre-syncope, tachycardia, etc.) or pulmonary (e.g., wheezing, throat-swelling, etc.) symptoms insufficiently controlled by conventional therapy (e.g., H1 or H2 blockers or corticosteroids); **OR**
    b. Unprovoked anaphylaxis; **OR**
    c. Hymenoptera or food-induced anaphylaxis in members with a negative test for specific IgE antibodies or a negative skin test; **OR**

iii. Used to improve tolerance while on immunotherapy (i.e., venom immunotherapy [VIT]); **OR**

4. Chronic rhinosinusitis with nasal polyposis (CRSwNP); AND

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

ii. Member must weigh between 30 kg (66 lbs.) and 150 kg (330 lbs.); **AND**

iii. Member has a serum total IgE level ≥ 30 IU/mL and ≤ 1500 IU/mL measured before the start of treatment; **AND**

iv. Provider attests that the member has ALL of the following:
    a. Diagnosis of bilateral sinonasal polyposis as evidenced by an endoscopy or computed tomography (CT); **AND**
    b. Member has impaired Health-Related Quality of Life due to ongoing nasal congestion, blockage, or obstruction with moderate to severe symptom severity; **AND**
    c. Member has at least **one** of the following symptoms:
        i. Nasal discharge
        ii. Facial pain or pressure
        iii. Reduction or loss of smell; **AND**

v. 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**

vi. Background intranasal corticosteroid will be continued with the use of omalizumab (Xolair), unless contraindicated.

II. Omalizumab (Xolair) is considered investigational when used for all other conditions, including but not limited to:
   A. Management of Immune Checkpoint Inhibitor related toxicity
   B. Esophagitis
   C. Interstitial cystitis
   D. Painful bladder syndrome
   E. Eosinophilic bronchitis
   F. Multi-food oral immunotherapy
   G. Bullous pemphigoid
   H. Peanut allergy
   I. Chronic spontaneous urticaria
   J. Solar urticaria
   K. Chronic urticaria
   L. Cholinergic urticaria
   M. Seasonal allergic rhinitis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, dupilumab, mepolizumab, reslizumab, etc.); **AND**
IV. A diagnosis of one of the following:
   i. Moderate to severe persistent allergic asthma; AND
      1. Member must weigh between 20 kg (44 lbs.) and 150 kg (330 lbs.); **AND**
      2. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **OR**
   ii. **Chronic idiopathic urticaria (CIU)**; **AND**
      1. Member has exhibited improvement or stability of disease symptoms from baseline using objective clinical evaluation tools (e.g., urticaria activity score [UAS7], angioedema activity score [AAS], Dermatology Life Quality Index [DLQI], Angioedema Quality of Life [AE-QoL], or Chronic Urticaria Quality of Life Questionnaire [CU-Q2oL]); **AND**
      2. Submitted current UAS7, AAS, DLQI, AE-QoL, or Cu-Q2oL was recorded within the past **30** days; **OR**
   iii. **Systemic mastocytosis**; **AND**
      1. Member has exhibited improvement or stability of disease symptoms compared to baseline (e.g., decreased frequency of exacerbations); **OR**
   iv. Chronic rhinosinusitis with nasal polyposis (CRSwNP); AND
      1. Member must weigh between 30 kg (66 lbs.) and 150 kg (330 lbs.); **AND**

2. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in nasal congestion/obstruction severity, reduction in nasal polyps); **AND**
3. Background intranasal corticosteroid (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of omalizumab (Xolair), unless contraindicated.

Supporting Evidence

I. There is a lack of evidence supporting treatment with dual use of biologic therapies and a potential for increased risk of side effects.

II. Omalizumab (Xolair) is FDA approved for moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (ICS), as add-on maintenance treatment for patients 18 years of age with chronic rhinosinusitis with nasal polyps (CRSwNP), and as chronic idiopathic urticaria in patients 12 years of age and older who remain symptomatic despite H1 antihistamine treatment.

- Omalizumab (Xolair) is not FDA approved for use in the setting of systemic mastocytosis; however, it is compendia recommended.

III. Omalizumab (Xolair) **prefilled syringes** have been FDA approved for self-administration for the treatment of asthma in patients 6 years and older, chronic idiopathic urticaria (CIU) in patients 12 years and older, and nasal polyps in patients age 18 years and older. According to the package insert, therapy should be initiated in a healthcare setting. Once therapy has been safely established, the healthcare provider may determine whether self-administration of Xolair prefilled syringe is appropriate, based on careful assessment of risk for anaphylaxis and risk reduction strategies. Patient-specific factors considered when selecting patients for self-administration include the following criteria:

- Patient should have no prior history of anaphylaxis, including to XOLAIR or other agents, such as latex, foods, drugs, biologics, etc.
- Patient should receive at least 3 doses of XOLAIR under the guidance of a healthcare provider with no hypersensitivity reactions
- Patient or caregiver is able to recognize symptoms of anaphylaxis
- Patient or caregiver is able to treat anaphylaxis appropriately
- Patient or caregiver is able to perform subcutaneous injections with XOLAIR prefilled syringe with proper technique according to the prescribed dosing regimen and Instructions for Use

IV. Moderate to severe persistent allergic asthma

- For patients 12 years of age and older, omalizumab (Xolair) was studied in 3 randomized, double-blind, placebo-controlled, multicenter trials. The patients enrolled in these trials were 12 to 76 years of age, with moderate to severe persistent asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE level between 30 and 700 IU/mL and body weight ≤150 kg. Patients with IgE levels less than 30 IU/mL, greater than 700 IU/mL, or a weight greater than 150 kg have not

been studied and efficacy has not been demonstrated in a randomized controlled clinical trial.

i. Trials 1 and 2: All patients were symptomatic and were treated with ICS/SABA. The primary endpoint was mean number asthma exacerbations per patient during steroid stable phase versus steroid reduction phase in comparison to placebo. In the stable steroid phase, the mean number of exacerbations per patient was 0.2 in the active arm compared to 0.3 in the placebo arm, p-value=0.005 (Trial 1) and 0.1 in the active arm compared to 0.4 in the placebo arm, p-value<0.001 (Trial 2). In the steroid reduction phase, the mean number of exacerbations per patient was 0.2 in the active arm compared to 0.4 in the placebo arm, p-value=0.004 (Trial 1) and 0.2 in the active arm compared to 0.3 in the placebo arm, p-value<0.001 (Trial 2).

ii. Trial 3: Long-acting beta2-agonists were allowed. Patients received at least 1000 mcg/day fluticasone propionate and a subset also received oral corticosteroids (OCS). The primary endpoint was percentage of patients with at least 1 exacerbation during steroid stable phase versus steroid reduction phase in comparison to placebo. In the stable steroid phase, the treatment difference in percentage of patients with at least one exacerbation was 0.9 (95% CI -9.7, 13.7) in the ICS only arm compared to 9.8 (95% CI -10.5, 31.4) in the OCS/ICS arm. In the steroid reduction phase, the treatment difference in percentage of patients with at least one exacerbation was -4.4 (95% CI -17.6, 7.4) in the ICS only arm compared to -0.2 (95% CI -22.4, 20.1) in the OCS/ICS arm.

- For patients 6 to <12 years of age, omalizumab (Xolair) was studied in one double-blind, placebo controlled, multi-center trial. All patients were required to have a baseline IgE level between 30 and 1300 IU/mL and body weight between 20 to 150 kg. The primary endpoint was the rate of asthma exacerbations during the 24-week, fixed steroid treatment phase, which was 0.45 in the active arm compared to 0.64 in the placebo arm (RR 0.69, 95% CI 0.53, 0.9).
- The Global Initiative for Asthma (GINA) 2020 update recommends the addition of respiratory biologics, with respect to their allergic biomarkers, after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 (medium dose ICS-LABA) or Step 5 (high dose ICS-LABA) therapy. Other controller options for Step 4 include high dose ICS-LABA or add-on tiotropium, or add-on LTRA. Other controller options for Step 5 include add-on anti-IL5, or add-on low dose OCS, though guidelines note to consider side effects.

V. Chronic idiopathic urticaria (CIU)

- Omalizumab (Xolair) was studied in two placebo-controlled, multiple-dose clinical trials. Patients received omalizumab (Xolair) 75 mg, 150 mg, or 300 mg or placebo by subcutaneous injection every 4 weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. Per the prescribing label, the 75-mg dose did not demonstrate consistent evidence of efficacy and is not approved for use in CIU. Clinical trials required a UAS7 score of greater than or equal to 16 with weekly reassessments to

objectively measure treatment benefit. The primary endpoints were mean weekly itch severity score and weekly hive count.

	XOLAIR 75mg	XOLAIR 150mg	XOLAIR 300mg	Placebo
n	77	80	81	80
Weekly Itch Severity Score				
Mean Baseline Score (SD)	14.5 (3.6)	14.1 (3.8)	14.2 (3.3)	14.4 (3.5)
Mean Change Week 12 (SD)	−6.46 (6.14)	−6.66 (6.28)	−9.40 (5.73)	−3.63 (5.22)
Difference in LS means vs. placebo	−2.96	−2.95	−5.80	
95% CI for difference	−4.71, −1.21	−4.72, −1.18	−7.49, −4.10	-
Weekly Hive Count Score †				
Mean Baseline Score (SD)	17.2 (4.2)	16.2 (4.6)	17.1 (3.8)	16.7 (4.4)
Mean Change Week 12 (SD)	−7.36 (7.52)	−7.78 (7.08)	−11.35 (7.25)	−4.37 (6.60)
Difference in LS means vs. placebo	−2.75	−3.44	−6.93	
95% CI for difference	−4.95, −0.54	−5.57, −1.32	−9.10, −4.76	-

VI. Systemic mastocytosis

- Omalizumab (Xolair) is recommended per NCCN guidelines for Systemic Mastocytosis for the treatment of mast-cell-mediator-related cardiovascular or pulmonary symptoms after prior trial of an H1 blocker, H2 blocker, and corticosteroids. Use of omalizumab (Xolair) for the management of Systemic Mastocytosis is supported by case studies and prospective reviews, though no clinical trials have been completed. Omalizumab (Xolair) has been found to prevent mast-cell-mediator-related cardiovascular or pulmonary symptoms despite use of conventional therapies and has been shown to improve tolerance while on immunotherapy.

VII. Chronic rhinosinusitis with nasal polyposis (CRSwNP)

- Omalizumab (Xolair) was studied as an add-on therapy with background intranasal corticosteroid in adult patients with CRSwNP with inadequate response to intranasal corticosteroids. Omalizumab (Xolair) was evaluated in two identical phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter trials. Trials enrolled patients aged 18 through 75 years with persistent bilateral nasal polyps, nasal congestion, impaired HRQoL, and weight 30-150 kg and serum IgE level 30- 1500 IU/mL. The primary endpoints were change from baseline to week 24 in endoscopic nasal polyp score (NPS) and mean daily nasal congestion score (NCS). Key secondary endpoints were change from baseline at week 24 in Sino-Nasal Outcome Test-22 (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, and Asthma Quality of Life Questionnaire (AQLQ).

	POLYP 1			**POLYP 2**		
	PBO N=66	**OMA N=72**	**Treatment Difference (95% CI), p-value**	**PBO N=65**	**OMA N=62**	**Treatment Difference (95% CI), p-value**
Primary Endpoint						
NPS (range, 0-8)	0.06 (0.16)	-1.08 (0.16)	-1.14 (-1.59 to -0.69) p<0.0001	-0.31 (0.16)	-0.9 (0.19)	-0.59 (-1.05 to 0.12) p<0.14
NCS (range, 0-3)	-0.35 (0.11)	-0.89 (0.1)	-0.55 (-0.84 to -0.25) p<0.0004	-0.20 (0.11)	-0.70 (0.11)	-0.50 (-0.80 to -0.19) p<0.0017
Secondary Endpoint						
SNOT-22 score (range, 0-110)	-8.58 (2.08)	-24.70 (2.01)	-16.12 (-21.86 to -10.38)	-6.55 (2.19)	-21.59 (2.25)	-15.04 (-21.26 to -8.82)

			p<0.0001			p<0.0001
UPSIT score (range, 0-40)	0.63 (0.90)	4.44 (0.84)	3.81 (1.38-6.24) p<0.0024	0.44 (0.81)	4.31 (0.83)	3.86 (1.57-6.15) p<0.0011
AQLQ score, OR of MCID (≥0.5-point improvement)	OR 3.71 (95% CI 1-13.71, p=0.0492)			OR 4.04 (95% CI 1.07-15.25, p=0.0396)		

MCID: minimal clinically important difference

- The American Academy of Allergy, Asthma, and Immunology (AAAAI), American College of Allergy, Asthma, and Immunology (ACAAI), and Joint Council of Allergy, Asthma, and Immunology (JCAAI) 2014 guidelines recommend short-term treatment with oral steroids in patients with CRSwNP "because it decreases nasal polyp size and symptoms". Additionally, guidelines recommend both intranasal corticosteroids and omalizumab for treatment of CRSwNP.

VIII. Abbreviated list of H1 antihistamine products:

*H1 Antihistamine Products (not all inclusive)
• fexofenadine • loratadine • desloratadine • cetirizine • levocetirizine • clemastine • diphenhydramine • chlorpheniramine • hydroxyzine • cyproheptadine • brompheniramine • triprolidine • dexchlorpheniramine • carbinoxamine

Investigational or Not Medically Necessary Uses

I. Omalizumab (Xolair) has not been adequately studied for the following conditions and does not have established safety and efficacy in these populations:
   A. Management of Immune Checkpoint Inhibitor related toxicity
      i. Though use is supported by NCCN guidelines for Management of Immunotherapy-related toxicities, there are no clinical trials demonstrating clinical efficacy or safety of the use of omalizumab (Xolair) in the treatment of Immune Checkpoint Inhibitor related toxicity.
   B. Ongoing clinical trials for the following conditions without outcomes demonstrating efficacy of treatment:
      i. Esophagitis
      ii. Interstitial cystitis
      iii. Painful bladder syndrome
      iv. Eosinophilic bronchitis
      v. Multi-food oral immunotherapy
      vi. Bullous pemphigoid

vii. Peanut allergy
viii. Chronic spontaneous urticaria
ix. Solar urticaria
x. Chronic urticaria
xi. Cholinergic urticaria
xii. Seasonal allergic rhinitis

Appendix

I. Table 1: Indication and dosing

Indication	Dose
Allergic Asthma	75 to 375 mg administered subcutaneously by a health care provider every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See tables below.
Chronic idiopathic urticaria	150 or 300 mg administered subcutaneously by a health care provider every 4 weeks. Dosing is not dependent on serum IgE (free or total) level or body weight.
Chronic rhinosinusitis with nasal polyposis	75 to 600 mg SC administered subcutaneously by a health care provider every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See tables below.
All other indications	150 or 300 mg administered subcutaneously by a health care provider every 4 weeks. Dosing is not dependent on serum IgE (free or total) level or body weight.

II. Table 2: Weight based dosing every 4 weeks in members ≥ 12 years

Omalizumab Doses Administered Every 4 Weeks (mg) in members ≥ 12 years				
Pre-treatment serum IgE (IU/mL)	**Body weight (kg)**			
	30 to 60	**> 60 to 70**	**> 70 to 90**	**> 90 to 150**
≥ 30 to 100	150	150	150	300
> 100 to 200	300	300	300	See the following table.
> 200 to 300	300	See the following table.	See the following table.	See the following table.

III. Table 3: Weight based dosing every 2 weeks in members ≥ 12 years

Omalizumab Doses Administered Every 2 Weeks (mg) in members ≥ 12 years				
Pre-treatment serum IgE (IU/mL)	**Body weight (kg)**			
	30 to 60	**> 60 to 70**	**> 70 to 90**	**> 90 to 150**
> 100 to 200	See previous table.	See previous table.	See previous table.	225
> 200 to 300	See previous table.	225	225	300
> 300 to 400	225	225	300	Do not dose.
> 400 to 500	300	300	375	Do not dose.
> 500 to 600	300	375	Do not dose.	Do not dose.
> 600 to 700	375	Do not dose.	Do not dose.	Do not dose

IV. Table 4: Weight based dosing every 2 or 4 weeks for in members who begin Xolair between the ages of 6 to <12 years

Omalizumab Doses Administered Every 2 or 4 Weeks (mg) for Pediatric Members with Asthma Who Begin Xolair Between the Ages of 6 to <12 Years											
Pre-treatment IgE (IU/mL)	Dosing Freq. (weeks)	Body Weight (kg)									
		20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
30-100	4	75	75	75	150	150	150	150	150	300	300
>100-200		150	150	150	300	300	300	300	300	225	300
>200-300		150	150	225	300	300	225	225	225	300	375
>300-400		225	225	300	225	225	225	300	300		
>400-500		225	300	225	225	300	300	375	375		
>500-600		300	300	225	300	300	375				
>600-700		300	225	225	300	375					
>700-900	2	225	225	300	375						
>900-1100		225	300	375							
>1100-1200		300	300								
>1200-1300		300	375								

Do Not Dose

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Policy Implementation/Update:

Action and Summary of Changes	Date
Update to supporting evidence (self-administration of Xolair)	05/2021
Updated policy to include chronic rhinosinusitis with nasal polyposis (CRSwNP) indication. Updated policy to include route of administration under Description, PBO program under Quantity Limits. For Initial Evaluation: added medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); asthma: removed moderate and severe asthma definition table in supporting evidence and built into criteria set, revised verbiage of previous combination therapy use and added “;OR a maximally tolerated ICS/LABA combination product”. For Renewal Evaluation: asthma: revised to updated renewal verbiage and consolidated list of clinical improvement examples; CIU and systemic mastocytosis: revised to updated renewal verbiage. For supporting evidence: removed subjective verbiage and included more detailed information regarding each policy indication.	03/2021
Convert to Policy format. Removed Management of Immune Checkpoint Inhibitor related toxicity criteria to investigational rational given lack of clinical evidence to support. Removed toxicity assessment in renewal portion as this is managed by the provider.	02/2020
Previous reviews	10/2019, 10/2018, 06/2018, 03/2018, 12/2017, 09/2017, 06/2017, 03/2017,

	12/2016, 09/2016, 07/2016, 07/2015, 09/2014, 04/2014, 02/2013, 06/2012
Policy created	01/2012

Policy Type: PA Pharmacy Coverage Policy: UMP180

Description

Omnipod Dash is an insulin delivery system used to manage blood glucose in patients with diabetes mellitus that are insulin dependent.

Length of Authorization

- Initial: One year
- Renewal: One year

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Omnipod	Pod	Diabetes Mellitus	15 pods/30 days
Omnipod Dash Pod	5 pack Pod		15 pods/30 days

Initial Evaluation

I. Omnipod, Omnipod Dash may be considered medically necessary when the following criteria are met:
   A. A diagnosis of one of the following:
      1. **Type I Diabetes Mellitus**; **OR**
      2. **Type II Diabetes Mellitus; AND**
         i. Member is insulin dependent; **AND**
         ii. Documentation of multiple injections of insulin per day (e.g more than 2 injections per day); **AND**
         iii. Documentation of member ability to self-test glucose at least 4 times daily while on insulin; **AND**
         iv. Documentation of member inability to self-inject insulin (e.g. unable to draw insulin from a vial or handle insulin pen); **OR**
            a. Documentation of member inability to self-adjust insulin dose (e.g sliding scale dosing).

II. Omnipod, Omnipod Dash is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. Non- insulin dependent Type II Diabetes Mellitus

Renewal Evaluation

I. Member has received a prior 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., management of blood glucose levels, A1c].

Supporting Evidence

I. Omnipod, Omnipod Dash Pod is an insulin delivery system that can provide up to 72 hours of continuous insulin delivery. It is a wearable Pod that is waterproof and can be worn anywhere the member would administer an injection. The Omnipod Dash system is designed to use rapid-acting U-100 insulin which the member would fill into the Pod. The Pod receives insulin delivery instructions from the Personal Diabetes Manager (PDM), a handheld device that controls and monitors the Pod's operations using wireless technology.
II. The pods are sold in a box of 5, and each pod has an approved wear time of 72 hours.

Investigational or Not Medically Necessary Uses

I. Non- insulin dependent Type II Diabetes Mellitus
   A. Use of Omnipod, Omnipod Dash insulin delivery system is not medically necessary for Type II Diabetes Mellitus in members that are not dependent on insulin.

References

1. Omnipod Dash [Prescribing Information]. Acton, MA: Insulet Corporation. https://www.myomnipod.com/AboutDASH

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy updated to add Omnipod and increase quantity level limits to allow every 48-hour change	03/2021
Policy created	04/2020

Policy Type: PA Pharmacy Coverage Policy: UMP144

Description

Methylnaltrexone bromide (Relistor), naldemedine (Symproic), and naloxegol (Movantik) are orally administered mu-opioid antagonists that act specifically in the peripheral tissues with inhibited central nervous system penetration at recommended dosages.

Length of Authorization

- Initial: Three months
- Renewal: 6 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
methylnaltrexone bromide (Relistor)	150 mg tablets	Treatment of opioid-induced constipation in adults with chronic non-cancer pain Treatment of opioid-induced constipation with advanced illness or pain caused by active cancer requiring opioid dosage escalation	90 tablets/30 days
	12 mg vial/syringe		30 single use vials or syringes/30 days
	8 mg vial/syringe		30 single use vials or syringes/30 days
naldemedine (Symproic)	0.2 mg tablets	Treatment of opioid-induced constipation in adults with chronic non-cancer pain	30 tablets/30 days
naloxegol (Movantik)	12.5 mg tablets		30 tablets/30 days
	25 mg tablets		30 tablets/30 days

Initial Evaluation

I. Methylnaltrexone bromide (Relistor), naldemedine (Symproic), and naloxegol (Movantik) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Diagnosis of **Opioid-Induced Constipation (OIC)** when the following are met:
      1. Treatment with the following has been ineffective, contraindicated, or not tolerated:
         i. Two different types of agents from the following OTC laxatives:
            a. Stool softener (e.g. docusate sodium); **OR**
            b. Osmotic agent (e.g. polyethylene glycol); **OR**
            c. Stimulant laxative (e.g. sennoside); **OR**
            d. Other; **AND**

ii. If the request is for methylnaltrexone bromide (Relistor):
    a. Treatment with all of the following has been ineffective, contraindicated, or not tolerated:
        i. naloxegol (Movantik); **AND**
        ii. naldemedine (Symproic)

II. Methylnaltrexone (Relistor), naldemedine (Symproic) and naloxegol (Movantik) are considered investigational when used for all other conditions, including but not limited to:
    A. Constipation not induced by opioids
    B. Post-operative ileus

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
III. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
IV. Member is continuing to receive chronic opioids; **AND**
V. Member has shown an improvement in the number of bowel movements they are having

Supporting Evidence

I. The American Gastroenterological Association (AGA) guidelines recommend the use of naloxegol (Movantik) and naldemedine (Symproic) for laxative-resistant patients with OIC. Methylnaltrexone bromide (Relistor) was given a conditional recommendation for laxative-resistant patients with OIC as the evidence was considered low quality. The AGA did not make a recommendation for lubriprostone (Amitiza®) as the evidence was low quality and inconsistent, with one trial not showing any statistical difference from placebo.
II. Methylnaltrexone bromide (Relistor) was studied in four trials compared against placebo. Patients were not on any background therapies in studies one and two. Studies four and five allowed patients to continue on their regular laxative regimen. The evidence is considered low quality with some studies having high rates of dropout and endpoints evaluated in studies four and five having unknown clinical benefit for patients.
    - Study one and two were randomized, double-blind, placebo-controlled trials evaluating 713 patients with OIC and chronic non-cancer pain. Methylnaltrexone bromide (Relistor) tablets and injection demonstrated a statistically significant response for proportion of responders compared to placebo. The percent difference was 13% (CI 3%, 23%) for study one and 20% (CI 10%, 31%) for study two.
    - Study three was a long-term, open-label, uncontrolled trial looking at 1,034 patients with OIC and chronic non-cancer pain. Safety was the primary endpoint with the most common adverse events being abdominal pain, diarrhea, nausea, and

psychiatric disorders. The mean change in bowel movements from baseline was 1.5 bowel movements per week (p<0.001).

- Study four and five were double-blind, placebo-controlled trials evaluating 287 patients with OIC and advanced illness (patients receiving palliative opioid therapy). Methylnaltrexone bromide (Relistor) injection demonstrated a statistically significant improvement in the proportion of patients with a rescue-free laxation within four hours of study medication compared to placebo. Results from study four were 62%, 58%, 14% (p<0.0001) for the 0.15 mg/kg dose, 0.3 mg/kg dose, and placebo, respectively, and study five results were 48% and 16% (p<0.0001) for methylnaltrexone bromide (Relistor) and placebo, respectively.

III. Naloxegol (Movantik) was studied in two randomized, double-blind, placebo-controlled trials in patients with OIC and chronic non-cancer pain. The primary endpoint for both studies evaluated response to therapy defined as ≥3 spontaneous bowel movements (SBMs) per week and a change from baseline of ≥1 SBM per week for at least nine out of the 12 study weeks and three out of the last four study weeks.

- Study one and two evaluated 1,352 patients comparing 12.5 mg and 25 mg of naloxegol (Movantik) against placebo. There was a statistically significant difference for both strengths compared to placebo in study one and only the 25 mg strength in study two. A treatment difference of 11.4% (2.4%, 20.4%) and 15% (5.9%, 24%) for 12.5 mg and 25 mg, respectively, was seen in study one and 10.3% (1.7%, 18.9%) in study two.

IV. Naldemedine (Symproic) was studied in four randomized, double-blind, placebo-controlled trials looking at patients with OIC and chronic non-cancer pain. The primary endpoint for both studies evaluated response to therapy defined as ≥3 SBMs per week and a change from baseline of ≥1 SBM per week for at least nine out of the 12 study weeks and three out of the last four study weeks.

- Study one and two were 12 week trials evaluating 1,080 patients comparing 0.2 mg of naldemedine (Symproic) against placebo. There was a statistically significant difference for naldemedine (Symproic) compared to placebo with a treatment difference of 13% (CI 5%, 21%) for study one and 19% (CI 11%, 27%) for study two.
- Study three was a 52 week trial evaluating 1246 patients comparing 0.2 mg of naldemedine (Symproic) against placebo. The primary outcome measured was treatment emergent adverse events which did not have any difference between treatment arms. There was sustained improvement in bowel movement frequency for naldemedine (Symproic) compared to placebo ~3.5 vs ~2.5, respectively (p<0.0001).
- Naldemedine (Symproic) was compared against placebo in a two week, randomized, double-blind, placebo-controlled trial with an open-label 12 week extension evaluating 193 patients with active cancer. Naldemedine (Symproic) had a statistically significant difference over placebo for the primary endpoint of proportion of SBM responders with a treatment difference of 36.8% (CI 23.7%, 49.9%).

Investigational or Not Medically Necessary Uses

I. These therapies have not been studied in the following conditions:
   A. Constipation not induced by opioids
   B. Post-operative Ileus

References

1. Relistor [Prescribing Information]. Bridgewater, NJ: Salix Pharmaceuticals, Inc. November 2018.
2. Movantik [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals. May 2019.
3. Symproic [Prescribing Information]. Raleigh, NC: BioDelivery Sciences International, Inc. April 2019.
4. Uptodate, Inc. Prevention and management of side effects in patients receiving opioids for chronic pain [database online]. Waltham, MA. Updated 11/11/19. Available at: http://www.uptodate.com/home/index.html. [Accessed 11/19/19].
5. Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. *Gastroenterology*. 2019;156(1):218-226.
6. Webster LR, Michna E, Khan A, Israel RJ, Harper JR. Long-Term Safety and Efficacy of Subcutaneous Methylnaltrexone in Patients with Opioid-Induced Constipation and Chronic Noncancer Pain: A Phase 3, Open-Label Trial. *Pain Med*. 2017;18(8):1496-1504.
7. Webster LR, Nalamachu S, Morlion B, et al. Long-term use of naldemedine in the treatment of opioid-induced constipation in patients with chronic noncancer pain: a randomized, double-blind, placebo-controlled phase 3 study. *Pain*. 2018;159(5):987-994.
8. Katakami N, Harada T, Murata T, et al. Randomized Phase III and Extension Studies of Naldemedine in Patients With Opioid-Induced Constipation and Cancer. *J Clin Oncol*. 2017;35(34):3859-3866.

Policy Implementation/Update:

Date Created	January 2018
Date Effective	February 2018
Last Updated	March 2018
Last Reviewed	03/2018

Action and Summary of Changes	**Date**
Transitioned criteria to policy: removed required trial and failure of lubiprostone (Amitiza) for all agents	11/2019

osilodrostat (Isturisa®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP190

Description

Osilodrostat (Isturisa) is an orally administered cortisol synthesis inhibitor. It inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
osilodrostat (Isturisa)	1 mg tablets	Cushing's disease	180 tablets/30 days
	5 mg tablets		
	10 mg tablets		

Initial Evaluation

I. Osilodrostat (Isturisa) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with endocrinologist; **AND**
   C. Documentation of baseline Urinary Free Cortisol (UFC) level; **AND**
   D. A diagnosis of **Cushing's disease** when the following are met:
      1. Pituitary surgery is not an option **OR** cortisol levels remain abnormal following attempted resection; **AND**
      2. 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); **AND**
      3. Treatment with pasireotide (Signifor) has been ineffective, contraindicated, or not tolerated.

II. Osilodrostat (Isturisa) is considered <u>investigational</u> 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 (e.g., cortisol level has decreased from baseline)

Supporting Evidence

I. The safety and efficacy of osilodrostat (Isturisa) has been studied inpatients 18 years of age or older, and there is no published data to support its use in pediatric patients.
II. Cushing's disease is a serious and complex disease state that requires the supervision of a specialist (e.g. endocrinologist).
III. Cushing's disease is a condition of pathological hypercortisolism that includes demonstrable clinical features. The goals of treating are to eliminate its primary cause and achieve remission so as to eliminate the associated signs, symptoms, and comorbidities and to improve quality of life (QOL).
IV. Osilodrostat (Isturisa) is indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.
V. Osilodrostat (Isturisa) was studied in one prospective, multicenter, open-label, phase III trial with a double-blind, placebo-controlled, randomized withdrawal period in 137 patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.
    - The primary efficacy outcome was the proportion of patients maintaining complete response a mean urinary free cortisol (mUFC) ≤ upper limit of normal (ULN) without a dose increase during the randomized withdrawal period at week 34.
    - At the time of the randomization (Week 26) all (100%) randomized patients were biochemically controlled (mUFC ≤ ULN). At the end of the 8-week randomized withdrawal period (Week 34 of study), the complete response rate in the osilodrostat (Isturisa) group dropped to 86.1% but was higher than that in the placebo group (29.4%).
    - The key secondary endpoint was the proportion of patients with mUFC≤ULN at week 24 (end of open-label osilodrostat treatment period 2) without dose-up titration weeks 13-24 and 72/137 patients met the endpoint
VI. 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 (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.
Guidelines have not been updated to include osilodrostat (Isturisa) in the treatment of Cushing's disease.

VII. There is a lack of head-to-head trials and scientific evidence to show superiority of one medication over the other, however more established therapies include steroidogenesis inhibitors (i.e. ketoconazole, metyrapone, mitotane, etomidate), pituitary-directed (i.e. cabergoline, pasireotide) and glucocorticoid antagonists (i.e. mifepristone). The safety and efficacy of osilodrostat (Isturisa) was assessed in a 48-week long study. Long term safety and efficacy has not been established.

Investigational or Not Medically Necessary Uses

I. Osilodrostat (Isturisa) has not been FDA-approved, or sufficiently studied for safety and efficacy for any other conditions or settings except for patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.

References

1. Isturisa [Prescribing Information]. Recordati Rare Disease, Inc: Lebanon, NJ USA 08833. March 2020.
2. Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, et al. Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, John Newell-Price, Martin O. Savage, Paul M. Stewart, Victor M. Montori, The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline, The Journal of Clinical Endocrinology & Metabolism, Volume 93, Issue 5, 1 May 2008, Pages 1526–1540, https://doi-org.liboff.ohsu.edu/10.1210/jc.2008-0125
3. American Association of Neurological Surgeons. Cushing's Syndrome/Disease. (n.d.). Retrieved June 29, 2020, from https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Cushings-Disease

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	07/2020

Policy Type: PA Pharmacy Coverage Policy: UMP049

Description

Ospemifene (Osphena) is an orally administered estrogen agonist and antagonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
ospemifene (Osphena)	60 mg tablets	Moderate to severe dyspareunia due to vulvar and vaginal atrophy associated with menopause; Moderate to severe vaginal dryness due to vulvar and vaginal atrophy associated with menopause	30 tablets/30 days	178807

Initial Evaluation

I. Ospemifene (Osphena) may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of **moderate to severe vaginal dryness; AND**
      1. Member is being treated for vaginal dryness as a symptom of vulvar and vaginal atrophy, due to menopause; **AND**
      2. Treatment with the following has been ineffective, contraindicated, or not tolerated:
         i. One systemic hormone replacement therapy (e.g., estradiol oral tablets, estradiol patch, estradiol injection); **AND**
         ii. One vaginal hormone replacement therapy (e.g., Estring, generic estradiol cream)

II. Ospemifene (Osphena) is an <u>excluded</u> medication when the following criteria below are met:
   A. A diagnosis of **moderate to severe dyspareunia** (difficult or painful sexual intercourse) as a symptom of vulvar and vaginal atrophy, due to menopause

Renewal Evaluation

I. Ospemifene (Osphena) may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of **moderate to severe vaginal dryness; AND**
      1. Member is being treated for vaginal dryness as a symptom of vulvar and vaginal atrophy, due to menopause; **AND**

2. Member has experienced symptomatic improvement (e.g., improvement in pain, discomfort, dryness, etc.)

II. Ospemifine (Osphena) is an excluded medication when the following criteria below are met:

A. A diagnosis of **moderate to severe dyspareunia** (difficult or painful sexual intercourse) as a symptom of vulvar and vaginal atrophy, due to menopause

Supporting Evidence

I. American College of Obstetricians and Gynecologist (ACOG) stated in their Clinical Guidelines on Management of Menopausal Symptoms that vaginal symptoms (e.g., dyspareunia, vaginal or vulvar dryness, discharge, itching) are best treated with systemic or topical hormone therapy.

II. Ospemifene (Osphena) is classified as an impotence drug according to First Databank. This is considered a categorical exclusion in the prescription benefit structure; however, coverage is allowed in the setting of moderate to severe vaginal dryness outside of the dyspareunia setting.

III. Dyspareunia is defined as difficult or painful sexual intercourse. Ospemifene (Osphena) for dyspareunia, a form of sexual dysfunction is in a category of medications that are not covered under the prescription benefit. Drugs used for sexual dysfunction are excluded from coverage. Please reference the member handbook/certificate of coverage for further information regarding this denial.

References

1. Oregon Insurance Division Bulletin INS 2014-1 Mental Health Parity.
2. Diagnostic and Statistical Manual of Mental Disorders (DSM) Versions IV-TR and V.
3. Osphena [prescribing information]. Shionogi Inc.: Florham Park, NJ;March 2018
4. Gracia C. The American College of Obstetricians and Gynecologist Clinical Guidelines on Management of Menopausal Symptoms. Am Fam Physician. 2014; 90(5):338-340.

Policy Implementation/Update:

Date Created	February 2016
Date Effective	February 2016
Last Updated	September 2019
Last Reviewed	03/2019, 09/2019

Action and Summary of Changes	**Date**
Updated policy to remove coverage in the setting of dyspareunia as this is an excluded benefit.	09/2019
Converted criteria to the new policy format. Added newly FDA approved indication of moderate to severe vaginal dryness due to vulvar and vaginal atrophy associated with menopause. The route for approval in the setting of vaginal dryness follows the ACOG Clinical Guidelines.	03/2019

Policy Type: PA Pharmacy Coverage Policy: UMP206

Description

Oxymetazoline (Upneeq) is an alpha-adrenergic receptor agonist ophthalmic solution.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
oxymetazoline (Upneeq)	0.1% solution dropperette	aponeurotic acquired blepharoptosis	30 dropperettes/30 days

Initial Evaluation

I. Oxymetazoline (Upneeq) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an ophthalmologist; **AND**
   C. A diagnosis of **aponeurotic acquired blepharoptosis** (i.e., not being used in mechanical blepharoptosis, Horner syndrome, myasthenia gravis) when the following are met:
      1. Provider attestation of **ALL** of the following:
         i. Member has functional impairment in activities of daily living due to blepharoptosis; **AND**
         ii. The *superior* visual field is less than 20 degrees when untapped; **AND**
         iii. There is at least a 20-degree improvement when taped; **AND**
         iv. There is a marginal reflex distance (MRD)-1 of 2.0 mm or less

II. Oxymetazoline (Upneeq) is considered investigational when used for all other conditions, including but not limited to:
   A. Non aponeurotic blepharoptosis

Renewal Evaluation

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

III. Provider attestation indicating member has exhibited improvements in points seen in visual field test

Supporting Evidence

I. Blepharoptosis, also known as ptosis, is a unilateral or bilateral dropping of the upper eyelid due to a congenital or acquired abnormality of the muscles that elevate the eyelid. Acquired blepharoptosis may be due different causes such as aponeurotic (usually age related), mechanical (e.g., eyelid mass), neurologic (e.g., Horner syndrome, myasthenia gravis), and myogenic (e.g., systemic muscular dysfunctions). Aponeurotic is the most common and is associated with aging. Surgery is the standard of care for patients who develop an obscured visual field due to ptosis and can also be considered for cosmetic purposes. However, surgery comes with known risks (e.g., failure of the eye to close completely, infection, edema, under correction/overcorrection, eyelid asymmetry, granuloma formation, and corneal foreign body sensation). Oxymetazoline (Upneeq) is an alternative to surgery in those who are not suitable candidates or those seeking a less costly, non-surgical option.

II. Oxymetazoline (Upneeq) was studied in two phase 3, double masked, randomized, vehicle-controlled trials in patients with acquired blepharoptosis. The primary endpoint was a change in the number of points seen in the top 4 rows of the Leicester Peripheral Field Test (LPFT) on treatment day 1 and 14. Patients included in trial 202 had a mean marginal reflex distance (MRD-1) of 1.04 ± 0.74 mm (Upneeq) and 1.07 ± 0.70 mm (vehicle) at baseline.

Endpoints	RVL-1201-201 (n=140)		RVL-1201-202 (n=164)	
	Upneeq	Vehicle	Upneeq	Vehicle
	n=94	*n=46*	*n=109*	*n=55*
Mean change in LPFT Day 1 (6 hours post instillation)	5.2 points	1.5 points	6.3 points	2.1 points
	Mean difference: 3.7 [1.8, 5.6] P<0.01		Mean difference: 4.2 [2.4, 6.1] P<0.01	
Mean change in LPFT Day 14 (2 hours post instillation)	6.4 points	2.2 points	7.7 points	2.4 points
	Mean difference: 4.2 [2.0, 6.0] P<0.01		Mean difference: 5.3 [3.7, 7.1] P<0.01	
Mean change in MRD-1 from baseline (highest change; day 14, 2 hours post-instillation)	MRD-1 endpoints not published		1.3 mm	0.4 mm
			P < 0.05	

III. Although oxymetazoline (Upneeq) showed a statistically significant improvement relative to vehicle for improving LPFT, the quality of the evidence is considered low as LPFT is a modified version of Humphrey visual field test that is not typically used in practice, coupled with limited information available on trial data, unknown components used as the vehicle product, and unknown safety with use over 42 days.

IV. Clinical trials noted above excluded certain acquired causes of blepharoptosis (i.e., mechanical, Horner syndrome, myasthenia gravis). Efficacy of oxymetazoline (Upneeq) outside of the aponeurotic acquired blepharoptosis population is unknown.

V. FDA approval of oxymetazoline (Upneeq) is specific to the adult population only. Although one of the clinical trials included patients 9 years and older, the youngest patient that received oxymetazoline (Upneeq) in that trial was 20 years old. Thus, safety and efficacy of oxymetazoline (Upneeq) has not been established in pediatric patients.

Investigational or Not Medically Necessary Uses

I. Oxymetazoline (Upneeq) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Non aponeurotic blepharoptosis

References

1. Upneeq [Prescribing Information]. RVL Pharmaceuticals, Inc.: Bridgewater, NJ. August 2020.
2. Korenfeld M, Kannarr S, Silverstein S, et. al. Effect of oxymetazoline on blepharoptosis: results of a phase 3 randomized, double masked, placebo-controlled study – Poster Presentation Presented at the American Academy of Optometry (AAO) Meeting – October 2019.
3. RVL Pharmaceuticals, Inc. Study of the Safety and Efficacy of RVL-1201 in the Treatment of Acquired Blepharoptosis. Available from https://clinicaltrials.gov/ct2/show/NCT02436759. NLM identifier: NCT02436759
4. UpToDate, Inc. Overview of ptosis. UpToDate [database online]. Waltham, MA. Last updated May 06, 2020. Available at: http://www.uptodate.com/home/index.html.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP051

Description

Palivizumab (Synagis) is a humanized monoclonal antibody directed against the fusion protein of respiratory syncytial virus (RSV).

Length of Authorization

- Initial: Five months
- Renewal: N/A

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
palivizumab (Synagis)	100 mg/1mL	Respiratory syncytial virus (RSV) prophylaxis	15 mg/kg (1 dose) per 28 days
	50 mg/0.5mL		

Initial Evaluation

I. Palivizumab (Synagis) may be considered medically necessary when the following criteria below are met:
   A. Therapy is given during the current RSV season, **AND**
   B. Member is being managed by, or in consultation with, a pulmonologist or cardiologist; **AND**
   C. A diagnosis of one of the following:
      1. **Preterm Infants WITHOUT congenital morbidities** (e.g. chronic lung disease of prematurity; or congenital heart disease); **AND**
         i. Member was born before 29 weeks, 0 days of gestation; **AND**
         ii. Member is less than 12 months of postnatal age; **OR**
      2. **Preterm Infants WITH Chronic Lung Disease (CLD)**; **AND**
         i. Member was born before 32 weeks, 0 days of gestation; **AND**
         ii. Member required respiratory support (supplement with greater than 21% oxygen) for at least the first 28 days after birth; **AND**
         iii. Member is less than 12 months of age; **OR**
         iv. Member is less than 24 months of age; **AND**
         v. Continues to require medical support (e.g., chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of second RSV season; **OR**
      3. **Infants and Children with Hemodynamically Significant Congential Heart Disease (CHD)**; **AND**
         i. Member is less than 12 months of age; **AND**
         ii. Member has moderate to severe pulmonary hypertension; **OR**
         iii. Member has cyanotic heart disease; **OR**

iv. Member has acyanotic heart disease; **AND**
    a. Member is receiving medication to control congestive heart failure; **AND**
    b. Member will require cardiac surgical procedures; **OR**

4. **Children undergoing cardiac transplantation during RSV season**; **AND**
    i. Member is less than 24 months of age; **OR**
5. **Infants with Anatomic Pulmonary Abnormalities or Neuromuscular disorder**; **AND**
    i. Member is less than 12 months of age; **AND**
    ii. Member has an impaired ability to clear secretions from the upper airway; **OR**
6. **Immunocompromised Children**; **AND**
    i. Member is less than 24 months of age; **AND**
    ii. Member is profoundly immunocompromised (e.g. undergoing chemotherapy, HIV, SCID, DiGeorge, IgA deficiency, Hypergammaglobulinemia etc.); **OR**
7. **Children with Cystic Fibrosis, Primary Ciliary Dyskinesia, or other rare lung disease**; **AND**
    i. Member is less than 12 months of age; **AND**
        a. Member has clinical evidence of chronic lung disease (CLD); **OR**
        b. Member has clinical evidence of nutritional compromise; **OR**
    ii. Member is less than 24 months of age; **AND**
        a. Member had a hospitalization for pulmonary exacerbation in the first year of life; **OR**
        b. Member has abnormalities on chest radiography/chest computed tomography that persist when stable; **OR**
        c. Member has a weight for length less than the 10th percentile

II. Palivizumab (Synagis) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
    A. Infants or children who were born after 32 weeks
    B. Infants and children with hemodynamically insignificant heart disease such as:
        1. Secundum atrial septal defect
        2. Small ventricular septal defect
        3. Pulmonic stenosis
        4. Uncomplicated aortic stenosis
        5. Mild coarctation of the aorta
        6. Patent ductus arteriosus
    C. Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure
    D. Infants with mild cardiomyopathy who are not receiving medical therapy for the condition
    E. Children in the second year (≥24 months) of life
    F. Children with Down syndrome without other comorbid conditions listed in the Initial Evaluation (section I) portion of this policy.

III. Palivizumab (Synagis) is considered investigational when used for all other conditions, including but not limited to:
   A. For the treatment of RSV

Supporting Evidence

I. For current RSV trends, refer to: http://www.cdc.gov/surveillance/nrevss/rsv/index.html. The CDC utilizes the past year's surveillance season data to predict the timing of the next year's outbreak.

II. Palivizumab (Synagis) is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients. The FDA approved palivizumab (Synagis) in 1998 for pediatric patients with a history of premature birth (<35 weeks of gestation), children with bonchopulmonary dysplasis (BPD), and those with hemodyanamically significant congenital heart disease (CHD).

III. The American Academy of Pediatrics (AAP) committee on infectious diseases (COID) has undertaken a systematic review of all recent, and older, peer-reviewed literature relating to the burden of respiratory syncytial virus (RSV) disease in infants and children, specifically focusing on publications that delineate children at greatest risk of serious RSV disease and studies that define pharmacokinetics, safety, and efficacy. Detailed input regarding this guidance has been solicited from 21 committees, councils, sections, and advisory groups within the AAP, as well as organizations outside the AAP. The updated (reviewed every 3 years) recommendations by AAP are based on review of the quality of all available data, as well as real world clinical impact of palivizumab (Synagis) prophylaxis for the population subset in the United States.

IV. Available clinical data and the AAP recommendations note that there is limited clinical benefit derived from palivizumab prophylaxis for otherwise healthy infants and children and therefore, should be limited to the patient population described in this policy. Furthermore, the package insert for palivizumab (Synagis) states: "Synagis is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease." And in the absence of a specific definition of "high risk" by the US FDA, the AAP has provided guidenace for determinining the "high risk" population characetistics which have been used to create this policy.

V. Palivizumab (Synagis) was evaluated in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization.
   - Trial 1 was conducted during a single RSV season with 1502 children who were less than or equal to 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (less than or equal to 36 weeks of gestation) who were less than or equal to 6 months of age at study entry.
     i. Results of Trial 1: 4.8% (49/1002) participants were hospitalized in the palivizumab (Synagis) group compared to 10.6% (52/500) participants were hospitalized in the placebo group.

- Trial 2 was conducted over four consecutive RSV seasons with 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease.
    i. Results of Trial 2: 5.3% (34/639) participants were hospitalized in the palivizumab (Synagis) group compared to 9.7% (63/648) participants were hospitalized in the placebo group.

VI. A technical review by the American Academy of Pediatrics (AAP) was completed in 2014 and the recommendation was palivizumab (Synagis) for RSV prophylaxis "cannot be considered as high-value health care for any group of infants" because there is minimal benefit, in addition to its high cost. From that technical review, AAP published the following guidance in 2014: Palivizumab (Synagis) Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection.

- The AAP states available data for infants born at 29 weeks, 0 days' gestation or later do not identify a clear gestational age cutoff for which the benefits of prophylaxis are clear. For this reason, infants born at 29 weeks, 0 days' gestation or later are not universally recommended to receive palivizumab (Synagis) prophylaxis. Infants 29 weeks, 0 days' gestation or later may qualify to receive prophylaxis on the basis of congenital heart disease (CHD), chronic lung disease (CLD), or another condition.

VII. For preterm infants born before 32 weeks, 0 days of gestational age, palivizumab (Synagis) prophylaxis is recommended if the infant developed chronic lung disease (CLD) of prematurity. This typically involves use of supplemental Oxygen (O_2) therapy during the first 28 days after birth to mitigate hypoxia and cyanosis. While normal O_2 saturation in inspired room air (FiO_2) is 20%, infants with CLD require supplementation with > 21% O_2 concentration. The Oxygen need is determined by the patient's disease severity and can range from 21% to up to 100%. Per WHO recommendations for treatment of CLD, supplemental Oxygen therapy should be initiated with 30% oxygen or air (if blended oxygen is not available), rather than with 100% oxygen. The use of progressively higher concentrations of oxygen should only be considered for newborns undergoing oxygen therapy if their heart rate is less than 60 beats per minute after 30 seconds of adequate ventilation with 30% oxygen or air.

VIII. AAP guidelines recommend palivizumab (Synagis) for infants with hemodynamically significant CHD. In this setting, the best therapeutic benefit is likely for infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and in infants with moderate to severe pulmonary hypertension. Decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects in the first year of life may be made in consultation with a pediatric cardiologist. According to recommendations from key experts in pediatric cardiology, infants with cyanotic heart defects (e.g. heart valve defects, Ebstein anomaly, hypoplastic left heart syndrome, Tetralogy of Fallot, Truncus arteriosus) are at a much higher risk of complications from RSV as compared to those with acyanotic heart defects (e.g. congential septal defects, patent ductus arteriosus, pulmonary stenosis, aortic stenosis). Consequently, prophylaxis using palivizumab (Synagis) may have a significant, real world clinical and potentially life-saving impact for the infant population with cyanotic heart disease. AAP guidelines recommend that the decision to use palivizumab (Synagis) in cyanotic heart disease patients must be made by or in consultation with a pediatric cardiologist.

IX. During the second year of life, consideration of palivizumab prophylaxis is recommended only for infants who satisfy the definition of CLD of prematurity and continue to require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-

month period before the start of the second RSV season. For infants with CLD who do not continue to require medical support in the second year of life prophylaxis is not recommended.

X. Although the National Perinatal Association 2018 Respiratory Syncytial Virus (RSV) Prevention Clinical Practice Guideline: An Evidence-Based Interdisciplinary Collaboration published additional guidance and new information as it relates to RSV, after reviewing the new information, the AAP still recommended their guidelines from 2014 as the new evidence did not change the cost-benefit analysis that was done.

Investigational or Not Medically Necessary Uses

I. The listed diagnoses are included in the AAP 2017 RSV Guidance as not medically necessary for immunoprophylaxis with palivizumab (Synagis)
   - A. Infants or children who were born after 32 weeks
   - B. Infants and children with hemodynamically insignificant heart disease such as:
     - i. Secundum atrial septal defect
     - ii. Small ventricular septal defect
     - iii. Pulmonic stenosis
     - iv. Uncomplicated aortic stenosis
     - v. Mild coarctation of the aorta
     - vi. Patent ductus arteriosus
   - C. Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure
   - D. Infants with mild cardiomyopathy who are not receiving medical therapy for the condition
   - E. Children in the second year (≥24 months) of life
   - F. Children with Down syndrome without other comorbid conditions listed in the Initial Evaluation (section I) portion of this policy.

II. Treatment of RSV
   - A. Safety and efficacy has not been established for the use of palicizumab (Synagis) for the treatment of RSV.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Formatting edits and minor edits to wording used in efforts to provide more clarity of policy intent; Addition of indication of 'cyanotic heart disease' as per AAP guidelines; Updated Supporting Evidence section to include more information surrounding clinical benefits of palivizumab (Synagis) prophylaxis and clarification that this policy follows AAP recommendations based on quality of clinical evidence instead of FDA approved indications listed in package insert	12/2020
Transitioned criteria into policy with supporting evidence, and incorporated the updated AAP RSV prophylaxis guidelines that details the specific coverage recommendations for: chronic lung disease in patients less than 24 months, patients less than 12 months with hemodynamically significant chronic heart disease, cardiac transplantation in patients less than 24 months, anatomic pulmonary abnormalities/neuromuscular disorder in patients less than 12 months, immunocompromised children, children with rare lung disease. Additionally, incorporated the recommendations from the updated AAP RSV prophylaxis guidelines to detail what diagnoses are not medically necessary for RSV prophylaxis/Synagis.	09/2019

panobinostat (Farydak®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP196

Description

Panobinostat (Farydak) is an orally administered histone deacetylase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: Six months (can only be renewed once)

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
panobinostat (Farydak)	10 mg capsules	Multiple Myeloma with ≥2 prior regimens, including bortezomib and an immunomodulatory agent	6 capsules/21 days
	15 mg capsules		
	20 mg capsules		

Initial Evaluation

I. Panobinostat (Farydak) 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. Not used in combination with any other oncology therapy unless outlined below; **AND**
   D. A diagnosis of **multiple myeloma** when the following are met:
      1. Provider attests member has received at least two prior regimens including both of the following:
         i. Bortezomib (Velcade); **AND**
         ii. Immunomodulatory agent (e.g., thalidomide, lenalidomide, pomalidomide); **AND**
      2. Provider attests panobinostat (Farydak) will be used in combination with one of the following:
         i. Bortezomib (Velcade) AND dexamethasone *only*; **OR**
         ii. Lenalidomide (Revlimid) AND dexamethasone *only*; **OR**
         iii. Carfilzomib (Kyprolis) *only*

II. Panobinostat (Farydak) is considered investigational when used for all other conditions, including but not limited to:
   A. Multiple myeloma when given as part of a quadruplet ("quad") regimen

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Medication is prescribed by, or in consultation with, an oncologist; **AND**
III. Member is responsive to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Member will not receive more than a total treatment duration of 48 weeks; **AND**
V. Provider attests panobinostat (Farydak) will be used in combination with one of the following:
   A. Bortezomib (Velcade) AND dexamethasone *only*; **OR**
   B. Lenalidomide (Revlimid) AND dexamethasone *only*; **OR**
   C. Carfilzomib (Kyprolis) *only*

Supporting Evidence

I. Panobinostat (Farydak) is FDA-approved for use in combination with bortezomib and dexamethasone and is indicated in the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
II. The recommended starting dose of panobinostat (Farydak) is 20 mg, taken orally once every other day for three doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for eight cycles. Treatment continuation may be considered for an additional eight cycles (total 16 cycles) for patients with clinical benefit, unless they have unresolved severe or medically significant toxicity. The total duration of treatment may be up to 16 cycles (48 weeks).
III. Panobinostat (Farydak) was studied in 768 subjects from one Phase 3, double-blind, placebo-controlled, multicentered, multi-country trial. The trial included subjects with one to three previous treatments. Subjects were randomized 1:1 to receive panobinostat (Farydak) + bortezomib and dexamethasone (PAN-BTZ-Dex) or placebo + bortezomib and dexamethasone (PBO-BTZ-Dex) stratified by prior use of bortezomib and the number of prior lines of anti-myeloma therapy. The primary endpoint was progression free survival (PFS), and a key secondary endpoint was overall survival (OS).
   - Median PFS was 11.99 months (95% CI 10.33-12.94) PAN-BTZ-Dex compared to 8.08 months (95% CI 7.56-9.23) PBO-BTZ-Dex, with HR 0.63 (95% CI 0.52-0.76) p<0.0001.

	Median Progression-Free Survival (95% CI, mo [n])		Hazard Ratio (95% CI)
	PAN-BTZ-Dex	Placebo-BTZ-Dex	
Prior use of immunomodulatory drugs (n=485)	13.14 (11.56-15.47)	10.41 (7.95-11.53)	0.54 (0.43-0.68)
Prior use of immunomodulatory drugs and bortezomib (n=193)	11.99 (9.69-13.90)	8.31 (6.14-12.32)	0.52 (0.36-0.76)
Previous use of immunomodulatory drugs, bortezomib, and two or more lines (n=147)	11.99 (9.69-13.37)	6.97 (4.86-13.40)	0.47 (0.31-0.72)

- Matured median OS was 40.3 months (95% CI 35-44.8) PAN-BTZ-Dex compared to 35.8 months (95% CI 29-40.6) PBO-BTZ-Dex, with HR 0.94 (95% CI 0.78–1.14) p=0.54.

	Median Overall Survival (95% CI, mo [n])		Hazard Ratio (95% CI)
	PAN-BTZ-Dex	Placebo-BTZ-Dex	
Prior use of immunomodulatory drugs (n=485)	36.2 (31.18–41.36)	29.4 (24.57–37.78)	0.94 (0.74–1.19)
Prior use of immunomodulatory drugs and bortezomib (n=193)	27.2 (24.21–34.63)	24.7 (17.48–35.38)	1.03 (0.72–1.47)
Previous use of immunomodulatory drugs, bortezomib, and two or more lines (n=147)	25.5 (19.58–34.33)	25.5 (19.58–34.33)	1.01 (0.68–1.50)

IV. Although the clinical trial evaluated subjects with one to three previous treatments, as stated in the package insert, the approval of panobinostat (Farydak) was based upon the efficacy and safety in a prespecified subgroup analysis of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent and a median of two prior therapies as the benefit to risk profile appeared to be greater in this more heavily pretreated population than in the overall trial population.

V. Panobinostat (Farydak) is associated with significant toxicity. Clinical trial discontinuation rate was 36% in the panobinostat (Farydak) group, due to adverse events, as compared to 20% in the placebo group. Moreover, discontinuation rate due to Grades 3 or 4 adverse events was 25% in the panobinostat (Farydak) group compared to 13% in the placebo group. However, split fill management is not applicable because only a total of six panobinostat (Farydak) capsules are given per 21-day cycle.

VI. Panobinostat (Farydak) is a REMS agent, carrying a black box warning for fatal and serious toxicities of severe diarrhea and cardiac toxicities.

- Common adverse events (≥20%) are diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting.
- Common non-hematologic abnormalities (≥40%) are hypophosphatemia, hypokalemia, hyponatremia, and increased creatinine.
- Common hematologic abnormalities (≥60%) are thrombocytopenia, lymphopenia, leukopenia, neutropenia, and anemia.

VII. Per NCCN V2.2021 guidelines, panobinostat (Farydak) + bortezomib and dexamethasone is a Category 1 “other recommended regimen” for previously treated multiple myeloma. Other combinations that do not include panobinostat (Farydak) are considered “preferred”. NCCN guidelines recommend that panobinostat (Farydak) + carfilzomib (Category 2A) OR panobinostat + lenalidomide and dexamethasone (Category 2A) may be useful in certain circumstances and state that such treatment is only indicated for patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent; guidelines do not define circumstances.

- Panobinostat (Farydak) + lenalidomide and dexamethasone was studied in a multicenter phase I/II study. Primary endpoint of phase II was ORR, which was 82%, and the clinical benefit rate was 91%.

- Panobinostat (Farydak) + carfilzomib was studied in a single-center, phase II study in 27 patients. Primary endpoint was ORR, which was 41%. PFS was 7.1 months.

Investigational or Not Medically Necessary Uses

I. Panobinostat (Farydak) has not been sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Quadruple ("quad") regimen
      i. Although triplet regimens remain the standard of care for multiple myeloma, 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.

Appendix

I. Table 1: Recommended Dosing Schedule of panobinostat (Farydak) in Combination with Bortezomib and Dexamethasone During Cycles 1 to 8

21-Day Cycle															
Cycles 1 to 8 (3-Week cycles)	**Week 1 Days**							**Week 2 Days**							**Week 3**
FARYDAK	1		3		5			8		10		12			Rest period
Bortezomib	1			4				8			11				Rest period
Dexamethasone	1	2		4	5			8	9		11	12			Rest period

II. Table 2: Recommended Dosing Schedule of panobinostat (Farydak) in Combination with Bortezomib and Dexamethasone During Cycles 9 to 16

21-Day Cycle															
Cycles 9 to 16 (3-Week cycles)	**Week 1 Days**							**Week 2 Days**							**Week 3**
FARYDAK	1		3		5			8		10		12			Rest period
Bortezomib	1							8							Rest period
Dexamethasone	1	2						8	9						Rest period

III. Table 3: Classification of Medications used for Multiple Myeloma

Proteasome Inhibitors	**Immunomodulatory Agents**	**Monoclonal Antibodies**	**Histone Deacetylase Inhibitors**	**B-cell Maturation Antigen-Directed Antibody**	**Chemotherapy**
• bortezomib • carfilzomib • ixazomib	• thalidomide • lenalidomide • pomalidomide	• elotuzumab • daratumumab • isatuximab-irfc	• panobinostat	• belantamab mafodotin-blmf	• cyclophosphamide • doxorubicin • cisplatin • etoposide • melphalan • bendamustine

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria transitioned to policy format. Removed requirements around counseling on side effects and attesting to lack of recent myocardial infarction or unstable angina. Addition of supporting evidence and additional combination agent options [addition of lenalidomide (Revlimid) and dexamethasone; or carfilzomib (Kyprolis)].	10/2020
Criteria created	03/2015

Parathyroid hormone (Natpara®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP167

Description

Parathyroid hormone (Natpara) is subcutaneously administered, FDA-approved hormone replacement therapy for hypoparathyroidism. Parathyroid hormone acts to regulate the body's calcium levels.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Parathyroid hormone (Natpara)	25 mcg/dose cartridge	Adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism	2 cartridges/28 days
	50 mcg/dose cartridge		2 cartridges/28 days
	75 mcg/dose cartridge		2 cartridges/28 days
	100 mcg/dose cartridge		2 cartridges/28 days

Initial Evaluation

I. Parathyroid hormone (Natpara) may be considered medically necessary when the following criteria below are met:
   A. Member is being treated for hypocalcemia due to hypoparathyroidism; **AND**
   B. Member does not have following:
      1. Hypoparathyroidism due to calcium-sensing receptor mutations
      2. Acute post-surgical hypoparathyroidism; **AND**
   C. Member does not have a history of Page's disease of bone, open epiphyses, radiation therapy involving the skeleton, or hereditary disorders predisposing to osteosarcoma; **AND**
   D. Member has tried and failed treatment with calcium supplements and active forms of vitamin D (e.g. calcitriol); **AND**
   E. Member will be treated with this medication adjunct to calcium and vitamin D

II. Parathyroid hormone (Natpara) is considered investigational when used for all other conditions, including but not limited to:
   A. Hypoparathyroidism due to calcium-sensing receptor mutation
   B. Acute post-surgical hypoparathyroidism

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
III. Member has exhibited improvement or stability of disease symptoms

Supporting Evidence

I. Parathyroid hormone (Natpara) is FDA approved as adjunctive therapy with calcium + vitamin D to control hypocalcemia in patients with hypoparathyroidism.
II. Parathyroid hormone (Natpara) acts to regulate the body's calcium levels. Parathyroid hormone increases the rate of bone turnover by stimulating osteoclast and osteoblast activity, which leads to calcium resorption from bone. The net effects of parathyroid hormone are increases in serum calcium and magnesium concentration and decreased phosphate concentration.
III. Parathyroid hormone (Natpara) has not been studied in patients with hypoparathyroidism due to calcium sensing receptor mutation or patients with acute post-surgical hypoparathyroidism.
IV. Parathyroid hormone (Natpara) has a Black Box warning for use in patients with increased risk of osteosarcoma. Due to this potential risk, parathyroid hormone (Natpara) should be used only in patients who cannot be well-controlled on calcium and active forms of vitamin D.

Investigational Uses

I. Parathyroid hormone (Natpara) is not intended for use in members with hypoparathyroidism due to calcium-sensing receptor mutations, or acute post-surgical hypoparathyroidism.

References

1. Natpara [Prescribing Information]. Lexington, MA: Shire-NPS Pharmaceuticals, Inc., 2018.

Policy Implementation/Update:

Date Created	January 2015
Date Effective	January 2015
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Criteria updated to new policy format.	11/2019

Description

Teriparatide, teriparatide (Forteo), and abaloparatide (Tymlos) are human parathyroid hormone related peptide [PTHrP (1-34)] analogs.

Length of Authorization

- Initial: 12 months
- Renewal: up to 12 months (only **one** renewal allowed)
  - **Teriparatide (Forteo)** and **teriparatide**: a maximum of **26 fills total**
  - **Abaloparatide (Tymlos)**: a maximum of **24 fills total**

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
teriparatide (Forteo)	250 mcg/mL	Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men	1 syringe/28 days
teriparatide (biosimilar formulation)	250 mcg/mL	Post-Menopausal Osteoporosis in Women Glucocorticoid-induced Osteoporosis	1 syringe/28 days
abaloparatide (Tymlos)	2000 mcg/mL	Post-Menopausal Osteoporosis in Women	1 syringe/30 days

Initial Evaluation

I. Abaloparatide (Tymlos), teriparatide (biosimilar formulation), and teriparatide (Forteo) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member will not have received treatment with a parathyroid hormone for more than two years during their lifetime; **AND**
   C. Will not be used in combination with other osteoporotic agents [e.g., denosumab (Prolia), bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid injection), calcitonin nasal spray, or raloxifene]; **AND**
   D. One of the following is met:
      1. Member has severe osteoporosis (T-score ≤ -3.5 in the absence of fracture or T-score ≤ -2.5 with fragility fracture); **OR**
      2. Member has a high risk of fracture defined as:
         i. History of osteoporotic fracture (fractures of spine, hip, wrist or humerus); **OR**
         ii. Multiple risk factors for fracture; **AND**

E. Treatment with ONE of the following has been ineffective, not tolerated, or ALL are contraindicated:
    1. bisphosphonates (e.g., alendronate, ibandronate, zoledronic acid injection)
    2. raloxifene
    3. calcitonin (Fortical); **AND**

F. For **teriparatide (biosimilar formulation) OR teriparatide (Forteo):**
    1. A diagnosis of one of the following:
        i. **Post-Menopausal Osteoporosis in Women**; **AND**
            a. Request is for teriparatide (biosimilar formulation) **AND** treatment with abaloparatide (Tymlos) has been ineffective, not tolerated or contraindicated; **OR**
            a. If request is for teriparatide (Forteo), treatment with teriparatide (biosimilar formulation) **AND** abaloparatide (Tymlos) has been ineffective, not tolerated or contraindicated; **OR**
        ii. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men; AND**
            a. Request is for teriparatide (Forteo) **AND** treatment with teriparatide (biosimilar formulation) has been ineffective, not tolerated or contraindicated; **OR**
        iii. **Glucocorticoid-induced Osteoporosis; AND**
            a. Member is taking ≥ 5 mg prednisone or its equivalent daily with an anticipated duration of ≥ 3 months; **AND**
            b. If request is for teriparatide (Forteo), treatment with teriparatide (biosimilar formulation) has been ineffective, not tolerated or contraindicated; **OR**

G. For **abaloparatide (Tymlos):**
    1. **A diagnosis of post-menopausal osteoporosis in women**.

II. Parathyroid hormones are considered investigational when used for all other conditions, including but not limited to:
    A. Osteoporosis prophylaxis
    B. Promote fracture healing
    C. Promote post-fusion healing; **AND**
    D. The use of abaloparatide (Tymlos) is considered investigational when use for:
        1. Primary Osteoporosis/Hypogonadal-related Osteoporosis; OR
        2. Glucocorticoid-induced Osteoporosis.
    E. The use of parathyroid hormones [abaloparatide (Tymlos) and/or teriparatide (Forteo)] for >2 years.

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**

II. Member has received a previous prior authorization approval for this agent; **AND**

III. Member has not received treatment with parathyroid hormone for more than a total of **two** years (i.e., the maximum treatment duration is two years during a lifetime); **AND**

IV. Not used in combination with other osteoporotic agents [e.g., denosumab (Prolia), bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid injection), calcitonin nasal spray, or raloxifene]; **AND**

V. Member has demonstrated clinical improvement [e.g. improved bone mineral density, reduction in fracture(s)] with parathyroid hormone therapy.

Supporting Evidence

I. Maximum duration of use is based on the dose dependent increase in the incidence of osteosarcoma. Cumulative use of parathyroid analogs for more than 2 years during a patient's lifetime is not recommended.

II. For the treatment of osteoporosis in postmenopausal women:
   A. The safety and efficacy of once-daily teriparatide (Forteo) and teriparatide, median exposure of 19 months, was examined in a double-blind, multicenter, placebo-controlled clinical study of 1637 postmenopausal women with osteoporosis (FORTEO 20 mcg, n=541). The absolute risk reduction for new fracture in favor of teriparatide (Forteo) was a 9.3% reduction in vertebral fracture; 95% CI (5.5 – 13.1).
   B. The safety and efficacy of abaloparatide (Tymlos) was evaluated in an 18-month, randomized, multicenter, double-blind, placebo-controlled clinical trial in postmenopausal women aged 49 to 86 years (mean age of 69) who were randomized to receive abaloparatide (Tymlos) 80 mcg (N = 824) or placebo (N = 821). The absolute risk reduction for fractures in favor of abaloparatide (Tymlos) was 3.6% reduction in vertebral fractures; 95% CI (2.1 – 5.4).

III. For the treatment of men with primary or hypogonadal osteoporosis:
   A. The safety and efficacy of once-daily teriparatide (Forteo) and teriparatide injection was examined in a double-blind, multicenter, placebo-controlled clinical study of 437 men with either primary (idiopathic) or hypogonadal osteoporosis (n=151) for a median exposure of 10 months. The results of that study were reported as the following: increased lumbar spine bone mass density (BMD) from baseline in 94% of men treated. Fifty-three percent of patients treated with teriparatide (Forteo) achieved at least a 5% increase in spine BMD, and fourteen percent of patients gained ≥10% in spine BMD.

IV. For the treatment of glucocorticoid-induced osteoporosis:
   A. The efficacy of teriparatide (Forteo) and teriparatide injection was assessed in a randomized, double blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥ 5 mg/day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to teriparatide (Forteo). In patients treated with teriparatide (Forteo), the mean percent change in BMD from baseline to endpoint was 7.2% at the lumbar spine, 3.6% at the total hip, and 3.7% at the femoral neck ($p<0.001$ all sites).

Investigational or Not Medically Necessary Uses

I. Osteoporosis Prophylaxis
   A. There is currently no evidence to support the use of parathyroid hormones for the prevention of postmenopausal osteoporosis.
II. Promote fracture healing and/or post fusion healing
   A. There is limited safety and efficacy evidence to support the use of parathyroid hormones in the setting of fracture healing and/or post fusion healing.
III. Abaloparatide (Tymlos) is only FDA-approved for the treatment of postmenopausal osteoporosis; there is currently a lack of sufficient evidence regarding safety and efficacy in other settings.

References

1. Forteo [Prescribing Information]. Indianapolis, IN: Eli Lilly and Company. October 2019.
2. Tymlos [Prescribing Information]. Waltham, MA: Radius Health, Inc. April 2017.
3. Teriparatide [Prescribing Information]. Morristown, NJ: Alvogen, Inc. November 2019.
4. Camacho PM, Petak SM, Binkley N, et al. American Association Of Clinical Endocrinologists And American College Of Endocrinology Clinical Practice Guidelines For The Diagnosis And Treatment Of Postmenopausal Osteoporosis. September 2016. Available at: https://doi.org/10.4158/EP161435.GL.
5. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline, The Journal of Clinical Endocrinology & Metabolism, Volume 97, Issue 6, June 2012, Pages 1802–1822. Available at: https://doi.org/10.1210/jc.2011-3045
6. Buckley L, Guyatt G, Fink HA, et al. American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. American College of Rheumatology, Volume 69, Issue 8, August 2017, Pages 1521-1537. Available at: https://www.rheumatology.org/Portals/0/Files/Guideline-for-the-Prevention-and-Treatment-of-GIOP.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria for the biosimilar teriparatide, requiring trial of the biosimilar prior to brand Forteo	11/2020
Added detail around maximum duration of approval [26 (monthly) fills] in order to provide more clarity around fill history. Addition of supporting evidence regarding maximum two year treatment duration	04/2020
Added in fill count to renewal duration, as well as updated to reflect a 28-day supply instead of 30-days in the Forteo QL table	02/2020
Criteria transitioned into policy format with the following additions: supporting evidence, investigational section, and a list of drugs that should not be used in combination with parathyroid hormones. Guidelines reviewed, and the following updates were made: differentiate between T-scores without fragility fracture and with fragility fracture, defined high risk fractures, and provided inclusion criteria for glucocorticoid-induced osteoporosis.	12/2019
Update criteria to include abaloparatide (Tymlos)	08/2017
Reviewed	10/2005, 01/2007, 12/2008, 06/2013, 02/2016, 06/2017, 12/2019
Date effective	03/2016
Policy created	09/2005

Policy Type: PA/SP Pharmacy Coverage Policy: UMP147

Description

Pasireotide diaspartate (Signifor) is a subcutaneous somatostatin analog solution that exerts its activity by binding to somatostatin receptors causing adrenocorticotropic hormone (ACTH) secretion to be inhibited thereby leading to decreased cortisol secretion.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
pasireotide diaspartate (Signifor)	0.3 mg/mL ampule	Cushing's disease	60 ampules/30 days
	0.6 mg/mL ampule		60 ampules/30 days
	0.9 mg/mL ampule		60 ampules/30 days
Provider Administered Agents*			
pasireotide pamoate (Signifor LAR)	20 mg vial	Acromegaly Cushing's disease	N/A
	40 mg vial		
	60 mg vial		

**Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit.*

Initial Evaluation

I. Pasireotide diaspartate (Signifor) 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; **AND**
   C. A diagnosis of **Cushing's disease** when the following are met:
      1. Pituitary surgery is not an option **OR** cortisol levels remain abnormal following attempted resection; **AND**
      2. 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. Pasireotide diaspartate (Signifor) is considered investigational when used for all other conditions, including but not limited to:
   A. Acromegaly

B. Pancreatic fistula, postoperative/prophylaxis
C. Carcinoid syndrome
D. Neuroendocrine tumor

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. cortisol level has decreased from baseline)

Supporting Evidence

I. Cushing's disease is a disorder that leads to excess cortisol and is usually due to a corticotropin (ACTH)-producing pituitary tumor. Goals of treatment include the reversal of clinical manifestations by normalizing cortisol secretion, damaging tumor eradication, and avoidance of permanent hormone deficiency which can leave a permanent dependence upon medications. The excess cortisol of Cushing's disease is primarily treated with transsphenoidal surgery (TSS) regardless of its cause. Although surgical treatment is optimal, medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Adrenal enzyme inhibitors are the most commonly used medications; however, adrenolytic agents, drugs that target a pituitary or ectopic tumor, and glucocorticoid-receptor antagonists have also been used.
II. Pasireotide diaspartate (Signifor) is indicated for the treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative.
III. Endocrine Society guidelines recommend medical therapy in cases were 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. Acromegaly
    A. Pasireotide diaspartate (Signifor) does not carry an FDA approval in the setting of acromegaly; however, the pasireotide pamoate (Signifor LAR) product is available in this setting.
    B. Pancreatic fistula, postoperative; prophylaxis
        i. Limited data shows reduction in relative risk only.
    C. Carcinoid syndrome
        i. Agent fails to improve symptom control or tumor response.

D. Neuroendocrine tumor
   i. Agent fails to improve symptom control or tumor response; use is not recognized by NCCN guidelines.

References

1. Signifor injection [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2019.
2. Signifor LAR injection [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; April 2019.
3. UpToDate, Inc. Overview of the treatment of Cushing's syndrome. UpToDate [database online]. Waltham, MA. Last updated October 30, 2019 Available at: http://www.uptodate.com/home/index.html.
4. Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807-31.

Policy Implementation/Update:

Action and Summary of Changes	Date
Changed criteria regarding previous therapy to require treatment with two agents to have been ineffective, not tolerated, or contraindicated. Updated the example for improvement or stability of disease symptoms	08/2020
Removal of UFC 24-hour urinary free cortisol level (UFC). Addition of age requirement and addition of previous trial of ketoconazole, metyrapone, or mitotane.	12/2019
Criteria created	07/2013

Policy Type: PA/SP Pharmacy Coverage Policy: UMP183

Description

Peanut allergen powder-dnfp (Palforzia) is an oral immunotherapy FDA-approved for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. The mechanism of action is unknown at this time.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
peanut allergen powder-dnfp (Palforzia)	0.5 mg – 6 mg capsule sprinkle	Peanut allergy	13 capsule sprinkles/1 day
	3 mg daily dose capsule sprinkle		45 capsule sprinkles/15 days
	6 mg daily dose capsule sprinkle		90 capsule sprinkles/15 days
	12 mg daily dose capsule sprinkle		45 capsule sprinkles/15 days
	20 mg daily dose capsule sprinkle		15 capsule sprinkles/15 days
	40 mg daily dose capsule sprinkle		30 capsule sprinkles/15 days
	80 mg daily dose capsule sprinkle		60 capsule sprinkles/15 days
	120 mg daily dose capsule sprinkle		30 capsule sprinkles/15 days
	160 mg daily dose capsule sprinkle		60 capsule sprinkles/15 days
	200 mg daily dose capsule sprinkle		30 capsule sprinkles/15 days
	240 mg daily dose capsule sprinkle		60 capsule sprinkles/15 days
	300 mg titration powder pack		15 capsule sprinkles/15 days
	300 mg maintenance capsule sprinkle powder pack		30 capsule sprinkles/30 days

Initial Evaluation

I. Peanut allergen powder-dnfp (Palforzia) may be considered medically necessary when the following criteria are met:
   A. Member is four to 17 years of age and request is for initial dose escalation; **OR**
      1. Member is four years of age or older and is up-dosing; **AND**
   B. Medication is prescribed by, or in consultation with an allergist or immunologist; **AND**
   C. The medication will not used in combination with Viaskin™ Peanut patch or other peanut desensitization therapy; **AND**
   D. A diagnosis of **peanut allergy** when the following are met:
      1. Documented medical history of severe peanut allergy, with reactions that cannot be managed with conventional therapies such as antihistamines (e.g., reaction

causes anaphylaxis, requires epinephrine use, allergy that can be triggered by smell); **AND**

2. Must have current prescription for epinephrine; **AND**
3. Medication used in conjunction with peanut-avoidant diet; **AND**
4. Member does not have severe or uncontrolled asthma; **AND**
5. Member does not have eosinophilic esophagitis

II. Peanut allergen powder-dnfp (Palforzia) is considered investigational when used for all other conditions, including but not limited to:

A. Initial dose escalation in members 18 years of age and older

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 is four to 17 years of age; **OR**

A. Member is four years of age or older and is up-dosing or in maintenance; **AND**

IV. Must have current prescription for epinephrine; **AND**

V. Medication used in conjunction with peanut-avoidant diet; **AND**

VI. Member does not have severe or uncontrolled asthma; **AND**

VII. Member does not have eosinophilic esophagitis; **AND**

VIII. The medication will not used in combination with Viaskin™ Peanut patch or other peanut desensitization therapy

Supporting Evidence

I. The pivotal Phase 3 double-blind, placebo-controlled trial (PALISADE) leading to FDA-approval of peanut allergen powder-dnfp (Palforzia) consisted of 551 subjects aged 4 through 55 years with peanut allergy. However, the primary efficacy analysis population included only those aged 4-17 years as there were very few patients 18 years and older in the trial. Thus, FDA-approval is specific to patients aged 4 through 17 years, although Up-Dosing and Maintenance may be continued in patients 4 years of age and older. To date, there is insufficient evidence to support the initiation of peanut allergen powder-dnfp (Palforzia) therapy past the age of 17 years. Studies in adults are on-going.

II. In the PALISADE trial subjects had confirmed peanut allergy diagnosis consisting of a clinical history of peanut allergy and an elevated IgE test ($\geq$ 0.35 kUA/L) or positive skin test (mean wheal diameter $\geq$ 3 mm larger than negative control). To be included in the trial subjects must have also had a reaction to an oral food challenge with dose limiting symptoms to no more than 100 mg of peanut protein (~ one third of a peanut kernel). Oral food challenges are not routinely done in practice but may be needed if the patient's clinical history and IgE test results do not clearly indicate an allergy.

III. A confirmed allergy diagnosis consisting of a clinical history of allergy along with confirmatory values (elevated IgE, positive skin test, or food challenge) is utilized as per guideline recommendations. The 2010 Guidelines for the Diagnosis and Management of Food Allergy in the United States indicate, "because individuals can develop allergic sensitization (as evidenced by the presence of allergen-specific IgE (sIgE)) to food allergens without having clinical symptoms on exposure to those foods, an sIgE-mediated food allergy requires both the presence of sensitization and the development of specific signs and symptoms on exposure to that food. Sensitization alone is not sufficient to define food allergy".

IV. The peanut allergen powder-dnfp (Palforzia) package insert and Risk Evaluation and Mitigation Strategy (REMS) program require peanut allergen powder-dnfp (Palforzia) be used in conjunction with a peanut-avoidant diet and prescribed with injectable epinephrine. Additionally, the package insert carries a black box warning for anaphylaxis that further states treatment should not be administered in patients with uncontrolled asthma.

V. Peanut allergen powder-dnfp (Palforzia) carries a warning and precaution for eosinophilic esophagitis as cases of eosinophilic esophagitis occurred in clinical trials (13.7% of patients during dose escalation). Use in patients with a history of eosinophilic esophagitis is contraindicated per the package insert. Eosinophilic esophagitis is inflammation and increased numbers of eosinophils in the esophagus. It can cause feeding disorders, vomiting, reflux symptoms, and abdominal pain in children; and dysphagia and esophageal food impactions in adolescents and adults. Eosinophilic esophagitis is a known complication of oral immunotherapy.

VI. Viaskin™ Peanut patch is a peanut desensitization therapy under review by the FDA. Safety and efficacy of combination use of peanut desensitization therapy is unknown.

VII. An evidence report by the Institute for Clinical and Economic Review (ICER) states there is only moderate certainty of a comparable, small, or substantial net health benefit and a small (but non-zero) likelihood of a negative net health benefit for peanut allergen powder-dnfp (Palforzia) compared with strict avoidance and rapid use of epinephrine (PI, promising, but inconclusive). This is due to net health benefit being driven by changes in quality of life and reductions in reactions to accidental exposure to peanuts, neither of which has been demonstrated. Additionally, the increase in patients treated who were able to tolerate 600 mg of peanut protein (~2 peanut kernels) during the exit food challenge in the trial compared with those treated with placebo (67.2% vs. 4.0%) is balanced by a significant increase in gastrointestinal symptoms, systemic allergic reactions, and epinephrine use.

VIII. Use of peanut allergen powder-dnfp (Palforzia) is reserved for members with a history of severe peanut allergy. Due to the safety risks noted above coupled with the unknown clinical significance and meaningfulness of improving tolerance of a single dose of 600 mg peanut protein. How tolerance of 600 mg of peanut protein relates to changes in quality of life and reductions in reactions to accidental exposure to peanuts was not evaluated in the clinical trial.

Investigational or Not Medically Necessary Uses

I. Peanut allergen powder-dnfp (Palforzia) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Initial dose escalation in members 18 years of age and older

i. Though the PALISADE trial included subjects aged 4-55 years, the prespecified primary analysis population consisted of the subjects aged 4-17 years who received at least one dose of study drug (n=496). Efficacy in those who were 18 and older (n=55) was evaluated as a secondary endpoint but did not show statistical significance.
ii. FDA-approval is specific to patients aged 4 through 17 years, although Up-Dosing and Maintenance may be continued in patients 4 years of age and older. To date, there is insufficient evidence to support the initiation of peanut allergen powder-dnfp (Palforzia) therapy past the age of 17 years. Studies in adults are on-going.

References

1. Palforzia [Prescribing information]. Aimmune Therapeutics, Inc: Brisbane, CA. January 2020.
2. Vickery BP, Vereda A, Casale TB, et al. AR101 Oral Immunotherapy for Peanut Allergy. N Engl J Med. 2018;379(21):1991-2001.
3. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. J Allergy Clin Immunol. 2014;134(5):1016-25.e43.
4. UpToDate, Inc. Investigational therapies for food allergy: Oral immunotherapy. UpToDate [database online]. Waltham, MA. Last updated Nov 25, 2019 Available at: http://www.uptodate.com/home/index.html.
5. UpToDate, Inc. Diagnostic evaluation of food allergy. UpToDate [database online]. Waltham, MA. Last updated Apr 23, 2019 Available at: http://www.uptodate.com/home/index.html.
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7. Sampson HA, Gerth van wijk R, Bindslev-jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012;130(6):1260-74.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2020

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

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

Initial Evaluation

I. **Pegfilgrastim-cbqv (Udenyca) and pegfilgrastim-bmez (Ziextenzo)** 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**

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 >2.0mg/dL) ; **OR**
   l. Chronic immunosuppression in the post-transplant setting including organ transplant

II. Pegfilgrastim (Neulasta, Neulasta Onpro), pegfilgrastim-jmdb (Fulphila), 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-cbqv (Udenyca) AND pegfilgrastim-bmez (Ziextenzo) have been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

I. Same as initial prior authorization policy criteria

Supporting Evidence

II. Indication listed under section I supported by FDA-labeled indication(s) or recommended per Compendia

References

1. Neupogen [package insert]. Thousand Oaks, CA; Amgen Inc; June 2016. Accessed March 2018.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated preferred products to add Ziextenzo (effective on 1/1/2021) and move Neulasta/Neulasta Onpro to non-preferred (effective 1/1/2021). Added Nyvepria, biosimilar to Neulasta.	11/2020
Updated policy to allow for 28 days supply	02/2020
Added Ziextenzo, biosimilar to Neulasta; update quantity limits to allow for 30 days supply	12/2019
Added Udenyca, biosimilar to Neulasta	01/2019
Neulasta, Neulasta Onpro preferred GCSF	12/2018
Added Fulphila, biosimilar to Neulasta	07/2018
Policy created	02/2018

peginterferon alfa-2B (Sylatron®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP098

Description

Peginterferon alfa-2b (Sylatron) is a subcutaneous interferon which induces cellular activities related to binding specific cell-surface membrane receptors. These include suppression of cell proliferation, antiviral activity and immunomodulating effects.

Length of Authorization

- Initial: Eight weeks
- Renewal: 12 months, maximum of five years of therapy

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
peginterferon-alfa 2b (Sylatron)	200 mcg subcutaneous powder for solution	Adjuvant treatment of melanoma with microscopic or gross nodal involvement	4 vials/ 28 days
	300 mcg subcutaneous powder for solution		
	600 mcg subcutaneous powder for solution		

Initial Evaluation

I. Peginterferon alfa-2b (Sylatron) 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 **melanoma** when the following are met:
      1. The member has stage III disease; **AND**
      2. The member has microscopic or gross nodal involvement; **AND**
      3. The member has had definitive surgical resection including complete lymphadenectomy within the past 84 days (12 weeks); **AND**
      4. Peginterferon alfa-2b is prescribed as adjuvant treatment; **AND**
      5. The prescribed dose does not exceed 6 mcg/kg per week for the first eight weeks, then 3 mcg/kg per week thereafter; **AND**
      6. Attestation from the provider that the member does **not** have any of the following:
         i. Hepatic decompensation (Child-Pugh Score >6, class B and C)
         ii. Autoimmune hepatitis

iii. Depression or other neuropsychiatric disorders

II. Peginterferon-alfa 2b (Sylatron) is considered investigational when used for all other conditions, including but not limited to:
   A. Hepatitis C
   B. Cholangiocarcinoma
   C. Hematological malignancies
   D. Solid tumors and malignancies outside of melanoma

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. Member has experienced response to treatment, such as stabilization of disease, decrease in disease spread, regression of disease; **AND**
V. The prescribed dose does not exceed 3 mcg/kg after the first eight weeks of therapy; **AND**
VI. Attestation from the provider that the member does **not** have any of the following:
   - Hepatic decompensation (Child-Pugh Score >6, class B and C)
   - Autoimmune hepatitis
   - Depression or other neuropsychiatric disorders

Supporting Evidence

I. Peginterfeon-alfa 2b (Sylatron) was evaluated in an open-label, randomized study of 1256 subjects with surgically resected stage III melanoma within 84 days (12 weeks) of regional lymph node dissection. The dose administered was 6 mcg/kg per week for eight weeks on average. Less than 1% received this dose for longer than nine weeks; thus, safety and efficacy for this dose for more than eight weeks is not FDA-approved and has not been sufficiently evaluated for safety and or efficacy.
II. Subjects were randomized to observation or peginterferon-alfa 2b (Sylatron) for up to five years. The primary outcome was relapse-free survival (RFS) or death from any cause, with overall survival (OS) as the secondary outcome. The RFS duration for peginterferon-alfa 2b (Sylatron) was 34.8 months versus 25.5 months for the observation arm. Safety and efficacy past five years of therapy has not been established, and OS benefits have not been established.
III. Peginterferon-alfa 2b (Sylatron) has a Black Box Warning for neuropsychiatric disorders, and may cause or aggravate severe depression or other psychiatric adverse events. Members with these conditions should only be started on therapy if the benefit outweighs the risks and should be monitored closely. Resolution of symptoms does not always occur upon discontinuation. Additionally, peginterferon-alfa 2b (Sylatron) is contraindicated in autoimmune hepatitis and those with hepatic decompensation.

IV. Vials of peginterferon-alfa 2b (Sylatron) are dose priced; therefore, vial size should be chosen to provide the appropriate dose and minimize waste.

V. As of November 2019, National Comprehensive Cancer Network treatment guidelines for cutaneous melanoma did not have recommendations for peginterferon-alfa 2b (Sylatron) in the setting of melanoma.

Investigational or Not Medically Necessary Uses

I. Peginterferon-alfa 2b (Sylatron) is not FDA-approved and has not been sufficiently evaluated for safety and/or efficacy in the following settings:
   A. Hepatitis C
   B. Cholangiocarcinoma
   C. Hematological malignancies
   D. Solid tumors and malignancies outside of melanoma

References

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Policy Implementation/Update:

Date Created	December 2012
Date Effective	January 2013
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Criteria updated to include age edit, stage of disease, place in therapy, maximum dose. Renewal criteria updated to current format and language, added specialist requirement, contraindications, dose check. Change of initial duration of approval, change to maximum coverage of five years.	11/2019

peginterferon alfa-2a (Pegasys®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP213

Description

Peginterferon alfa-2a (Pegasys) is a subcutaneous pegylated interferon which induces cellular activities related to binding specific cell-surface membrane receptors. These include suppression of cell proliferation, antiviral activity, and immunomodulating effects.

Length of Authorization

- Initial:
  - Chronic Hepatitis B: 48 weeks
  - All other indications: 12 months
- Renewal:
  - i. For Polycythemia Vera AND Essential Thrombocythemia: 12 months
  - ii. For all other indications: None

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Peginterferon Alfa-2a (Pegasys; Pegasys ProClick)	180 µg/mL vial	Chronic Hepatitis B; Chronic Hepatitis D; Polycythemia Vera; Essential Thrombocythemia	4 vials/30 days
	180 µg/0.5 mL prefilled syringe		4 syringes/30 days
	135 µg/0.5 mL autoinjector		4 autoinjectors/30 days
	180 µg/0.5 mL autoinjector		4 autoinjectors/30 days

Initial Evaluation

I. **Peginterferon Alfa-2a (Pegasys)** may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, a gastroenterologist, hepatologist, infectious disease specialist, hematologist, or an oncologist; **AND**
   B. The medication will be used as monotherapy; **AND**
   C. Member has not previously experienced disease progression while on peginterferon Alfa-2a (Pegasys) for the treatment of indications listed in this policy; **AND**
   D. Provider attestation that the member does **not** have any of the following:
      i. Hepatic decompensation (Child-Pugh Score> 6, Class B and C)
      ii. Autoimmune hepatitis
      iii. Depression or other neuropsychiatric disorders; **AND**
   E. A diagnosis of one of the following:
      1. **Chronic Hepatitis B; AND**
         i. Member is 3 to 17 years old; **AND**

a. Provider attests to **ALL** of the following:
    i. Member is hepatitis B e-antigen (HBeAg) positive; **AND**
    ii. Member is noncirrhotic; **AND**
    iii. Member has elevated serum alanine aminotransferase (ALT) more than twice the upper limit of normal (ULN); **OR**

ii. Member is 18 years of age or older; **AND**
    a. Documentation of hepatitis B (HBV) viral load less than 12 months old (i.e. serum HBV > 100,000 copies/mL or HBV DNA levels > 2000 IU/mL); **OR**

2. **Chronic Hepatitis D; AND**
    i. Diagnosis of chronic hepatitis D (HDV) confirmed by a quantifiable HDV RNA; **AND**
    ii. Provider attests the member has active liver disease (e.g. elevated serum ALT, or liver biopsy); **OR**
3. **Polycythemia Vera; OR Essential Thrombocythemia; AND**
    i. Member is 18 years of age or older; **AND**
    ii. Provider attests that the member has high-risk disease; **AND**
    iii. Treatment with generic hydroxyurea has been ineffective, contraindicated, or not tolerated

II. Peginterferon Alfa-2a (Pegasys) is considered not medically necessary when used for:
    A. Treatment of chronic hepatitis C (HCV)

III. Peginterferon Alfa-2a (Pegasys) is considered investigational when used for all other conditions, including but not limited to:
    A. Malignant melanoma
    B. Renal cell carcinoma
    C. Hairy cell leukemia
    D. Myelofibrosis
    E. Systemic mastocytosis
    F. Chronic myelogenous leukemia (CML)

Renewal Evaluation

I. Member has not been established on therapy by use of free samples, manufacturer coupons or otherwise; **AND**
II. Member has received previous prior authorization for this agent through THIS health plan; **AND**
III. Provider attestation that the member does **not** have any of the following: i. Hepatic decompensation (Child-Pugh Score> 6, Class B and C)
    ii. Autoimmune hepatitis
    iii. Depression or other neuropsychiatric disorders; **AND**
IV. Member has diagnosis of **Polycythemia Vera, or Essential Thrombocythemia; AND**

V. Member has experienced response to therapy such as disease stabilization or remission (e.g. complete or partial response)

Supporting Evidence

I. Interferons, a family of naturally occurring small protein molecules or glycoproteins, are produced by cells in response to viral infections or various synthetic or biologic inducers. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. Interferons have been found to mediate antiviral, antiproliferative, and immunomodulatory activities. Peginterferon alfa-2a (Pegasys®) is a covalent conjugate of recombinant alfa-2a interferon. Other types of alfa interferon such as Peginterferon alfa-2b (PegIntron®, Sylatron™) are covered under separate PA policies based on their respective indications.

II. Given the treatment complexities associated with the indications listed in this policy, use of peginterferon alfa-2a (Pegasys) should be prescribed by a specialist practicing in the respective area of specialty.

III. Patients with chronic hepatitis B are at an increased risk to develop cirrhosis, liver failure, and liver cancer. Hepatitis B e-antigen (HBeAg) and Hepatitis B viral DNA (HBV DNA) are both markers of HBV replication and their presence provides a rationale for initiating therapy to stop the progression of liver disease. In the past, the ability to detect HBV DNA in the serum by hybridization assays was a major factor in determining which patients should be treated. This assay is sensitive enough to detect viral DNA when it is present in amounts ≥ 105 copies/ml and consequently this viral level became an important benchmark in treatment algorithms. As improvements in viral detection have advanced it has become apparent that it is not possible to designate a single HBV DNA value that can differentiate between inactive hepatitis B carriers and patients suffering from chronic hepatitis B.

IV. There are several agents currently indicated for treatment of chronic HBV. They include Peg-interferon, lamivudine, telbivudine, entecavir, tenofovir and adefovir. AASLD guidelines recommend peginterferon alfa-2a, entecavir, or tenofovir as preferred initial therapy for adults with immune-active chronic HBV infection. peginterferon alfa-2b is not FDA approved for chronic hepatitis B; however, there are studies that support its use for this indication. Overall, the quality of evidence is considered low for this setting.

V. Interferon therapy is not recommended in patients with decompensated cirrhosis because it increases their risk for developing bacterial infections and it can potentially worsen their condition.

VI. Peginterferon alfa-2a (Pegasys) was evaluated in multiple phase 3, randomized clinical trials, as monotherapy and in combination with lamivudine, for patients with HBV infection. All subjects were adults with compensated liver disease, had chronic HBV infection and evidence of HBV replication (serum HBV greater than 500,000 copies/mL for HBeAg-positive patients and greater than 100,000 copies/mL for HBeAg-negative patients). All subjects had serum ALT between 1 and 10 times the upper limit of normal (ULN). Treatment with peginterferon alfa-2a (Pegasys) exhibited significant serological, virological, and histological responses at the treatment interval of 24 weeks. Co-administration of lamivudine with Pegasys did not result in additional sustained response as compared to Pegasys monotherapy.

VII. In the setting of chronic hepatitis C (HCV), the sustained virological response (SVR) is defined as undetectable HCV RNA in 12 weeks (SVR 12) or 24 weeks (SVR 24) after treatment completion.

Cure rate, which achieves SVR, is more than 99%. SVR is generally associated with resolution of liver disease in patient without cirrhosis, but in the patient with cirrhosis there remains risk of life-threatening complications.

VIII. Ppeginterferon alfa-2a (Pegasys) has been studied as monotherapy and in combination with ribavirin in seven randomized, active-controlled clinical trials. Pooled population analysis showed the participants in these trials had HCV genotype 1 through 6, were of ages 5 years and above, and had detectable viral load at treatment initiation. Therapeutic responses were observed at median 12 weeks of treatment and durability of response sustained up to the 48-week trial window. Recommended total duration of therapy for peginterferon alfa-2a (Pegasys) is up to 48 weeks (per FDA-approval).

IX. The only guideline recommended treatment of chronic hepatitis D is interferon alfa (IFN-a). Peginterferon alfa is the drug of choice without clear differences in efficacy between peginterferon alfa-2a (Pegasys) or peginterferon alfa-2b (Pegintron). Treatment success, defined as undetectable HDV RNA at 24 weeks after completing treatment, ranges from 23% to 57%. Late relapses can occur with longer follow-up, leading to very low rates of sustained HDV-RNA undetectability. In the multicenter HIDIT-1 (Hep-Net-International-Delta-Hepatitis-Intervention-Study 1) study of peginterferon alfa-2a (Pegasys) for 48 weeks with or without adefovir, 40% of patients achieved an undetectable HDV-RNA level 24 weeks after completing therapy, but at a mean follow-up 4.3 years later, only 12% remained undetectable.

X. Although not FDA-approved, use of peginterferon alfa-2a (Pegasys) is supported by NCCN guidelines (category 2A recommendation) for the treatment of essential thrombocythemia (ET) and polycythemia vera (PV). PV and ET are BCR-ABL1–negative myeloproliferative neoplasms. Both diseases are characterized by a clonal myeloid proliferation with excessive production of blood elements. The hallmarks of ET and PV include an increased risk of thrombohemorrhagic complications, and a variable risk of transformation to myelofibrosis (MF) and/or acute myeloid leukemia (AML). Recommended use of peginterferon alfa-2a (Pegasys) in these settings is based on multiple clinical trials and retrospective studies. Notably, a phase 2 open-label clinical trial assessed Pegasys for induction of complete (CR) and partial (PR) hematologic responses in patients with high-risk ET (n=65) or PV (n=50), who were either refractory or intolerant to HU. The overall response rates (ORRs; CR/PR) at 12 months were 69.2% (43.1% and 26.2%) in ET patients and 60% (22% and 38%) in PV patients. This clinical trial was further extended to a confirmatory phase 3 trial using hydroxyurea as active comparator (N=168), wherein similar ORR was observed in the treatment arm. The treatment efficacy was comparable to hydroxyurea.

XI. For PV and ET patient populations, high-risk disease is defined by a history of thrombosis, age >60 years, a history of bleeding (ET only), platelet counts >1500 X 10^9/L in ET and >1000 X 10^9/L in PV, vasomotor symptoms (erythromelalgia, severe migraine headaches), significant or symptomatic splenomegaly, and the presence of diabetes or uncontrolled hypertension. However, younger patients (<60 years) without any other defining factors may qualify for cytoreductive therapy with peginterferon alfa-2a (Pegasys) when hydroxyurea is contraindicated (e.g. during pregnancy).

XII. There is lack of efficacy and safety data for use of peginterferon alfa-2a (Pegasys) in pediatric population with ET and/ or PV.

Investigational or Not Medically Necessary Uses

I. Peginterferon alfa-2a (Pegasys) has been investigated for safety and efficacy in some the following indications. Safety and efficacy have not been established in all of the following:

A. Chronic hepatitis C: Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of chronic hepatitis C (HCV) infection in compensated liver disease, the WHO and AALSD guidelines no longer recommend interferon-based regimens for HCV infection. Recently updated 2019 AASLD guidelines for treatment of hepatitis C recommend use of newer direct antiviral agents (DAA) as preferred treatment regimens. Overall, it is guideline consensus that peginterferon alfa-2a based treatments have relatively lower efficacy, longer onset of action and higher safety concerns. Therefore, use of peginterferon alfa-2a is recommended for limited situations when all DAA are contraindicated.

B. Myelofibrosis: NCCN guideline for myeloproliferative neoplasms recommends use of peginterferon alfa-2a (Pegasys) as 'useful in certain circumstances' as a possible alternative to ruxolitinib (Jakafi) and hydroxyurea, only when cytoreduction is considered symptomatically beneficial. This recommendation stems from a retrospective case study and observational single-center open-label trial in 30 patients, wherein 7% CR and 30% PR were reported. Overall quality of evidence is considered low.

C. Systemic mastocytosis: peginterferon alfa-2a (Pegasys) was included in NCCN guidelines for systemic mastocytosis (SM) (category 2A recommendation) as a possible treatment option for advanced SM patients. This recommendation is restricted to patients with slowly progressing disease without need for rapid cytoreduction. Tyrosine kinase inhibitors (TKI), midostaurine (Rydapt), and cladribine remain preferred therapeutic options in this space. Guidelines note that alfa interferon has recently fallen out of favor because of its slow onset of action and poor tolerability. Given the potential harmful effects of kinase inhibitors on germ cells and cladribine on the fetus (both pregnancy category D), alfa interferon may be an option in pregnancy. However, there are no supporting clinical trials to establish the efficacy and safety of peginterferon alfa-2a (Pegasys) in this patient population.

D. Chronic myelogenous leukemia (CML): NCCN guidelines recommend use of interferon alfa for management of CML during pregnancy due to contraindication to use of tyrosine kinase inhibitors (TKI) and hydroxyurea in this population. It is noted that if introduced earlier (during 1st trimester), the use of interferon may preserve molecular remission after discontinuation of TKI or HU. However, data are insufficient to establish the use of peginterferon alfa-2a (Pegasys) in pregnancy.

E. Renal cell carcinoma (RCC): interferon-alfa was studied in RCC as an adjuvant therapy for high-risk, clear cell, localized RCC post nephrectomy. Randomized trials in patients who had locally advanced, completely resected RCC showed no delay in time to relapse or improvement in survival with adjuvant therapy.

F. Malignant melanoma: Interferon alfa-2b (Intron A) and peginterferon alfa-2b (Sylatron) have supporting clinical evidence and are FDA-approved for malignant melanoma. Safety and efficacy of peginterferon alfa-2a (Pegasys) has not been established in these settings.

G. Hairy cell leukemia: NCCN guidelines for hairy cell leukemia recommend peginterferon alfa-2a as a possible alternative for the treatment of relapsed/ refractory hairy cell leukemia. However, purine analogs (cladribine, pentostatin) and rituximab remain preferred

therapeutic options in this space. In a 1995 phase III intergroup study (N=319), efficacy and safety of pentostatin was compared with that of interferon alfa with a treatment follow-up of median 57 months. Subjects receiving Pentostatin reported higher complete remission (CR) rates versus those with interferon alfa treatment (76% vs 11%; p< 0.0001) along with longer relapse-free survival (RFS) (not reached vs 20 months; p< 0.0001). NCCN guidelines note that with the advent of purine analogs, the role of interferon alfa as a treatment option for hairy cell leukemia is limited.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria update: Transition from criteria to policy format and review of FDA-approved and guideline supported indications for peginterferon alfa-2a (Pegasys). Added supporting evidence for all indications listed in the policy. Removed indication of chronic hepatitis C per current AALSD and WHO guideline recommendation. Reviewed available evidence for indications listed under not medically necessary and investigational uses and added relevant clinical information to supporting evidence section	12/2020
Previous reviews and updates	12/2012; 08/2012; 12/2011; 12/2008; 11/2007
Criteria created	01/2006

Policy Type: PA/SP Pharmacy Coverage Policy: UMP148

Description

Pegvaliase (Palynziq) is a PEGylated phenylalanine-metabolizing enzyme that works to reduce blood phenylalanine concentrations by converting phenylalanine to ammonia and transcinnamic acid.

Sapropterin dihydrochloride (Kuvan) is a synthetic form of the cofactor BH4 (tetrahydrobiopterin) for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates phenylalanine to form tyrosine. BH4 activates residual PAH enzyme, improving normal phenylalanine metabolism and decreasing phenylalanine levels.

Length of Authorization

- Initial:
  - Pegvaliase (Palynziq): Six months
  - Sapropterin dihydrochloride (Kuvan): Two months
- Renewal:
  - Pegvaliase (Palynziq): 12 months
  - Sapropterin dihydrochloride (Kuvan): 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
pegvaliase (Palynziq)	2.5 mg/0.5 mL	Phenylketonuria (PKU)	60 syringes/30 days
	10 mg/0.5 mL		
	20 mg/1 mL		
sapropterin dihydrochloride (Kuvan)	100 mg tablets		20 mg/kg/day
	100 mg powder for oral solution		
	500 mg powder for oral solution		

Initial Evaluation

I. Pegvaliase (Palynziq) and sapropterin dihydrochloride (Kuvan) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a metabolic diseases specialist or a provider who specializes in the treatment of phenylketonuria and other metabolic disorders; **AND**
   B. Documentation of current blood phenylalanine concentration is submitted; **AND**
   C. Documentation of current compliance with a phenylalanine restricted diet is submitted; **AND**
   D. Member is going to continue to restrict phenylalanine from their diet; **AND**

E. A diagnosis of **phenylketonuria (PKU)** when the following are met:

1. *[Only for pegvaliase (Palynziq)];*
   - i. Member is 18 years of age or older; **AND**
   - ii. Member has uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management [e.g., phenylalanine restricted diet, Kuvan (sapropterin)]; **AND**
   - iii. Not used in combination with sapropterin dihydrochloride (Kuvan); **OR**
2. *[Only for sapropterin dihydrochloride (Kuvan)];*
   - i. Member has tetrahydrobiopterin- (BH4-) responsive PKU; **AND**
   - ii. Member has uncontrolled blood phenylalanine concentrations greater than 360 micromol/L on existing management [e.g., phenylalanine restricted diet]; **AND**
   - iii. Not used in combination with pegvaliase (Palynziq).

II. Pegvaliase (Palynziq) and sapropterin dihydrochloride (Kuvan) is considered investigational when used for all other conditions, including but not limited to:

A. Liver Cirrhosis and Portal Hypertension
B. Autism spectrum disorder
C. Gastroparesis
D. 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. Medication is prescribed by, or in consultation with, a metabolic diseases specialist or a provider who specializes in the treatment of phenylketonuria and other metabolic disorders; **AND**
IV. Documentation of current compliance with a phenylalanine restricted diet is submitted; **AND**
V. Member is going to continue to restrict phenylalanine from their diet; **AND**
VI. Documentation of current blood phenylalanine concentration is submitted; **AND**
VII. Attestation of member compliance to therapy with pegvaliase (Palynziq) or dihydrochloride (Kuvan); **AND**
VIII. Member had a response to pegvaliase (Palynziq) therapy; defined as:
- At least a 20% reduction in blood phenylalanine levels from baseline; **OR**
- Blood phenylalanine concentration less than or equal to 600 micromol/L; **OR**

IX. Member had a response to sapropterin dihydrochloride (Kuvan) therapy; defined as:
- At least a 30% reduction in in blood phenylalanine levels from baseline

Supporting Evidence

I. Phenylketonuria (PKU) is an inherited disorder that increases the levels of a substance called phenylalanine in the blood. If PKU is not treated, phenylalanine can build up to harmful levels in the body causing intellectual disability and other serious health problems. Seizures, delayed development, behavioral problems, and psychiatric disorders are also common. Considering all the aspects of this disease state and that it is crucial to identify if a member is responding to therapy, the medication needs to be prescribed by, or in consultation with, a metabolic diseases specialist or a provider who specializes in the treatment of phenylketonuria and other metabolic disorders.

II. For sapropterin dihydrochloride (Kuvan) the response to therapy is determined by change in blood phenylalanine following treatment. If blood phenylalanine does not decrease from baseline at 10 mg/kg per day, the dose may be increased to 20 mg/kg per day. Patients whose blood phenylalanine does not decrease after 1 month of treatment at 20 mg/kg per day are non-responders and treatment should be discontinued.

III. For pegvaliase (Palynziq) the response to therapy is determined by change in blood phenylalanine following treatment. In patients who have not achieved a response (at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 micromol/L) after 16 weeks of continuous treatment with the maximum dosage of 40 mg once daily, pegvaliase (Palynziq) should be discontinued.

IV. It is crucial for treatment and prevention of disease progression to obtain the blood levels of phenylalanine prior to treatment start.

V. According to the American College of Medical Genetics and Genomics (ACMG) Practice Guidelines, dietary therapy, with restriction of dietary phenylalanine intake, remains the mainstay of therapy for PAH deficiency. The goal of the diet is to provide enough natural protein for the patient to be healthy and grow normally with sufficient restriction to keep blood phenylalanine in the treatment range. PKU medication is not a replacement for diet.

VI. Pegvaliase (Palynziq) is indicated to reduce blood phenylalanine concentrations in adult patients with PKU who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management [e.g., phenylalanine restricted diet, Kuvan (sapropterin)].

VII. The safety and efficacy of pegvaliase (Palynziq) in pediatric patients has not been assessed in clinical trials and therefor there is no robust evidence to support the use.

VIII. There is no robust clinical trial data to show an increase benefit and the safety profile of concomitant use of pegvaliase (Palynziq) and sapropterin dihydrochloride (Kuvan).

IX. Sapropterin dihydrochloride (Kuvan) is indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive PKU. Kuvan is to be used in conjunction with a Phe-restricted diet.

Investigational or Not Medically Necessary Uses

I. Pegvaliase (Palynziq);
   A. There is limited or no published clinical trial data to support the use of pegvaliase (Palynziq) in conditions other than PKU.

II. Sapropterin dihydrochloride (Kuvan);
   A. Liver Cirrhosis and Portal Hypertension
      i. A randomized, blinded, and placebo controlled trial was conducted to assess the effects of sapropterin dihydrochloride (Kuvan) on hepatic and systemic hemodynamics in patients with liver cirrhosis and portal hypertension. The trial data showed that sapropterin dihydrochloride (Kuvan), did not reduce portal pressure in patients with cirrhosis.
   B. Autism spectrum disorder (ASD)
      i. A prospective 16-week open-label outpatient treatment trial of sapropterin dihydrochloride (Kuvan) for core and associated ASD symptoms in 2–6-year-old children with confirmed language and/or social delays extended the understanding of the effect of BH_4 treatment on the cognitive and behavioral symptoms of individuals with ASD
      ii. The results of a double-blind placebo-controlled crossover study, designed to examine the tetrahydrobiopterin pathway genes in autism, indicated a possible effect of BH4 treatment in children with autistic disorder, but the study does not have enough power and it wasn't designed to show efficacy and safety of the use of sapropterin dihydrochloride (Kuvan) in the treatment of autism spectrum disorder. There is no robust safety and efficacy data to support the use of sapropterin dihydrochloride (Kuvan) in patients with autism spectrum disorder.
   C. Gastroparesis
      i. One small open label trial consisting of low quality evidence. Further evaluation is needed to support the use of sapropterin dihydrochloride (Kuvan) in this setting.
   D. Schizophrenia
      i. One small open label trial consisting of low quality evidence is available with ongoing trials recruiting as of 2019. Further evaluation is need to support use of sapropterin dihydrochloride (Kuvan) in this setting.

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13. ClinicalTrials.gov. Impact of KUVAN® on Gastric Relaxation in Women With Diabetic Gastroparesis. NCT01135186.
14. ClinicalTrials.gov. Kuvan in People With Schizophrenia and Schizoaffective Disorder. NCT01706965.

Policy Implementation/Update:

	sapropterin dihydrochloride (Kuvan)	pegvaliase (Palynziq)
Date Created	January 2009	July 2018
Date Effective	February 2009	August 2018
Last Updated	December 2019	
Last Reviewed	December 2019	

Action and Summary of Changes	Date
• Updated criteria to policy format and combined separate polices into one • Ensured sapropterin dihydrochloride (Kuvan) is not used in combination with pegvaliase (Palynziq) • Requirement of member requesting sapropterin dihydrochloride (Kuvan) to have tetrahydrobiopterin- (BH4-) responsive PKU • Added criteria to require documentation of current blood phenylalanine concentration and of current compliance with a phenylalanine restricted diet • Adjusted requirement of phenylalanine levels in use of sapropterin dihydrochloride (Kuvan) to be greater than 360 micromol/L for all ages • Updated renewal duration with Kuvan to 1 year to align with Palynziq	12/2019

pegvisomant (Somavert®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP149

Description

Pegvisomant (Somavert) selectively binds to growth hormone (GH) receptors on cell surfaces, where it blocks the binding of endogenous GH, and thus interferes with signal transduction. Inhibition of GH action results in decreased serum concentrations of insulin-like growth factor-I (IGF-I), as well as other GH-responsive serum proteins, including IGF binding protein-3 (IGFBP-3), and the acid-labile subunit (ALS).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
pegvisomant (Somavert)	10 mg vial	Acromegaly	60 vials/30 days
	15 mg vial		60 vials/30 days
	20 mg vial		30 vials/30 days
	25 mg vial		30 vials/30 days
	30 mg vial		30 vials/30 days

Initial Evaluation

I. Pegvisomant (Somavert) 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; **AND**
   C. A diagnosis of **acromegaly** when the following are met:
      1. Diagnosis is confirmed by elevated serum IGF-1 for member's age and gender, (including laboratory reference range); **OR**
         a. If normal IGF-1, elevated growth hormone level nadir of > 1 ng/mL during an oral glucose tolerance test (OGTT); **AND**
      2. Documentation of inadequate response to surgery or radiation therapy; **AND**
      3. Treatment with octreotide (Sandostatin), cabergoline, or bromocriptine (Parlodel) has been ineffective, contraindicated, or not tolerated

II. Pegvisomant (Somavert) is considered <u>investigational</u> 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 (improvements in sleep apnea, tissue swelling, headache, arthralgias); **AND**
IV. Serum IGF-1 level has decreased from baseline or normalized (according to the lab reference range based on member age and gender)

Supporting Evidence

I. Acromegaly is a hormonal disorder that occurs when the pituitary gland produces too much growth hormone (GH). Typically, this is caused by adenomas (benign tumor) on the pituitary gland. Diagnosis typically occurs in middle-aged adults; however, symptoms can appear at any age. Surgical intervention is the preferred treatment.
II. According to the American Association of Clinical Endocrinologists (AACE) guidelines, medical therapy is pursued in patients with a tumor that cannot be completely removed surgically, have no compressive tumor effects, are poor surgical candidates, or prefer medical management. Goals of therapy include the normalization of biochemical variables, reversal of mass-effects of the tumor, improvement in signs, symptoms, and comorbidities of disease, and the minimization of long-term mortality risk. In most patients, medical therapy is used as adjuvant treatment in the setting of persistent disease despite surgical intervention.
III. AACE guidelines recommend a random IGF-1 value (a marker of integrated GH secretion) to be measured for diagnosis and as post-intervention therapeutic monitoring. A serum IGF-1 level should be remeasured at 12 weeks; a normal IGF-1 value is consistent with surgical remission. If a repeat serum IGF-1 value is reduced from baseline, but is still elevated at 12 weeks, an additional repeat testing is done in another 9 to 12 weeks to determine the presence of delayed biochemical normalization, before proceeding with potential surgical re-exploration, medical therapy, or radiation therapy. Additionally, an oral glucose tolerance test is also utilized as a diagnostic tool, especially in conditions that are associated with lower IGF-1 concentrations (e.g., hypothyroidism, malnutrition, uncontrolled type 1 diabetes, liver failure, renal failure, oral estrogen use) where the diagnosis of acromegaly could be missed. Inability to suppress serum GH to less than 1 ng/mL after glucose administration is considered the diagnostic criterion for acromegaly and is the gold standard for determining control of GH secretion after surgical treatment.
IV. Per guidelines, there are three classes of medical therapy: dopamine agonists (e.g. caberfoline, bromocriptine), somatostatin analogues (e.g. octreotide, lanreotide), and a GH-receptor antagonist (e.g. pegvisomant). Dopamine agonists are considered first-line medical therapy as they are relatively inexpensive in comparison to alternative medical therapy options and have simple oral administration.
V. With the administration of pegvisomant (Somavert), serum IGF-1 should be measured alone to monitor the dose efficacy. There is no benefit from the measurement of serum GH in

conjunction with pegvisomant (Somavert) therapy. GH levels increase when pegvisomant (Somavert) is administered, and the GH levels have no effect on pegvisomant (Somavert) dosing.

Investigational or Not Medically Necessary Uses

I. There is limited to no evidence to support the use of pegvisomant (Somavert) in any other condition.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of confirmed diagnosis requirements (elevated IGF-1 o**r** GH level). Added requirement of reduced or normalized IGF-1 levels at renewal. Updated initial approval duration from 12 months to 6 months.	05/2020
Addition of renewal criteria. Added age requirement of 18 years or older. Added requirement for agent to be prescribed by or in consultation with an endocrinologist.	12/2019
Policy created	01/2006

pemigatinib (Pemazyre™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP191

Split Fill Management*

Description

Pemigatinib (Pemazyre) is an orally administered fibroblast growth factor receptor 2 (FGFR2) inhibitor, with activity against FGFR2 fusions or rearrangements in cholangiocarcinoma cells.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Pemigatinib (Pemazyre)	13.5 mg tablet	Previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma in adults with FGFR2 fusions or rearrangements	14 tablets/21 days
	9 mg tablet		
	4.5 mg tablet		

Initial Evaluation

I. Pemigatinib (Pemazyre) is considered investigational when used for all conditions, including but not limited to cholangiocarcinoma.

Renewal Evaluation

I. N/A

Supporting Evidence

I. Pemigatinib (Pemazyre) is the first targeted therapy for cholangiocarcinoma that harbors FGFR2 fusions or rearrangements. Pemigatinib (Pemazyre) is a second-line chemotherapy option. Guideline preferred first line chemotherapy is gemcitabine and cisplatin, while second-line options include mFOLFOX, FOLFIRI, and regorafenib (Stivarga).

II. Pemigatinib (Pemazyre) was evaluated in FIGHT-202, an open-label, single-arm, multi-cohort Phase 2 trial. Patients (N=146) with locally advanced or metastatic CCA, previously treated with at least 1 chemotherapy were included. FDA approval was based on the overall response rate (ORR) in patients with FGFR2 gene fusion or rearrangements.

III. The primary efficacy endpoint was objective response rate (ORR). Secondary endpoints were progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Based on analysis of this clinical trial data, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as, the lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy has not yet been confirmed.

IV. Pemigatinib (Pemazyre) received accelerated approval from the FDA based on ORR and DOR. Continued approval for this drug may be contingent upon verification of clinical benefit in confirmatory trials. There is a Phase 3 trial underway to assess pemigatinib (Pemazyre) monotherapy versus gemcitabine + cisplatin in the first-line treatment of CCA with FGFR2 alterations.

V. The safety profile of pemigatinib (Pemazyre) was based on adverse reactions observed in all cohorts during CT (N=146). The most common adverse events (≥20% incidence) included hyperphosphatemia, alopecia, nausea, diarrhea, nail toxicity, back pain, fatigue, dysgeusia, dry eyes, and serous retinal detachment. There are no specific contraindications to pemigatinib (Pemazyre); however, warnings and precautions include: ocular toxicity, hyperphosphatemia, GI toxicity and renal function. Pemigatinib (Pemazyre) showed 9% treatment discontinuation rate, 14% dose reductions rate, and 42% dose interruption rate due to adverse events.

VI. As of June 2020, The National Comprehensive Cancer Network (NCCN) treatment guideline for hepatobiliary cancer has included pemigatinib (Pemazyre) as second-line treatment with a Category 2A recommendation. Pemigatinib (Pemazyre) is useful in treatment of tumor with confirmed FGFR2 fusions or rearrangements; and which are refractory to first line chemotherapy.

Investigational or Not Medically Necessary Uses

I. Pemigatinib (Pemazyre) has not been sufficiently studied for safety and efficacy for any other 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.*

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11. 11. A study to evaluate the efficacy and safety of pemigatinib versus chemotherapy in unresectable or metastatic cholangiocarcinoma (FIGHT-302), clinicaltrials.gov; NCT03656536. https://clinicaltrials.gov/ct2/show/NCT03556536.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	06/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP085

Split Fill Management*

Description

Pexidartinib (Turalio) is an oral kinase inhibitor FDA-approved for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

Length of Authorization

- Initial: Six months, split fill for the first three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
pexidartinib (Turalio)	200 mg capsule	Tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery	120 capsules/30 days	207496 207495

Initial Evaluation

I. Pexidartinib (Turalio) may be considered medically necessary when the following criteria below 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 orthopedic surgeon; **AND**
   C. Member has a confirmed diagnosis of symptomatic tenosynovial giant cell tumor; **AND**
   D. A surgical/orthopedic oncologist or orthopedic surgeon has evaluated that the member is not a candidate for surgery; **AND**
   E. Member does <u>not</u> have preexisting increased serum transaminases such as ALT and AST or an indication of hepatotoxicity; **AND**
   F. The medication is used as a monotherapy

II. Pexidartinib (Turalio) is considered investigational when used for all other conditions, including but not limited to:
   A. Metastatic tenosynovial giant cell tumor (TGCT)
   B. Active cancer that requires therapy (e.g. surgical, chemotherapy, or radiation therapy)
   C. Pexidartinib (Turalio) is used in combination with other tyrosine kinase inhibitors that also target colony-stimulating factor (CSF1) or the CSF1 receptor (CSF1R) (e.g., imatinib, nilotinib, sorafenib, or sunitinib)

Renewal Evaluation

I. Pexidartinib (Turalio) may be considered for continuation of therapy when the following criteria below are met:
   A. Member has an absence of unacceptable toxicity from the medication; **AND**
   B. Clinical documentation showing symptomatic/disease improvement(s) including
      1. Stable or improved range of motion of affected joint; **OR**
      2. Stable or improved pain in affected joint; **OR**
      3. Stable or improved in stiffness of affected joint

Supporting Evidence

I. Pexidartinib (Turalio) is FDA-approved for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.
II. Tenosynovial giant cell tumor is also referred to as giant cell tumor of the tendon sheath (GCTTS) or pigmented villonodular synovitis (PVNS).
III. Patients with recurrent and/or relapsed TGCT may typically undergo surgical interventions, however, if further surgery would result in significant morbidity or functional impairment, systemic therapy such as pexidartinib (Turalio) may be beneficial.
IV. Pexidartinib (Turalio) was studied in a clinical trial with two parts:
   - Part 1: A randomized, double-blind, multicenter, Phase 3 study (n=120) patients with symptomatic advanced TGCT for whom surgical removal of the tumor would be associated with potentially worsening functional limitation or severe morbidity. The primary efficacy outcome in Part 1 was overall response rate (ORR): 39% (24 of 61) with pexidartinib (Turalio) vs. 0% with placebo at week 25 ($p<0.0001$); 53% at data cutoff.
   - Part 2: An open-label, Phase 3 trial for patients (n=78; 30 from the placebo group) who completed the part 1, evaluating ORR of the patients on the crossover treatment. The primary efficacy outcome in Part 2 was ORR: 30% (9 of 30) at week 25; 53% (16 of 30) at data cutoff.
V. Pexidartinib (Turalio) has boxed warnings and REMS program for the risk of serious and potentially fatal liver injury and embryo-fetal toxicity.
VI. Common adverse events (>20%) in the clinical trial were: hair color change (67%), fatigue (54%), AST increase (39%), nausea (38%), ALT increase (28%), and dysgeusia (25%).
VII. Most common grade 3 or 4 adverse events occurring at a higher incidence in patients treated with pexidartinib (Turalio) were increases in liver enzymes. Hepatic adverse events were also the

most common cause of treatment interruption, dose reduction (38% combined), or treatment discontinuation (13%) in the pexidartinib (Turalio) group.

VIII. In the clinical trial (ENLIVEN), pexidartinib (Turalio) was used as a single-agent therapy.

Investigational or Not Medically Necessary Uses

I. All condition(s) listed as investigational use
   A. These conditions are parts of the exclusion criteria from the ENLIVEN clinical trial. Safety and efficacy of pexidartinib (Turalio) for these conditions are not studied and unknown.

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

References

1. Turalio [Prescribing Information]. Daiichi Sankyo, Inc. Basking Ridge, NJ. August 2019.
2. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet*. 2019;394(10197):478-487. doi: 10.1016/S0140-6736(19)30764-0.
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Policy Implementation/Update:

Date Created	September 2019
Date Effective	November 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	**Date**
Policy created	09/2019

pimavanserin (Nuplazid®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP053

Description

Pimavanserin (Nuplazid) is an orally administered atypical antipsychotic that works as a selective serotonin inverse agonist with an unknown mechanism of action.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
pimavanserin (Nuplazid)	34 mg capsules	Parkinson's disease psychosis	30 capsules/30 days	203479, 203276
	17 mg tablets		60 tablets/30 days	192903, 192710
	10 mg tablets		30 tablets/30 days	203478, 203281

Initial Evaluation

I. Pimavanserin (Nuplazid) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. A diagnosis of **Parkinson's disease psychosis** with symptoms of hallucinations and delusions when the following are met:
      1. Symptoms of hallucinations and delusions have continued after reductions in current medications for Parkinson's disease OR reductions in medications are not possible based on provider attestation; **AND**
      2. Treatment with clozapine (Clozaril®) has been ineffective, intolerable, or contraindicated

II. Pimavanserin (Nuplazid) is considered investigational when used for all other conditions, including but not limited to the diagnosis of:
   A. Alzheimer's disease
   B. Schizophrenia

Renewal Evaluation

I. Noted reduction in delusions and hallucinations.

Supporting Evidence

I. Pimavanserin (Nuplazid) is indicated for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis for patients 18 years of age and older.

II. Pimavanserin (Nuplazid) was studied in a 6-week, randomized, placebo-controlled, parallel-group study in 199 patients with a diagnosis of Parkinson's disease (PD) and psychotic symptoms.
    - The primary efficacy outcome was the change from baseline to week 6 in a PD-adapted scale for the assessment of positive symptoms (SAPS-PD).
    - A positive effect was seen on both hallucination and delusion components of the SAPS-PD for pimavanserin (Nuplazid) versus placebo [-3.06 (-4.91, -1.2)]. Although statistically significant, the clinical relevance of this result is unclear.
    - No difference in motor function was observed between pimavanserin (Nuplazid) and placebo.

III. Pimavanserin (Nuplazid) was studied in multiple unpublished clinical trials that either failed to demonstrate efficacy or were terminated early due to trial failure.

IV. Pimavanserin (Nuplazid) was FDA-approved under the breakthrough therapy and priority review designation where preliminary clinical evidence indicated pimavanserin (Nuplazid) may demonstrate substantial improvement over current available therapies. In addition, the FDA-medical reviewer recommended against FDA-approval.

V. Clozapine has been studied in two four-week, placebo-controlled trials, as well as, two smaller trials comparing clozapine and quetiapine. Clozapine demonstrated improved global impression scores, improved psychotic symptom assessment scores, and similar motor and cognitive function compared with patients on placebo.

VI. The Movement Disorder Society rated clozapine as more efficacious compared to quetiapine which was deemed to have insufficient evidence, and does not make any recommendation on pimavanserin (Nuplazid).

References

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Policy Implementation/Update:

Date Created	July 2016
Date Effective	August 2016
Last Updated	September 2019
Last Reviewed	September 2019

Action and Summary of Changes	Date
Transition from criteria to policy: Included requirements to attempt dose reduction in parkinson's medications, and specified what members must try and fail.	September 2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP225

Split Fill Management*

Description

Ponatinib (Iclusig) is an orally administered tyrosine kinase inhibitor with activity against unmutated and mutated BCR-ABL including the threonine-to-isoleucine mutation at position 315 (T315I).

Length of Authorization

- Initial: three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication*	Quantity Limit
ponatinib (Iclusig)	10 mg tablet	CP-CML with resistance or intolerance to two prior kinase inhibitors; AP-CML, BP-CML, and Ph+ ALL for whom no other kinase inhibitors are indicated; T315I-positive CML (any phase) or T315I-positive Ph+ ALL	30 tablets/30 days
	15 mg tablet		30 tablets/30 days
	30 mg tablet		30 tablets/30 days
	45 mg tablet		30 tablets/30 days

*CML = chronic myeloid leukemia, CP = chronic phase, AP = accelerated phase, BP = blast phase, Ph+ = Philadelphia chromosome positive, ALL = acute lymphoblastic leukemia

Initial Evaluation

I. Ponatinib (Iclusig) 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 is <u>not</u> used in combination with any other oncology therapy; **AND**
   D. A diagnosis of **Chronic Phase-Chronic Myeloid Leukemia (CP-CML); AND**
      1. Documented resistance, or intolerance to, <u>two</u> prior tyrosine kinase inhibitors (TKIs) (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif); **OR**
      2. Documented positive T315I mutation
   E. A diagnosis of **Accelerated Phase- Chronic Myeloid Leukemia (AP-CML), Blast Phase-Chronic Myeloid Leukemia (BP-CML), or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ALL); AND**

1. Provider attestation that all other TKIs used to treat AP-CML, BP-CML, or Ph+ALL (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif) have been ineffective, not tolerated, contraindicated or not indicated; **OR**
2. Documented positive T315I mutation

I. Ponatinib (Iclusig) is considered investigational when used for all other conditions, including but not limited to:
   A. Newly diagnosed CP-CML

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 this applies, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Will not be used with any other oncology therapy; **AND**
IV. Disease response to treatment defined by stabilization of disease or decrease in rate of disease progression.

Supporting Evidence

I. Ponatinib (Iclusig) is an oral tyrosine kinase inhibitor with activity against unmutated and mutated BCR-ABL, including the threonine-to-isoleucine mutation at position 315 (T315I), which is present in around 20% of patients with tyrosine kinase inhibitor-resistant disease.
II. Ponatinib (Iclusig) carries three FDA approved indications and is used in the treatment of patients with chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors, accelerated phase (AP) or blast phase (BP) CML, Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase inhibitors are indicated, and T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL.
III. The original FDA approval for ponatinib (Iclusig) took place in 2012 and was based on the PACE clinical trial which evaluated safety and efficacy of ponatinib (Iclusig). Post-marketing studies submitted to the FDA included a 5 year follow up PACE study and an ongoing OPTIC clinical trial, which informed of the optimal dosing in patients with CP-CML.
IV. The PACE clinical trial was an open label, single arm, phase II study in adult subjects with CML (all phases) or Ph+ ALL with resistance/intolerance to dasatinib or nilotinib, or development of T315I mutation after tyrosine kinase inhibitor (TKI) therapy. There were 270 subjects in CP-CML, 85 subjects in AP-CML, 62 subjects in BP-CML, and 62 subjects in Ph+ALL. These subjects were further randomized based on T315I mutation status. Nearly one-third of subjects (29%) had the T315I mutation. The primary efficacy endpoint of major cytogenic response (MCyR) by 12 months of treatment was met in 51% of those with resistance or intolerance to prior TKI therapy and in 70% of those with a positive T315I mutation status in the CP-CML cohort. In AP-CML, BP-CML, and Ph+ALL the primary endpoint was major hematologic response (MaHR) by 6 months of treatment which was met in 57% of those with prior resistance or intolerance to TKI therapy and in 50% of those with a positive T315I mutation status in the AP-CML cohort. MaHR was met in

35% of those with resistance or intolerance to prior TKI therapy and in 33% of those with a positive T315I mutation status in the BP-CML/Ph+ALL cohort.

V. The five year follow up study of ponatinib (Iclusig) demonstrated a continued clinical benefit in patients with heavily treated CML or Ph+ALL. The types of adverse events reported were generally similar to those reported previously and included rash (47%), abdominal pain (46%), thrombocytopenia (46%), headache (43%), and constipation (41%). Dose related adverse events included cardiovascular, cerebrovascular, and peripheral vascular events. The cumulative incidence of arterial occlusive events (AOEs) was 25% in the overall population (serious AOEs, 20%) and 31% in the CP-CML population (serious AOEs, 26%); higher cumulative incidence in CP-CML correlates with the longer duration of treatment.

VI. OPTIC is an ongoing phase 2, open label, randomized, multicenter clinical trial evaluating response-based dosing regimens of ponatinib (Iclusig) with the aim of optimizing its efficacy and safety in patients with CP-CML who are resistant or intolerant to prior TKI therapy. Interim results at 21 months of follow up show benefit of ponatinib (Iclusig) in all three dosing regimens studied (15 mg, 30 mg, and 45 mg), with the 45 mg starting dose showing greatest efficacy results. Thus far, the FDA has made recommendations to start with the 45 mg dose which could subsequently be titrated down to 15 mg upon achievement of <1% BCR-ABL1. Primary analysis will provide a refined understanding of the benefit: risk profile of three different starting doses of ponatinib (Iclusig).

VII. For the treatment of Ph+ALL, current NCCN guidelines recommend dasatinib (Sprycel) and imatinib (Gleevec) as the preferred agents as well as other TKIs such as bosutinib (Bosulif), nilotinib (Tasigna), or ponatinib (Iclusig). Moreover, certain TKIs are contraindicated with specific BCR-ABL1 mutations; ponatinib (Iclusig) is the only TKI without any contraindicated mutations.

VIII. For the treatment of CP-CML, current NCCN guidelines recommend the following agents depending on the patient's risk score and mutation profile: imatinib (Gleevec), bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna), or ponatinib (Iclusig) when there's resistance to two prior TKIs. For the treatment of AP-CML and BP-CML, preferred regimens include bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna), or ponatinib (Iclusig) with omacetaxine (Synribo) cited as being useful in certain circumstances.

Investigational or Not Medically Necessary Uses

I. Ponatinib (Iclusig) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Newly diagnosed CP-CML
      i. Ponatinib (Iclusig) was studied as a first line agent in patients newly diagnosed with CP-CML and showed an increase in risk of serious adverse reactions 2-fold compared to imatinib (Gleevec) 400 mg once daily. This prospective randomized clinical trial was subsequently halted for safety. Ponatinib (Iclusig) treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. Ponatinib (Iclusig) is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

References

1. ICLUSIG (ponatinib) [package insert]. Cambridge, MA: ARIAD Pharmaceuticals, Inc.; December 2020.
2. NCCN Guidelines. Chronic Myeloid Leukemia. Version 3.2021-January 13, 2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cml_blocks.pdf. Accessed on March 7, 2021.
3. NCCN Guidelines. Acute Lymphoblastic Leukemia. Version 2.2020-October 23, 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/all_blocks.pdf. Accessed on March 7, 2021.
4. Cortes, Jorge E et al. "Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial." Blood vol. 132,4 (2018): 393-404. doi:10.1182/blood-2016-09-739086
5. Cortes, Jorge E et al. "A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias." The New England journal of medicine vol. 369,19 (2013): 1783-96. doi:10.1056/NEJMoa1306494

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy criteria transitioned to a new format; criteria changes include the removal of laboratory monitoring requirements (blood counts, hepatic enzyme tests, serum lipase) and monitoring of atrial thrombotic events, addition of a new dosage forms 10 mg and 30 mg tablets, and addition of requiring two prior TKIs in CP-CML, consistent with the FDA labeling change.	03/2021
Policy criteria created	05/2013

Policy Type: PA/SP Pharmacy Coverage Policy: UMP220

Split Fill Management*

Description

Pralsetinib (Gavreto) is an orally administered kinase inhibitor of RET.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
pralsetinib (Gavreto)	100 mg capsules	RET Fusion-Positive Non-Small Cell Lung Cancer; RET-Mutant Medullary Thyroid Cancer; RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory	120 capsules/30 days

Initial Evaluation

I. **Pralsetinib (Gavreto)** is considered investigational when used for all indications, including but not limited to Non-Small Cell Lung Cancer (NSCLC) and Thyroid Cancer.

Renewal Evaluation

I. N/A

Supporting Evidence

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers. Pralsetinib (Gavreto) is the second FDA-approved RET-targeted therapy, joining selpercatinib (Retevmo).

II. RET fusion-positive NSCLC, advanced or metastatic: First-line treatments include cabozantinib (Cometriq®) or vandetanib (Caprelsa®) (both off-label for lung cancer), combinations of platinum-based chemotherapy, anti-PD-1/PD-L1 therapy, pemetrexed (Alimta®), and bevacizumab. In the second-line setting, additional options include various immunotherapy and chemotherapy treatments (e.g., taxanes, gemcitabine); however, all of these therapies show poorer outcomes in this population vs. non-RET mutated NSCLC.

- NCCN guidelines include pralsetinib (Gavreto) and selpercatinib (Retevmo) as preferred first-line and subsequent-line therapy after other options have failed (recommendation

Category 2a). Cabozantinib (Cometriq) and vandetanib (Caprelsa) are listed as useful in certain circumstances, with a Category 2a and 2b recommendation, respectively. ESMO guidelines mention pralsetinib (Gavreto) and selpercatinib (Retevmo) for RET-mutated NSCLC; however, given the limited data, enrollment in clinical trials is encouraged.

III. RET-mutant MTC, advanced or metastatic: Systemic treatment may be warranted for high volume, symptomatic or progressive MTC. General treatment options include cabozantinib (Cometriq) or vandetanib (Caprelsa).
   - NCCN guidelines recommend cabozantinib (Cometriq) and vandetanib (Caprelsa) as Category 1 preferred options. Selpercatinib (Retevmo) is listed as a Category 2a preferred therapy for those with RET-mutations in both the locoregional, symptomatic, and unresectable setting, as well as the recurrent or persistent settings. Enrollment in clinical trial has a Category 2a recommendation.

IV. RET fusion-positive thyroid cancer: In persistent/recurrent or metastatic disease, RAI is recommended. In those not amenable to RAI, general treatment options include lenvatinib (Lenvima®) or sorafenib (Nexavar®).
   - NCCN guidelines recommend lenvatinib (Lenvima) and sorafenib (Nexavar) as Category 2a with lenvatinib (Lenvima) preferred. Selpercatinib (Retevmo) is the preferred therapy for RET fusion-positive disease, Category 2a.

V. Pralsetinib (Gavreto) has not been included in treatment guidelines for thyroid cancer.

VI. Pralsetinib (Gavreto) is being evaluated in one Phase 1/2, dose expansion and escalation, multi-cohort, open-label, single-arm trial. Interim results showed potential antitumor activity via overall response rate (ORR) and duration of response (DoR). These indications were approved under the accelerated pathway and continued approval may be contingent upon verification of clinical benefit in confirmatory trials. The primary outcome is ORR, and the secondary outcomes include DoR and proportion of patients with DoR six months or greater.

VII. For RET fusion-positive NSCLC: Patients were advanced or metastatic and were either treatment naïve or progressed on platinum-based chemotherapy. For RET-mutant MTC, patients were either treatment naïve or progressed on cabozantinib (Cometriq) or vandetanib (Caprelsa). All patients had progressed on standard of care for RET-fusion-positive TC.

Clinical Efficacy in Pretreated Patients			
Outcome	**RET Fusion+ NSCLC (n=87)**	**RET-Mutant MTC (n=55)**	**RET Fusion-Positive TC (n=9)**
ORR (%)	57% (46, 68)	60% (46, 73)	89% (52, 100)
CR (%)	5.7%	1.8%	0
PR (%)	52%	58%	89%
DoR (mo)	NR (15.2-NE)	NR (15.1, NE)	NR (NE, NE)
DoR ≥ 6 mo (%)	80%	79%	100%
Clinical Efficacy in Treatment-Naïve Patients			
Outcome	**RET Fusion+ NSCLC (n=27)**	**RET-Mutant MTC (n=29)**	**RET Fusion-Positive TC***
ORR (%)	70% (50, 86)	66% (46, 82)	N/A
CR (%)	11%	10%	
PR (%)	59%	55%	
DoR (mo)	9 (6.3-NE)	NR (NE, NE)	
DoR ≥ 6 mo (%)	58%	84%	

*All patients were refractory to standard therapy.

VIII. The quality of the evidence is considered low given the open-label and single-arm trial design and small sample size; thus, true medication efficacy remains uncertain given the nature of observational data. Additionally, outcomes such as ORR and DoR have not been correlated with clinically meaningful outcomes such as improved survival or quality of life.

IX. Phase 3 trial, AcceleRET, is planned to evaluate pralsetinib (Gavreto) in advanced or metastatic, RET fusion-positive NSCLC versus platinum-based chemotherapy. It will be evaluated in an open-

label, randomized trial for first-line metastatic systemic therapy. Outcomes of interest include PFS, OS, time to intracranial progression, and quality of life. This international trial has a target enrollment of 250 patients, with an estimated completion date of 2024.

X. Safety data is based on a pooled population of 438 patients. Common adverse events (AE) that occurred ≥15% or more of the population: fatigue, constipation, musculoskeletal pain, hypertension, edema, diarrhea, dry mouth, cough, and pneumonia. Serious AE that occurred ≥2%: pneumonia, sepsis, UTI, pyrexia, increased ALT/AST, and phosphatase, and decreased lymphocytes, neutrophils, hemoglobin, phosphate, calcium, sodium, and platelets. Fatal AE occurred in 5% of patients (pneumonia and sepsis) in the NSCLC cohort. Warnings and precautions: interstitial lung disease, hypertension, hepatotoxicity, hemorrhage, tumor lysis syndrome, impaired wound healing, and embryo-fetal toxicity.

XI. Dose reductions due to AE occurred in up to 67% of patient, which varied by cohort. Dose reductions occurred in up to 44%, and permanent discontinuation rate in up to 15%. The true safety profile of pralsetinib (Gavreto) remains unknown given the observational evaluation.

Investigational or Not Medically Necessary Uses

I. Pralsetinib (Gavreto) has not yet been sufficiently studied for safety and efficacy for any condition.

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

References

1. Gavreto [Prescribing Information]. Blueprint Medicines Corporation. Cambridge, MA. December 2020.
2. Retevmo [Prescribing Information]. Eli Lilly and Company. Indianapolis, IN. May 2020.
3. Adeniran AJ, Ahu Z, Gandhi M, et al. Correlation between genetic alterations and microscopic features, clinical manifestations, and prognostic characteristics of thyroid papillary carcinomas. Am J Surg Pathol. 2006. 30(2): 216-222.
4. Drilon A, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. Nat Rev Clin Oncol. 2018a Mar;15(3):151-67.
5. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Treatment Guidelines V8.2020. September 21, 2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx.
6. European Society for Medical Oncology. Metastatic non-small-cell lung cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 15, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP080

Description

Pretomanid is an orally administered nitroimidazooxazines antimycobacterial agent.

Length of Authorization

- Initial: six months
- Renewal: N/A

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
pretomanid	200 mg tablet	Pulmonary tuberculosis that is extensively drug resistant (XDR), treatment intolerant, or nonresponsive multi-drug resistant (MDR)	30 tablets/30 days	TBD

Initial Evaluation

I. Pretomanid 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 a pulmonologist or infectious disease specialist; **AND**
   C. A diagnosis of **pulmonary extensively drug resistant (XDR), treatment-intolerant, or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)** when the following are met:
      1. Documentation of resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable antimicrobial (e.g., amikacin, kanamycin, or capreomycin); **AND**
      2. Documentation of intolerance to para-aminosalicyclic acid (PAS), ethionamide, aminoglycosides or fluoroquinolones; **AND**
      3. The member will be using pretomanid in combination with bedaquiline (Situro) AND linezolid (Zyvox) for the duration of therapy; **AND**
      4. The member will have directly observed treatment (DOT) plan in place

II. Pretomanid is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. The use of pretomanid in combination with drugs other than bedaquiline (Situro) and linezolid (Zyvox)
   B. Drug-sensitive (DS) tuberculosis
   C. Latent infection due to Mycobacterium tuberculosis
   D. Extra-pulmonary infection due to Mycobacterium tuberculosis

E. Multidrug-resistant tuberculosis that is not treatment-intolerant or nonresponsive to standard therapy

Supporting Evidence

I. Pretomanid was studied in a Phase 3, open-label trial with 109 adult patients with pulmonary TB that are XDR, treatment intolerant, or non-responsive MDR. In that trial, the safety and efficacy of pretomanid in combination with bedaquline and linezolid was assessed.

Definition of TB Types	
Drug-resistant TB	TB caused by an isolate of Mycobacterium tuberculosis (M. tuberculosis) that is resistant to one or more antituberculous drugs
Multidrug-resistant TB (MDR-TB)	TB caused by an isolate of M. tuberculosis that is resistant to both isoniazid (INH) and rifampin and possibly additional agents
Extensively drug-resistant TB (XDR-TB)	TB caused by an isolate of M. tuberculosis that is resistant to at least INH, rifampin, and fluoroquinolones as well as either aminoglycosides (e.g. amikacin, kanamycin) or capreomycin or both
Totally drug-resistant TB (TDR-TB)	TB caused by an isolate of M. tuberculosis resistant to all locally tested medications

II. The primary efficacy outcome was the incidence of bacteriologic failure, relapse, or clinical failure through follow up until six months after the end of treatment; of the 107 patients assessed, 12 (11%) patients were classified as treatment failure, while 95 (89%) patients were classified as treatment success. Treatment success was defined as culture negative status at six months post treatment.

III. No pediatric patients were included in the trial.

IV. Pretomanid was only studied in combination with bedaquiline (Situro) and linezolid (Zyvox).

V. Patients that were included in the trial demonstrated resistance to isoniazid, rifamycins, a fluroquinolone and an injectable antimicrobial, and had intolerance to para-aminosalicyclic acid (PAS), ethionamide, aminoglycosides or fluoroquinolones.

Investigational or Not Medically Necessary Uses

I. Safety and efficacy has not been established for the use of pretomanid in combination with drugs other than bedaquiline (Situro) and linezolid (Zyvox).

II. Pretomanid was FDA-approved on an accelerated approval pathway under the Limited Population Pathway for Antibacterial and Antifungal Drugs. As stated in the label, the approval of this indication is based on limited clinical safety and efficacy data. Therefore, the use of this drug is indicated for a very specific population of patients, and antimicrobial stewardship practices should be applied when treating this population of patients. Therefore, the use of pretomanid in setting

other than the label indication [pulmonary extensively drug resistant (XDR), treatment-intolerant, or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)], is considered experimental and investigational.

References

1. Pretomanid [Prescribing Information]. Mylan: Hyderabad, India. August 2019.
2. Sirturo [Prescribing information]. Janssen Therapeutics: Titusville,NJ. December 2012.
3. Center for Disease Control and Prevention: Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm?s_cid=rr6209a1_e
4. World Health Organization: WHO Guidelines on Tuberculosis. Available at: https://www.who.int/publications/guidelines/tuberculosis/en/
5. The Food and Drug Administration: FDA Briefing Document on Pretomanid 200 mg Tablet. Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC). June 2019. Available at: https://www.fda.gov/media/127592/download
6. Clinicaltrial.gov

Policy Implementation/Update:

Date Created	September 2019
Date Effective	November 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	**Date**

prucalopride (Motegrity™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: Step Pharmacy Coverage Policy: UMP054

Description

Prucalopride (Motegrity) is an orally administered 5-HT_4 agonist for the treatment for chronic idiopathic constipation.

Length of Authorization

- Initial/Renewal: 12 months

Coverage Criteria

I. Prucalopride (Motegrity) may be considered medically necessary when the following criteria below are met:
   A. Treatment with generic (Amitiza), and generic (Linzess) have been ineffective, contraindicated, or not tolerated.

Policy Type: PA/SP Pharmacy Coverage Policy: UMP145

Description

Ambrisentan (generic, Letairis®), bosentan (generic, Tracleer®), and macitentan (Opsumit®) are endothelin receptor agonists (ERA) that inhibit the binding of endothelin – a vasoconstrictive peptide – to its receptors (ET_A and ET_B) in the endothelium and smooth muscle cells which results in vasodilation.

Riociguat (Adempas®) stimulates soluble guanylate cyclase (sGC) – a receptor for nitric oxide and an enzyme in the cardiopulmonary system. It sensitizes sGC to endogenous nitric oxide by stabilizing nitric oxide-sGC binding and directly stimulating sGC via a different binding site. Stimulating the nitric oxide-sGC-cGMP pathway, leads to an increased generation of cGMP and subsequent vasodilation.

Iloprost (Ventavis®) inhalation solution, treprostinil (Tyvaso®) inhalation solution, treprostinil (Orenitram®) tablets for oral use, treprostinil (Remodulin®) injection for subcutaneous use and selexipag (Uptravi®) tablets for oral use are prostacyclin vasodilators. They directly vasodilate pulmonary and systemic arterial vascular beds, inhibit platelet aggregation, and inhibit smooth muscle cell proliferation.

Length of Authorization

- Initial:
  - i. Ambrisentan (generic, Letairis), bosentan (generic, Tracleer), and macitentan (Opsumit): Three months
  - ii. Riociguat (Adempas), iloprost (Ventavis), treprostinil inhalation (Tyvaso), treprostinil tablet (Orenitram), treprostinil injection (Remodulin) and selexipag (Uptravi)]: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
ambrisentan (Letairis)	5 mg tablets	Pulmonary arterial hypertension (PAH)	30 tablets/30 days
	10 mg tablets		
generic ambrisentan	5 mg tablets		30 tablets/30 days
	10 mg tablets		
bosentan (Tracleer)	32 mg tablet for oral suspension		120 tablets/30 days
	62.5 mg film-coated tablet		60 tablets/30 days
	125 mg film-coated tablet		
generic bosentan	32 mg tablet for oral suspension		120 tablets/30 days
	62.5 mg film-coated tablet		60 tablets/30 days
	125 mg film-coated tablet		
macitentan (Opsumit)	10 mg tablet		30 tablets/30 days

riociguat (Adempas)	0.5 mg tablets	Chronic thromboembolic pulmonary hypertension (CTEPH); Pulmonary arterial hypertension (PAH)	90 tablets/30 days
	1 mg tablets		
	1.5 mg tablets		
	2 mg tablets		
	2.5 mg tablets		
iloprost (Ventavis)	10 mcg/mL inhalation solution ampule	Pulmonary arterial hypertension (PAH)	9 cartons of 30 ampules per 30 day supply
	20 mcg/mL inhalation solution ampule		
treprostinil (Tyvaso)	1.74 mg/2.9 mL inhalation solution ampule	Pulmonary arterial hypertension (PAH); Pulmonary hypertension (PH) Due to Interstitial Lung Disease (ILD)	1 Inhalation System Starter Kit (28 ampule carton)/ 1st 28 days of initiation therapy 1 Inhalation System Refill Kit (28 ampule carton)/28 days 7 Four Pack Cartons with one foil pouch containing four 2.9 mL ampules/28 days
treprostinil (Remodulin)	5 mg/mL injection solution	Pulmonary arterial hypertension (PAH)	up to 50 ng per kg per minute subcutaneously or intravenously
	10 mg/mL injection solution		
	20 mg/20 mL injection solution		
	50 mg/20 mL injection solution		
	100 mg/20 mL injection solution		
	200 mg/20 mL injection solution		
treprostinil (Orenitram)	0.125 mg ER tablet		90 extended-release oral tablets/30 days
	0.25 mg ER tablet		
	1 mg ER tablet		
	2.5 mg ER tablet		
	5 mg ER tablet		
selexipag (Uptravi)	200 mcg		140 oral use tablets/28 days
	400 mcg		Titration pack (140 count – 200mcg oral use tablets + 60 count – 800mcg) 60 oral use tablets/30 days
	600 mcg		
	800 mcg		
	1000 mcg		
	1200 mcg		
	1400 mcg		
	1600 mcg		

Initial Evaluation

I. Ambrisentan (Letairis), generic ambrisentan, bosentan (Tracleer), generic bosentan, macitentan (Opsumit), riociguat (Adempas), iloprost (Ventavis) inhalation solution, treprostinil (Tyvaso)

inhalation solution, treprostinil (Orenitram), treprostinil injection (Remodulin), and selexipag (Uptravi) 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 three years of age or older and request is for bosentan (generic, Tracleer); **AND**
B. Medication is prescribed by, or in consultation with, cardiologist or pulmonologist; **AND**
C. A diagnosis of one of the following:
   1. Pulmonary arterial hypertension (PAH) (WHO) Group 1 with WHO Functional Class II-IV symptoms); **AND**
      a. An acute vasoreactivity test has been performed; **AND**
         i. Results were negative; **OR**
         ii. Results were positive; **AND**
            a) Treatment with a calcium channel blocker (CCB) (e.g. amlodipine, diltiazem, felodipine, nifedipine, nicardipine, or verapamil) has been ineffective after <u>three months</u> of therapy, unless contraindicated, or not tolerated; **AND**
      b. Treatment with a phosphodiesterase type-5 (PDE-5) inhibitor [e.g. sildenafil 20 mg three times daily or tadalafil 40 mg daily] has been ineffective after <u>three months</u> of therapy, contraindicated, or not tolerated; **OR**
         i. The request is for **<u>generic ambrisentan</u>** in combination with a phosphodiesterase type-5 (PDE-5) inhibitor [e.g. sildenafil 20 mg three times daily or tadalafil 40 mg daily]; **AND**
      c. The request is for **<u>generic ambrisentan, generic bosentan, macitentan (Opsumit), or riociguat (Adempas)</u>**; **OR**
      d. The request is for **<u>brand</u> <u>ambrisentan (Letairis)</u>**; **AND**
         i. Generic ambrisentan has been ineffective, contraindicated, or not tolerated; **OR**
      e. The request is for **<u>brand</u> <u>bosentan (Tracleer)</u>**; **AND**
         i. Generic bosentan has been ineffective, contraindicated, or not tolerated; **OR**
      f. The request is for **<u>iloprost (Ventavis)</u>** <u>inhalation solution</u> or **<u>treprostinil (Tyvaso)</u>** <u>inhalation solution</u>; **AND**
         i. Treatment with an endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)] has been ineffective, contraindicated, or not tolerated; **OR**
      g. The request is for **<u>treprostinil (Orenitram)</u>** or **<u>selexipag (Uptravi)</u>**; **AND**
         i. Treatment with an endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)] has been ineffective, contraindicated, or not tolerated; **OR**
      h. The request is for **<u>generic treprostinil injection solution</u>** (generic Remodulin); **OR**
            1) The request is for brand **<u>Remodulin</u>** and generic treprostinil injection solution has been ineffective, contraindicated, or not tolerated; **AND**

i. Member has WHO Class IV symptoms or is classified as high risk (poor prognosis) [*see appendix table 1*]; **OR**

ii. The member is classified as low risk (good prognosis); **AND**

2) Treatment with an ERA (e.g., bosentan, ambrisentan), AND either a PDE5 inhibitor (e.g., sildenafil, tadalafil) OR Adempas (riociguat) has been ineffective, contraindicated, or not tolerated; **OR**

iii. Member is transitioning from epoprostenol to treprostinil (Remodulin)

2. **Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4)**; **AND**
   i. Member has inoperable CTEPH; **OR**
   ii. Member had a surgery for CTEPH performed; **AND**
   iii. The request is for **riociguat (Adempas); OR**
3. **Pulmonary Hypertension (PH) Due to Interstitial Lung Disease (ILD) (WHO Group 3); AND**
   i. Diagnosis confirmed with chest high-resolution computed tomography (HRCT) imaging**; AND**
   ii. Diagnosis confirmed with a right heart catheterization (RHC)**; AND**
   iii. Member does NOT have PH caused by obstructive lung disease (e.g., chronic obstructive pulmonary disease [COPD], bronchiectasis) or hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation); **AND**
   iv. The request is for treprostinil (Tyvaso)

II. Ambrisentan (Letairis) is considered investigational when used for all other conditions including but not limited to:

A. Chronic thromboembolic pulmonary hypertension (CTEPH)
B. Digital ulcers in systemic sclerosis
C. Lowering Portal Pressure in Patients with Liver Cirrhosis
D. Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis
E. Sarcoidosis

III. Bosentan (Tracleer) is considered investigational when used for all other conditions including but not limited to:

A. Chronic obstructive pulmonary disease - Pulmonary hypertension
B. Chronic thromboembolic pulmonary hypertension (CTEPH)
C. Digital ulcers in systemic sclerosis
D. Essential hypertension
E. Raynaud phenomenon in systemic sclerosis
F. Thromboembolic pulmonary hypertension, chronic

IV. Macitentan (Opsumit) is considered investigational when used for all other conditions including but not limited to:
   A. Chronic thromboembolic pulmonary hypertension (CTEPH)
   B. Digital ulcers in systemic sclerosis
   C. Glioblastoma

V. Riociguat (Adempas) is considered investigational when used for all other conditions including but not limited to:
   A. Systemic sclerosis-associated digital ulcers

VI. Treprostinil (Tyvaso) is considered investigational when used for all other conditions including but not limited to:
   A. Pulmonary hypertension (PH) WHO Groups II-V
      - Group II - Left heart disease, including congestive heart failure (CHF)
      - Group III – Chronic obstructive pulmonary disease (COPD), bronchiectasis; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
      - Group IV - Chronic thrombotic and/or embolic disease
      - Group V - Sarcoidosis
   B. Chronic thromboembolic pulmonary hypertension (CTEPH)

VII. Iloprost (Ventavis), treprostinil (Orenitram, Remodulin) and selexipag (Uptravi) are considered investigational when used for all other conditions, including but not limited to:
   A. Pulmonary hypertension (PH) WHO Groups II-V
      - Group II - Left heart disease, including congestive heart failure (CHF)
      - Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
      - Group IV - Chronic thrombotic and/or embolic disease
      - Group V – Sarcoidosis
   B. Chronic thromboembolic pulmonary hypertension (CTEPH)

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. improved exercise capacity and tolerance, reduced number of hospitalizations, improvement in WHO functional class).

Supporting Evidence

I. Patients with PH are classified into five clinical groups based on cause of PH.
   a. Group 1: pulmonary arterial hypertension (PAH) which has several causes (e.g., inheritable causes, drugs, connective tissue disease)
   b. Group 2: PH due to left-sided heart disease
   c. Group 3: PH due to chronic lung disorders and hypoxemia
   d. Group 4: PH due to pulmonary artery obstructions
   e. Group 5: PH due to unidentified mechanisms

II. The safety and efficacy of bosentan (Tracleer) in pediatric patients was evaluated in an open-label, uncontrolled study with 19 pediatric PAH patients aged 3 to 15 years. Patients had primary pulmonary hypertension (n = 10) or PAH related to congenital heart diseases (9 patients) and were WHO functional class II or class III at baseline. Patients were dosed with bosentan for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the study. Hemodynamics were measured in 17 patients. The mean decrease in (pulmonary vascular resistance) PVR was 389 dyn·sec·cm^{-5}, which was similar to the effect seen in adults. Hemodynamic improvements from baseline were similar with or without co-administration of epoprostenol.

*Normal PVR value is <250 dyn·sec·cm$^{-5,}$ but PAH patients, depending on the severity of the disease state, have a significantly higher PVR value. A Systematic Review and Meta-Analysis of 12 studies was done and baseline PVR value of the PAH patients included in the study was 668.6±219.1 <250 dyn·sec·cm^{-5}.

III. Clinical studies of ambrisentan (Letairis), macitentan (Opsumit), riociguat (Adempas), iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi) did not include patients younger than 18 years to determine whether they respond differently from older patients. Safety and efficacy in pediatric patients has not been established.

IV. PH is a progressive and life-threatening disease. The medications as well as the disease state should be managed by a specialist.

PAH

V. The American College of Chest Physicians (CHEST) guideline for Therapy for PAH in adults suggests that patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a medical center with experience in the performance and interpretation of vasoreactivity testing. Contraindications to acute vasoreactivity testing include a low systemic BP, low CO, or the presence of FC IV symptoms. Patients who demonstrate acute vasoreactivity – in the absence of right-sided heart failure or contraindications to CCB therapy – according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB. CCBs are considered primary therapy.

VI. Lacking head-to-head comparisons of pharmacologic agents for the treatment of PAH, there is insufficient evidence to determine if one agent is superior to another.

VII. Ambrisentan (Letairis), bosentan (Tracleer), and macitentan (Opsumit) are indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in adults to improve exercise ability and decrease clinical worsening.

a. Studies with bosentan (Tracleer) establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). The primary study endpoint was 6-minute walk distance; however, symptoms and functional status was also assessed. In both trials, treatment with Tracleer resulted in a significant increase in exercise ability. The improvement in walk distance was apparent after 1 month of treatment and fully developed by about 2 months of treatment.

b. Ambrisentan (Letairis) and macitentan (Opsumit) effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients who were included in this study had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), or PAH caused by congenital heart disease with repaired shunts (8%). The primary study endpoint was a 6-minute walk distance. An increase in 6-minute walk distance was observed after 4 weeks of treatment with Letairis, with a dose-response observed after 12 weeks of treatment.

c. Macitentan (Opsumit) effect on progression of PAH was demonstrated in a multi-center, long-term, placebo-controlled study in 742 patients with symptomatic PAH WHO FC II-IV. The primary study endpoints were time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy), lung transplantation, initiation of IV or subcutaneous (SC) prostanoids, or "other worsening of PAH" during double-blind treatment plus 7 days. Other worsening was defined as all of the following: a sustained ≥15% decrease from baseline in 6MWD, worsening of PAH symptoms (worsening of WHO FC), and need for additional treatment for PAH. All of these other worsening events were confirmed by an independent adjudication committee, blinded to treatment allocation. Treatment with OPSUMIT 10 mg resulted in a 45% reduction in the occurrence of the primary endpoint.

VIII. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram), treprostinil (Remodulin), and selexipag (Uptravi) are synthetic analogs of prostacyclin indicated for the treatment of PAH (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (WHO Class), and lack of deterioration. Injectable treprostinil (Remodulin) also carries FDA approval for transition from epoprostenol.

IX. Studies in Iloprost (Ventavis) establishing effectiveness included predominately patients with WHO Functional Class III-IV symptoms, etiologies of idiopathic or heritable PAH (65%), or PAH associated with connective tissue diseases (23%). The primary efficacy endpoint was clinical response at 12 weeks with a composite endpoint defined by: improvement in exercise ability (6-minute walk test) by at least 10% versus baseline evaluated 30 minutes after dosing,

improvement with at least one WHO FC versus baseline, and no death or deterioration of pulmonary hypertension. The percentage of patients who had a minimum increase of at least 10 percent in the distance walked within six minutes at week 12 was slightly, but not significantly, higher in the iloprost group than in the placebo group. The absolute change in the 6MWD was significantly larger in the iloprost group. More patients in the iloprost group than in the placebo group had an improvement in the severity of heart failure, as assessed by the WHO FC.

X. Studies in treprostinil (Tyvaso) to establish effectiveness included predominately patients with WHO Functional Class III symptoms, etiologies of idiopathic or heritable PAH (56%), or PAH associated with connective tissue diseases (33%). While there is long-term data on use of treprostinil (Tyvaso) by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil (Tyvaso) has been on a background of bosentan (Tracleer) (an endothelin receptor antagonist) or sildenafil (Revatio) (a phosphodiesterase type 5 inhibitor).

XI. Per the package insert, the study in treprostinil (Orenitram), that established effectiveness included predominately patients with WHO functional class II-III symptoms, etiologies of idiopathic or heritable PAH (75%), or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of treprostinil (Orenitram) on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.

XII. Treprostinil injection (Remodulin) is indicated for subcutaneous or intravenous use only as a continuous infusion. The package insert states treprostinil injection is preferably infused subcutaneously but can be administered by a central intravenous line if the subcutaneous route is not tolerated. Treprostinil can be self-administered subcutaneously by continuous infusion, via a subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. 2019 CHEST guidelines recommend use of treprostinil injection (Remodulin) for patients with continued progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents; or in patients with WHO functional class IV.

XIII. Effectiveness of selexipag (Uptravi) was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

XIV. ACCF/AHA guidelines indicate oral ERA or PDE-5 inhibitor therapy as first line treatment for lower risk PAH patients. There is insufficient safety and efficacy evidence to establish that any one oral therapy for PAH is clearly superior to another. Treatment guidelines do support combination therapy of PDE, ERA, and prostanoid agents.

XV. For patients with WHO functional class II or III 2019 CHEST guidelines recommend the combination of ambrisentan and tadalafil as first line therapy. This is based on data from the AMBITION trial. The trial involved 605 patients with WHO functional class II or III PAH. Patients were randomly assigned to receive once-daily ambrisentan plus tadalafil or to either drug alone. Doses were titrated from 5-10 mg/day for ambrisentan and from 20-40 mg/day for tadalafil. Treatment with the combination was associated with an approximately 50% reduction in risk for clinical failure compared with either drug alone (P = .0002), with improved exercise ability as well as decreased disease progression and hospitalization.

XVI. Due to the lack of head-to-head comparisons of pharmacologic agents for the treatment of PAH, and their differing burdens and risks to patients, CHEST guidelines recommend that drug therapy be chosen on the basis of a methodical evaluation of disease severity and the risk for further short-term deterioration. The optimal method of evaluation has not yet been studied; therefore, all treatment decisions should be informed by patient preferences, goals, and assessments of health-related quality of life.

CTEPH

Riociguat (Adempas) is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with persistent/recurrent CTEPH after surgical treatment, inoperable CTEPH or PAH to improve exercise capacity and WHO functional class. Medical therapy prior to surgery is not indicated because there is no evidence to show it improves hemodynamic or mortality outcomes after surgery.

PH due to ILD

XVII. WHO Group 3 PH can be further broken down to specific causes. Those causes are:

- Obstructive lung disease (e.g., COPD or bronchiectasis)
- Restrictive lung disease (e.g., ILD, kyphoscoliosis)
    - Other lung disease with mixed obstruction and restriction (eg, pulmonary fibrosis with emphysema)
- Hypoxia without lung disease (e.g., high altitude, sleep apnea, obesity hypoventilation)
- Developmental lung disorders (e.g., bronchopulmonary dysplasia, congenital lobar emphysema)

XVIII. FDA approval for treprostinil (Tyvaso) is specific to PH associated with ILD as that was the population evaluated in clinical trials.

XIX. The safety and efficacy of treprostinil (Tyvaso) inhalation solution for the treatment of patients with PH due to ILD was studied in a Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled trial.

a. Patients were adults with Group 3 pulmonary hypertension diagnosed by right heart catheterization. The mean age was 66.5 years, 46.9% were female and majority had the diagnosis of idiopathic interstitial pneumonia (in 44.8%).
b. Primary efficacy outcome measure of difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16 was met with a difference of 31.12 m (95% confidence interval [CI], 16.85 to 45.39; P<0.001).
c. Clinical worsening was evaluated as a secondary endpoint and occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; P=0.04 by the log-rank test)
d. There was no significant between-group difference in patient-reported quality of life as assessed with the SGRQ or in the distance–saturation product at week 16
e. The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. Serious adverse events occurred in 23.3% of the patients who received inhaled treprostinil and in 25.8% of those who received placebo.

XX. Patients who have shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy were excluded from the clinical trial. There is a lack of clinical trial data to show that Treprostinil (Tyvaso) would be effective or safe in this patient population.

Investigational Uses

I. Ambrisentan (generic, Letairis);
   A. Chronic thromboembolic pulmonary hypertension (CTEPH)
      a. AMBER I is a phase 3, randomized, double-blind, placebo controlled, parallel group, 16-week study evaluating the safety and efficacy of ambrisentan and placebo in subjects with inoperable CTEPH. AMBER II is an open-label, extension study of the long-term safety, tolerability, and efficacy.
      b. These studies were terminated early due to futility of enrollment. This was due to several factors, including an unexpectedly low screening rate (~20% of expected) and high screening failure rate (approaching 60%, mostly due to concerns regarding inoperability raised by the central adjudication committee).
   B. Digital ulcers (DU) in systemic sclerosis
      a. A pilot study was conducted to evaluate the efficacy of ambrisentan in the treatment and prevention of digital ulcers in patients with systemic sclerosis and they found that ambrisentan did not prevent the development of new DU over a 4-week time period after 24 weeks. A placebo-controlled study with more patients will be necessary to conclusively assess the effects of ambrisentan on DUs. There is no robust data to support the use of ambrisentan in DUs.
   C. Lowering Portal Pressure in Patients with Liver Cirrhosis
      a. A phase II, single-arm, open-label study to characterise the effect on portal pressure, the effect on renal function and the pharmacokinetic profile of ambrisentan in patients with decompensated cirrhosis is being conducted but no results have been published yet.
   D. Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis
      a. A Phase 3, randomized, double-blind, placebo-controlled, multi-center, parallel-group study to evaluate the efficacy and safety of ambrisentan in subjects with idiopathic pulmonary fibrosis and pulmonary hypertension called ARTEMIS-PH was terminated.
   E. Sarcoidosis
      a. Ambrisentan was studied for Sarcoidosis Associated Pulmonary Hypertension in a single group assignment, open-label clinical trial and suggested a possible benefit of this drug in selected patients. However, the study was a prospective, open-label, proof of concept trial of ambrisentan that wasn't powered enough to show robust safety and efficacy data to support the use.
      b. There is limited or no published clinical trial data to support the use of ambrisentan in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that

were conducted either had very few patients, data was not published, or the studies were terminated.

II. Bosentan (Tracleer)

A. Chronic obstructive pulmonary disease - Pulmonary hypertension

a. In a 12-week randomized trial (N=30) in patients with severe, or very severe, COPD who did not have severe pulmonary hypertension at rest, there was no significant between-group difference in change from baseline in the mean 6-minute walking distance. Additionally, from baseline to week 12, the mean arterial partial pressure of oxygen significantly decreased in the bosentan group compared with placebo. Health-related quality of life scores (Short-Form-36 Health Survey) also significantly worsened in the bosentan group compared with placebo.

b. In a small, open-label study (N=32), addition of bosentan to best supportive care (BSC) improved the 6-minute walking distance and WHO functional class compared with patients receiving BSC alone. Bosentan plus BSC did not significantly improve baseline pulmonary volumes (functional vital capacity, forced expired volume in 1 second), cardiac index, arterial blood gases (partial pressure of oxygen and carbon dioxide), or quality of life (St. George questionnaire).

c. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline does not recommend use of bosentan for treating patients with severe COPD.

B. Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

a. Bosentan was studied in a prospective, phase III, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability in 157 patients with inoperable CTEPH (NCT00313222). The primary outcome was change from baseline to week 16 in 6MWD and change from baseline to week 16 in pulmonary vascular resistance (PVR) at rest. A statistically significant treatment effect (TE) on PVR was demonstrated: -24.1% of baseline (95% confidence interval [CI]: -31.5% to -16.0%; $p < 0.0001$). Mean TE on 6-min walk distance was +2.2 m (95% CI: -22.5 to 26.8 m; $p = 0.5449$) which is not statistically significant.

b. The BENEFIT open-label, extension study in patients with inoperable CTEPH. In total, 148 of the patients who received randomized treatment rolled over into the extension. The trial data has not been published.

c. There is limited clinical trial data to support the use of bosentan in CTEPH. The clinical trial showed very limited efficacy and safety data.

C. Digital ulcers in systemic sclerosis

A. In a double-blind, placebo-controlled study, 122 patients with limited or diffuse systemic sclerosis, according to American College of Rheumatology criteria, and documented digital ulcer within the previous 12 months were randomized 2:1 to treatment with oral bosentan (79 patients) or placebo (43 patients). Mean patient age was 51.8 years, and 63% of patients had digital ulcers at baseline. In patients receiving bosentan, the number of new digital ulcers was significantly reduced compared with placebo (P=0.0083), averaging 1.4 and 2.7 new ulcers per patient, respectively. Of patients with digital ulcers at baseline, an average of 1.8 new ulcers occurred per

bosentan-treated patient and an average of 3.6 new ulcers occurred per placebo-treated patient, a reduction of 50% (*P*=0.0075). There was a slight improvement in Scleroderma Health Assessment Questionnaire (SHAQ) scores that did not reach statistical significance, except for hand function which was significantly improved in bosentan-treated patients. In patients with diffuse scleroderma with digital ulcers at baseline, 11% of bosentan-treated patients developed 4 or more new ulcers and 0% developed 7 or more new ulcers, compared with 50% and 20% of patients in the placebo group. There was no significant difference in time to complete or partial healing of ulcers between groups; however, there was a slight trend toward slower healing in patients treated with bosentan. Adverse effects of bosentan included diarrhea (7 [8.9%] patients) and elevated transaminase levels (9 [11.4%] patients). Five patients in the bosentan group withdrew because of abnormal liver function tests.

D. Essential hypertension
   a. There is no evidence that differentiates safety and efficacy of bosentan from other traditional medications (diuretics, CCB, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and alfa and beta blockers).

E. Raynaud phenomenon in systemic sclerosis
   a. Data from controlled and uncontrolled trials evaluating bosentan (Tracleer) in the management of secondary Raynaud phenomenon demonstrate conflicting results in clinical and microvascular assessments. According to evidence-based international consensus-derived recommendations, bosentan has no confirmed efficacy in the treatment of active digital ulcers in systemic sclerosis patients but is effective in the prevention of digital ulcers, particularly multiple ulcers, and should be considered after other therapies have failed.

F. Thromboembolic pulmonary hypertension, chronic
   a. A systematic review identified 2 randomized trials of 182 patients with chronic thromboembolic pulmonary hypertension that compared 16 weeks of treatment with bosentan (Tracleer) versus placebo. Bosentan (Tracleer) significantly improved the cardiopulmonary hemodynamic parameters of cardiac index and pulmonary vascular resistance. Bosentan (Tracleer) did not significantly affect the 6-minute walk distance, mean pulmonary arterial pressure, risk of functional class deterioration, or risk of clinical worsening. The risk of liver function abnormality was significantly increased with bosentan (Tracleer).

III. Macitentan (Opsumit);

A. Chronic thromboembolic pulmonary hypertension (CTEPH)
   a. The safety, tolerability and efficacy of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension were evaluated in MERIT-1 and MERIT-2:
      i. MERIT-1 is a prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group, 24-week study to assess the efficacy, safety and tolerability in 80 patients. The primary efficacy endpoint is defined as the pulmonary vascular resistance (PVR) at rest at week 16 expressed as percent of baseline PVR at rest and the geometric mean PVR at rest decreased to 73·0%

(95% CI 63·6–83·8) of the baseline value in the macitentan group, corresponding to a mean decrease from baseline of 206 dyn·s/cm^5, and decreased to 87·2% (95% CI 78·5–96·7) of the baseline value in the placebo group, corresponding to a mean decrease from baseline of 86 dyn·s/cm^5 (ratio of geometric means 0·84, 95% CI 0·70–0·99, p=0·041). The trial did not include patients from the United States of America, included a small patient population and was short term.

ii. MERIT-2 is an ongoing, long-term, multicenter, single-arm, open-label extension study of the MERIT-1 study, to assess safety, tolerability and efficacy. Results from this trial have not been reported at this time.

b. There is insufficient clinical trial data to support the use of macitentan in patients with CTEPH. Clinical trials are ongoing to further evaluate macitentan for CTEPH.

B. Digital ulcers in systemic sclerosis

a. A prospective, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability of macitentan in patients with ischemic digital ulcers associated with systemic sclerosis was terminated.

b. Two international, randomized, double-blind, placebo-controlled trials (DUAL-1, DUAL-2) were conducted in patients with systemic sclerosis and active digital ulcers at baseline. The primary outcome for each trial was the cumulative number of new digital ulcers from baseline to week 16. The results of the studies do not support the use of macitentan for the treatment of digital ulcers in this patient population.

C. Glioblastoma

a. A single-center, open-label, phase 1 study of concurrent therapy with macitentan, radiotherapy, and temozolomide, followed by maintenance therapy with macitentan and temozolomide in subjects with newly diagnosed glioblastoma was terminated due to low recruitment.

b. A Phase 1/1b, open-label study in patients with recurrent glioblastoma to assess the safety and tolerability of macitentan in combination with dose-dense temozolomide was terminated because the results did not clearly support continuing development in recurrent GBM.

c. There is limited or no published clinical trial data to support the use of macitentan in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, terminated, or data was not published.

IV. Riociguat (Adempas);

A. Systemic sclerosis-associated digital ulcers

a. Seventeen participants (eight placebo, nine riociguat) were randomized at five centers. Baseline characteristics were comparable between the treatment groups, except for participants who were randomized to placebo were older and had longer disease duration. Treatment with riociguat did not reduce the number of DU net burden compared with placebo at 16 weeks. Open-label extension suggests that longer duration is needed to promote DU healing, which needs to be confirmed in a new trial.

b. The conducted trials are not powered enough and show low or no efficacy. There is limited to no published clinical trial data to support the use of riociguat (Adempas) in conditions other than persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) or Pulmonary Arterial Hypertension (PAH).

VIII. Treprostinil (Tyvaso);

A. Pulmonary hypertension (PH) WHO Groups II-V

- Group II - Left heart disease, including congestive heart failure (CHF)
- Group III – Non-ILD lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis; Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema); Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
- Group IV - Chronic thrombotic and/or embolic disease
- Group V – Sarcoidosis

There is limited or no published clinical trial data to support the use of treprostinil (Tyvaso) in conditions other than PAH and PH due to ILD. The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

IX. Iloprost (Ventavis), treprostinil (Orenitram) and selexipag (Uptravi);

A. Pulmonary hypertension (PH) WHO Groups II-V

- Group II - Left heart disease, including congestive heart failure (CHF)
- Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
- Group IV - Chronic thrombotic and/or embolic disease
- Group V – Sarcoidosis

B. There is limited or no published clinical trial data to support the use of iloprost (Ventavis), treprostinil (Orenitram) and selexipag (Uptravi) in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

IV. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi);

A. Chronic thromboembolic pulmonary hypertension (CTEPH) – WHO Group IV

a. There is insufficient data to support the use of selexipag (Uptravi) in patients with inoperable or persistent/recurrent after surgical and/or interventional treatment CTEPH. Clinical trials are ongoing, and results are not yet available.

b. There is limited or no published clinical trial data to support the use of iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi) in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

Appendix

I. Table 1: PAH Determinants of Prognosis (ACCF/AHA Guidelines)

Determinants of Risk	Lower Risk (Good Prognosis)	Higher Risk (Poor Prognosis)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class†	II, III	IV
6MW distance‡	Longer (greater than 400 m)	Shorter (less than 300 m)
CPET	Peak VO2 greater than 10.4 mL/kg/min	Peak VO2 less than 10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP less than 10 mm Hg, CI greater than 2.5 L/min/m2	RAP greater than 20 mm Hg, CI less than 2.0 L/min/m2
BNP§	Minimally elevated	Significantly elevated
*Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions.		
†WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class.		
‡6MW distance is also influenced by age, gender, and height.		
§As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.		
6MW indicates 6-minute walk; BNP, brain natriuretic peptide. CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO2, average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; and WHO, World Health Organization.		

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Policy Implementation/Update:

Action and Summary of Changes	Date
• Added new indication of PH due to ILD for treprostinil (Tyvaso) • Added treprostinil injection (Remodulin) into policy • Removed requirement of PDE-5 monotherapy for 3 months in those requesting generic ambrisentan in combination with a PDE-5 • Added requirement of prior endothelin receptor antagonist if requesting Ventavis or Tyvaso in PAH	06/2021
• Updated renewal section with standard renewal language • Added chronic thromboembolic pulmonary hypertension (CTEPH) as an investigational indication to bosentan (generic, Tracleer), ambrisentan (generic, Letairis), macitentan (Opsumit) and selexipag (Uptravi)	03/2020

• Updated the criteria into policy format
• Added acute vasoreactivity test criteria to apply to all agents
• Added age limit to reflect clinical trial data
• Combined criteria for bosentan (generic, Tracleer), ambrisentan (generic, Letairis)& macitentan (Opsumit) with riociguat (Adempas) criteria and Iloprost (Ventavis), treprostinil (Tyvaso and Orenitram), selexipag (Uptravi)
• Quantity limit change iloprost (Ventavis) and bosentan (Letairis) to reflect the dosing in the package insert
• Treprostinil (Orenitram) 5mg doseage form added
• Added criteria because generic bosentan and generic ambrisentan became available we are driving patients to a more cost effective option;
  ○ Prior to getting bosentan (Tracleer), member has tried generic bosentan and treatment has been ineffective, contraindicated, or not tolerated
  ○ Prior to getting ambrisentan (Letairis), member has tried generic ambrisentan and treatment has been ineffective, contraindicated, or not tolerated
• Added generic bosentan and generic ambrisentan to the policy
	12/2019

• Added Uptravi for P&T 5/4/16 • Reviewed policy	3/29/2016
• Updated formatting. • Added Tyvaso and Orenitram, removed question regarding initial 6 minute walking distance and required trial and failure of generic sildenafil only for oral prostanoid.	03/17/2016
• Criteria update: Validated place in therapy and recommendations. • Removed questions regarding contraindications, warnings/precautions. • Updated header, footer and formatting [riociguat (Adempas)] • Reviewed	03/14/2016

Policy created and effective [iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi)]	Prior to 3/17/2016 (no date available)
Policy created [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]	03/2016
Previously reviewed [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]	03/2014, 03/2016
Criteria for ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit) created	01/2013

Policy Type: PA/SP Pharmacy Coverage Policy: UMP055

Description

Obizur is an antihemophilic factor indicated for the treatment of bleeding episodes in adults with acquired hemophilia. Obizur is not indicated for the treatment of congenital hemophilia A or von Willebrand disease.

Length of Authorization

- Initial: 6 months
- Renewal: 6 months

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit
Obizur, antihemophilic factor (recombinant), porcine sequence	500 units	**Treatment of bleeding episodes in adults with acquired hemophilia A:** • Minor and moderate: Loading dose of 200 IU/kg, followed by maintenance dose titrated to maintain recommended factor VIII trough levels at 50-100 IU/dL every four to 12 hours • Major: Minor and moderate: Loading dose of 200 IU/kg, followed by maintenance dose titrated to maintain recommended factor VIII trough levels at 100-200 IU/dL (to treat acute bleed) every four to 12 hours, then 50-100 IU/dL (after acute bleed is controlled) every four to 12 hours	**Treatment of bleeding episodes in adults with acquired hemophilia A:** Up to the number of doses requested every 28 days

Initial Evaluation

I. Obizur may be considered medically necessary when the following criteria below are met:
   A. Member has a confirmed diagnosis of **acquired hemophilia A (acquired factor VIII deficiency)** when the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Diagnosis of acquired factor VIII deficiency has been confirmed by blood coagulation testing; **AND**
      3. Used as treatment of bleeding episodes; **AND**
      4. Obizur is not being used for congenital hemophilia A or von Willebrand disease

II. Obizur is considered investigational when used for congenital hemophilia or von Willebrand disease, or 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

I. Acquired inhibitors of coagulation are antibodies that either inhibit the activity or increase the clearance of a clotting factor. The most common autoantibodies that affect clotting factor activity and lead to a bleeding disorder are directed against, and interfere with, the activity of factor VIII. This condition is also called acquired hemophilia.

II. Obizur is a recombinant, B domain-deleted porcine (pig) factor VIII indicated for the treatment of patients with autoantibodies to factor VII (i.e. patients with an acquired factor VIII inhibitor). It is not approved for use in patients with congenital (i.e. inherited) hemophilia A.

III. The safety and efficacy of Obizur was established in a small prospective study in patients with an acquired factor VIII inhibitor and severe bleeding. Obizur controlled bleeding in 86% of patients.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of Obizur in any other condition.

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Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	Date
New policy created for Obizur	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP150

Description

Regorafenib (Stivarga) is an orally administered kinase inhibitor acting on various membrane-bound and intracellular kinases.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
regorafenib (Stivarga)	40 mg tablets	Gastrointestinal stromal tumor, locally advanced, unresectable or metastatic disease after treatment with imatinib and sunitinib; Colorectal cancer, metastatic, previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy, an anti-VEGF therapy, and if RAS wild type an anti-EGFR therapy; Hepatocellular (liver) carcinoma, previously treated with sorafenib	84 tablets/28 days

Initial Evaluation

I. Regorafenib (Stivarga) 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. Not used in combination with any other oncolytic medication (i.e., used as monotherapy); **AND**
   D. A diagnosis of one of the following:
      1. **Colorectal Cancer**; **AND**
         i. The member has metastatic (stage IV) disease; **AND**
         ii. The member has previously progressed on or after a fluoropyrimidine [e.g., capecitabine, fluorouracil (5-FU)], oxaliplatin, AND irinotecan-containing chemotherapy; **AND**
         iii. The member has previously progressed on or after an anti-VEGF therapy [e.g., bevacizumab (Avastin)]; **AND**

iv. The member is KRAS-mutated; **OR**
    a. If KRAS wild-type, the member has been treated with an anti-EGFR therapy [e.g., cetuximab (Erbitux), panitumumab (Vectibix)]; **OR**

2. **Gastrointestinal Stromal Tumor**; **AND**
    i. The member has locally advanced (stage III), unresectable or metastatic (stage IV) disease; **AND**
    ii. The member has previously progressed on or after imatinib (Gleevec) AND sunitinib (Sutent); **OR**
3. **Hepatocellular Carcinoma; AND**
    i. The member has previously progressed on or after sorafenib (Nexavar)

II. Regorafenib (Stivarga) is considered investigational when used for all other conditions, including but not limited to:
    A. Biliary cancer, cholangiocarcinoma
    B. Esophagogastric cancer (esophageal, gastroesophageal, gastric)
    C. Non-small cell lung cancer
    D. Renal cell carcinoma
    E. Soft tissue sarcoma
    F. Adenoid cystic carcinoma
    G. Urothelial carcinoma
    H. 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. The medication is prescribed by, or in consultation with an oncologist or hematologist; **AND**
IV. Regorafenib (Stivarga) will not be used in combination with other oncolytic medications (i.e., will be used as monotherapy); **AND**
V. Documentation of clinical response to therapy, such as stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

I. Regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled study in adults with metastatic colorectal cancer after failure of standard therapy. The trial included 760 subjects that had been previously treated with fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapy, as well as bevacizumab (Avastin). All but one subject with KRAS wild-type disease received ANTI-EGFR therapy [cetuximab (Erbitux), panitumumab (Vectibix)].

Regorafenib (Stivarga) showed a statistically significant improvement in overall survival (OS) compared to placebo [6.4 months vs. 5 months; HR 0.77 (CI 0.64-0.94), p – 0.0102].

II. The safety and efficacy of regorafenib (Stivarga) for gastrointestinal stromal tumors (GIST) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial in adults with unresectable, locally advanced or metastatic disease. Subjects had been previously treated with imatinib (Gleevec) and sunitinib (Sutent). The medication showed a statistically significant improvement in progression-free survival (PFS) [PFS was 4.8 vs. 0.9 months; HR 0.27 (0.19-0.39), p<0.0001]; however, there was no statistical difference in OS. This may have been influenced by cross-over to active therapy after disease progression on placebo.

III. The clinical safety and efficacy of regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial in adults with hepatocellular carcinoma. All subjects had documented disease progression on sorafenib (Nexavar), and those that had discontinued sorafenib (Nexavar) due to toxicity rather than disease progression were ineligible for the trial; thus, safety and efficacy with regorafenib (Stivarga) prior to progression on or after sorafenib (Nexavar) has not been established. Overall survival was the primary outcome and was statistically significant in favor of regorafenib (Stivarga) over placebo [10.6 vs. 7.8 months; HR 0.63 (0.5-0.79), p<0.0001].

IV. For all indications regorafenib (Stivarga) is dosed at 160 mg per day on days 1-21 of each 28-day cycle. Product availability is 40 mg tablets.

Investigational or Not Medically Necessary Uses

I. Regorafenib (Stivarga) has not been sufficiently studied for safety or efficacy and/or is currently being evaluated in clinical trials for the following indications:
   A. Biliary cancer, cholangiocarcinoma
   B. Esophagogastric cancer (esophageal, gastroesophageal, gastric)
   C. Non-small cell lung cancer
   D. Renal cell carcinoma
   E. Soft tissue sarcoma
   F. Adenoid cystic carcinoma
   G. Urothelial carcinoma
   H. Ovarian cancer

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Policy Implementation/Update:

Date Created	January 2013
Date Effective	February 2013
Last Updated	November 2019
Last Reviewed	01/2013, 02/2013, 04/2014, 09/2014, 11/2019

Action and Summary of Changes	**Date**
Prior authorization transitioned to policy format. Addition of age edit, addition of monotherapy requirement. Renewal criteria transitioned to current formatting and language, and increase from three to 12 month approval.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP228

Description

Relugolix is an orally administered gonadotropin-releasing hormone (GnRH) antagonist.

Length of Authorization

- Initial: 12 months
- Renewal:
  - i. Orgovyx: 12 months
  - ii. Myfembree: 12 months, total (lifetime) fills not to exceed 24 28-day fills

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
relugolix (Orgovyx)	120 mg tablets	Prostate cancer	**Initial**: 30 tablets/28 days for one month **Maintenance**: 30 tablets/30 days
relugolix/estradiol/norethindrone (Myfembree)	40 mg/1 mg/0.5 mg tablets	Heavy menstrual bleeding associated with uterine fibroids (leiomyoma)	28 tablets/28 days

Initial Evaluation

I. **Relugolix (Orgovyx)** or **relugolix/estradiol/norethindrone (Myfembree)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. For **relugolix (Orgovyx):**
      1. A diagnosis of **prostate cancer**; **AND**
         i. Medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
         ii. Provider attestation the member is castration sensitive; **AND**
         iii. Prostate cancer is advanced or metastatic (Stage III or IV); **AND**
         iv. Treatment with a GnRH agonist (e.g., leuprolide [Lupron]), has been ineffective, not tolerated, or all GnRH agonists are contraindicated; **OR**
            a. The member has a history of a major adverse cardiovascular event (MACE) (e.g., myocardial infarction, stroke); **AND**
         v. Degarelix (Firmagon) has been ineffective, not tolerated, or is contraindicated; **AND**

vi. Relugolix (Orgovyx) is medically necessary for the treatment of prostate cancer over GnRH agonists and degarelix (Firmagon). (Note – preference for oral administration or other convenience does not meet medical necessity); **OR**

C. For **relugolix/estradiol/norethindrone (Myfembree)**:

1. A diagnosis of **heavy menstrual bleeding associated with uterine fibroids** (leiomyoma); **AND**
   i. Medication is prescribed by, or in consultation with, an obstetrician/gynecologist; **AND**
   ii. Member does **not** have a history of osteoporosis (defined as 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**
   iii. At least one hormonal contraceptive treatment (oral, IUD, implant, etc.) has been ineffective, not tolerated, or ALL are contraindicated; **AND**
   iv. Treatment with tranexamic acid has been ineffective, not tolerated, or is contraindicated; **AND**
   v. Provider attestation that the member has not previously been treated with elagolix/estradiol/norethindrone (Oriahnn).

II. Relugolix is considered investigational when used for all other conditions, including but not limited to:

A. Endometriosis, treatment or symptom management
B. Castration-resistant prostate 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 so, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. **Relugolix (Orgovyx):**

A. Documentation of disease response to treatment (e.g., stabilization of disease or decrease in tumor size or tumor spread, reduction in serum testosterone or PSA); **OR**
B. Provider attestation that continuation of therapy is necessary if the member has had disease progression; **OR**

IV. **Relugolix/estradiol/norethindrone (Myfembree):**

A. Member has exhibited improvement in symptoms (reduction in menstrual blood loss, pain reduction, improvement in quality of life, etc.); **AND**
B. Provider attestation the member has not previously received treatment with elagolix/estradiol/norethindrone (Oriahnn); **AND**
C. The member has not received treatment for more than 24 months

Supporting Evidence

I. Relugolix (Orgovyx) is a gonadotropin-releasing hormone (GnRH) receptor antagonist, FDA-approved for the treatment advanced prostate cancer. A 360 mg loading dose (three tablets) is administered on day one, then a maintenance dose of 120 mg (one tablet) is taken once daily. It is one of several androgen deprivation therapies (ADT) available. Other options include GnRH agonists such as leuprolide (Lupron), goserelin (Zoladex), triptorelin (Telstar/Triptodur), histrelin (Supprelin LA, Vantas), and GnRH agonist [degarelix (Firmagon)], all of which are injectable medications. Additionally, surgical orchiectomy is an option when prompt castration is required. Reducing serum testosterone to castrate levels is warranted for the treatment of prostate cancer, and all of these methods are highly effective. Androgen deprivation therapy is a hallmark of treatment, and is generally continued, if tolerated, even if there is progressive disease and/or if other prostate cancer medications are started. Given the specialization of the condition and treatment options, therapy should be prescribed by, or in consultation with, an oncologist.

II. The GnRH agonists are highly utilized for the treatment of advanced or metastatic prostate cancer. They are known to cause a testosterone surge upon initiation, with a subsequent decrease in serum testosterone three-to-four weeks after starting treatment. For patients at risk for these symptoms, an antiandrogen therapy (e.g., flutamide, nilutamide, bicalutamide) may be administered concurrently for the first few weeks of GnRH agonist treatment. Some agents are available in every-three-month injections and are generally well tolerated

III. The GnRH antagonists, degarelix (Firmagon), and now relugolix (Orgovyx), are successful at mitigating the testosterone surge and may rapidly reduce testosterone; although, the rapidity of testosterone suppression with GnRH antagonists has not been linked to superior clinical benefit over the GnRH agonists in the general population likely to utilize these therapies.

IV. Relugolix (Orgovyx) was evaluated in one Phase 3, randomized, open-label, non-inferiority (NI) trial vs. leuprolide (Lupron) over 48 weeks in patients with advanced or metastatic disease. Up to 13% of patients had previous ADT, 30% had previous radiotherapy, and 14% had a history of major adverse cardiovascular event (MACE). There was a washout period of three months for those previously treated with degarelix (Firmagon) and one year for those on GnRH agonist therapy. Those with a MACE in the six months before the trial were excluded. All patients included in the trial were adults, which is the expected population to be diagnosed with prostate cancer. At this time the safety and efficacy of relugolix (Orgovyx) in pediatric patients remains unknown; however, it would be very rare for a pediatric patient to develop prostate cancer.

V. The primary outcome was cumulative sustained castration rate of less than 50 ng/dL from day 29 through 48 weeks. Results were 96.7% of patients for relugolix (Orgovyx) and 88.8% for leuprolide (Lupron), with a difference of 7.9% (CI 4.1-11.8). Additionally, a notable secondary outcome was castration relapse free survival (CRFS) at 48 weeks. This was 74% for relugolix (Orgovyx) and 75% for leuprolide (Lupron) (HR 1.03, CI 0.68-1.57, p=0.84). Both of these outcomes showed NI of relugolix (Orgovyx) to leuprolide (Lupron). Statistically, relugolix (Orgovyx) was superior to leuprolide (Lupron) in the primary outcome; however, both therapies showed a very high rate of sustained castration. At this time definitive data are lacking to indicate clinical superiority of either product in regard to medication efficacy.

VI. There were several other secondary outcomes measured: probability of testosterone suppression to less than 50 ng/dL on day four and day 15, prostate specific antigen (PSA)

response on day 15 and day 29, probability of profound testosterone suppression (less than 20 ng/dL) on day 15. These were all superior for relugolix (Orgovyx) over leuprolide (Lupron). This is expected given the mechanistic differences of the therapies. Given the known initial testosterone surge with GnRH agonists, castrate levels would be expected three-to-four weeks after medication initiation. The results confirm the rapidity of testosterone suppression for relugolix (Orgovyx), as expected for a GnRH antagonist.

VII. Rate of overall adverse events (AE) was consistent across both groups. Common AE (greater than 10%) that occurred in both groups included laboratory abnormalities, increase glucose levels, increase triglycerides, musculoskeletal pain, increased hemoglobin, ALT/AST increases, constipation, and diarrhea.

VIII. Serious AE occurred in 9.8% of the relugolix (Orgovyx) group, and 15.3% of the leuprolide (Lupron) group. For relugolix (Orgovyx) sAE: myocardial infarction (0.8%), AKI (0.6%), hemorrhage (0.6%), and UTI (0.5%).

IX. The MACE rate was 2.9% for relugolix (Orgovyx) and 6.2% for leuprolide (Lupron), overall. This was further pronounced in the subgroup of patients that had a previous MACE. Rates were 3.6% and 17.8%, respectively. In the group without a previous MACE, rates were 2.8% and 4.2%, respectively. From the data, it is predicted that GnRH antagonists may have a favorable safety profile in those with history of a MACE, such as myocardial infarction and stroke. Options include degarelix (Firmagon) as well as relugolix (Orgovyx), and current data are lacking to indicate clinical favorability between these two agents.

X. **Relugolix/estradiol/norethindrone (Myfembree)** was evaluated in the setting of heavy menstrual bleeding associated with uterine fibroids (leiomyoma). 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), uterine artery embolization, hysterectomy, and endometrial ablation.

XI. 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.

XII. 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.

XIII. 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, relugolix/estradiol/norethindrone (Myfembree) will join elagolix/estradiol/norethindrone (Oriahnn) for the treatment of this indication. 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.

XIV. Relugolix/estradiol/norethindrone (Myfembree) was evaluated in two Phase 3, double-blind, randomized, placebo-controlled trials over 24 weeks. Therapy was evaluated in premenopausal women with heavy menstrual bleeding and diagnosis of uterine fibroids, confirmed via ultrasonography. Patients with osteoporosis or osteopenia were excluded.

XV. Primary outcome: percentage of participants with treatment response (blood loss volume < 80 mL and ≥ 50% reduction in volume). Secondary outcomes: proportion of patients reaching amenorrhea, change in blood loss volume, pain, distress from bleeding and pelvic discomfort, and participants that had a change in hemoglobin of 2 g/dL or more in those that had anemia at baseline. These outcomes were statistically and clinically significant over placebo. In clinical trials, relugolix/estradiol/norethindrone (Myfembree) did not reduce uterine fibroid volume.

XVI. Relugolix was also evaluated as monotherapy in a randomized, blinded, NI trial vs. leuprorelin (Lupron). Relugolix showed to be NI to leuprorelin (Lupron) in the following outcomes: blood loss, amenorrhea, uterine volume, fibroid volume, hemoglobin improvement, pain, and quality of life. Estrogenic AE and decrease in BMD were notable; thus, the manufacturer is pursuing combination therapy with estradiol and norethindrone to mitigate these concerns. A limitation of the trial is the majority of patients received leuprorelin (Lupron) 1.88 mg, rather than the standard U.S. dose of 3.75 mg. Comparative safety and efficacy data to the 3.75 mg dose of leuprorelin (Lupron) is currently unknown.

XVII. Rate of overall AEs was consistent for placebo and active therapy. No deaths occurred in the trials and serious AEs were rare. There were a few cases of ankle fracture in those that received relugolix/estradiol/norethindrone (Myfembree). At week 24 the BMD at lumbar spine and total hip were similar between groups. AE leading to treatment discontinuation occurred in 4-11% of patients. Common AE included the following: hot flash (6-11% vs. 4-8% for placebo) and hypertension (5% vs. 0% for placebo). Other AE that occurred in ≥ 5% of patients included headache, arthralgia, cough, nausea, URI, fatigue, and anemia. Long term safety is currently unknown but will be better understood with results from long-term safety extension trials. The FDA has indicated that use of Myfembree should be limited to 24 months due to the risk of continued bone loss with use, which may not be reversible.

Investigational or Not Medically Necessary Uses

I. Relugolix has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Endometriosis, treatment or symptom management
   B. Castration-resistant prostate cancer

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA Pharmacy Coverage Policy: UMP056

Description

Rifaximin (Xifaxan) is an orally administered rifamycin antibacterial agent that inhibits bacterial RNA synthesis by binding to bacterial DNA-dependent RNA polymerase.

Length of Authorization

- Initial:
  - i. Irritable Bowel Syndrome with Diarrhea (IBS-D): one time approval
  - ii. Hepatic encephalopathy: six months
  - iii. Traveler's diarrhea: one time approval
- Renewal:
  - i. IBS-D: one-time approval, maximum of three fills per lifetime
  - ii. Hepatic encephalopathy: 12 months
  - iii. Traveler's diarrhea: N/A

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
rifaximin (Xifaxan)	550 mg tablets	Treatment of irritable bowel syndrome with diarrhea (IBS-D).	42 tablets/ 14 days	150969, 152498
		Hepatic encephalopathy recurrence.	60 tablets/30 days	
	200 mg tablets	Travelers' diarrhea caused by noninvasive strains of Escherichia coli	9 tablets/3 days	088395, 088393

Initial Evaluation

I. Rifaximin (Xifaxan) may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      i. **Irritable Bowel Syndrome with Diarrhea (IBS-D)**; **AND**
         a. Member is 18 year of age or older; **AND**
         b. Rifaxamin (Xifaxan) is prescribed by or in consultation with a gastroenterologist; **AND**
         c. Treatment with at least <u>three therapies from different groups</u> have been tried and failed, not tolerated or all are contraindicated (please note, if one or more groups is contraindicated, a trial of three agents from the remaining classes will be required):
            a. Group 1: antidiarrheal (e.g., loperamide, bismuth subsalicylate, diphenoxylate/atropine, paregoric)
            b. Group 2: bile acid sequestrant (e.g., cholestyramine, colestipol)
            c. Group 3: antispasmodic (e.g., dicyclomine, hyoscyamine)

d. Group 4: Tricyclic serotonergic agent: (e.g., amitriptyline, nortriptyline, imipramine, desipramine)

OR

ii. **Traveler's diarrhea**; **AND**

a. Member is 12 years of age or older; **AND**

b. Treatment with azithromycin (Zithromax) or a fluoroquinolone (e.g., ciprofloxacin) have been ineffective, not tolerated, or BOTH are contraindicated; **OR**

iii. **Hepatic encephalopathy**; **AND**

a. Member is 18 year of age or older; **AND (a or b)**

a. Treatment with lactulose has been ineffective, contraindicated, or not tolerated; **OR**

b. Rifaxamin (Xifaxan) will be used as add-on treatment

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

A. Small Intestinal Bacterial Overgrowth (SIBO)

Renewal Evaluation

I. **Irritable Bowel Syndrome with Diarrhea (IBS-D); AND**

A. There has been a 10 week treatment-free period since prior approval of rifaximin (Xifaxan); **AND**

B. The member has not had more than two prior treatments with rifaximin (Xifaxan). A maximum of three approvals is allowed per lifetime for the treatment of IBS-D; **OR**

II. **Hepatic encephalopathy; AND**

A. Clinical documentation indicating disease stability or improvement.

Supporting Evidence

I. Rifaximin (Xifaxan) is indicated for adults and pediatric patients 12 years of age and older with travelers' diarrhea, and adults older than 18 years of age with hepatic encephalopathy or IBS-D. Infectious Diseases Society of America clinical practice guidelines recommend treatment with fluoroquinolones or azithromycin as first line treatment of travelers' diarrhea.

II. The FDA approved dose is 200 mg three times daily for three days for traveler's diarrhea.

III. The American Association for the Study of Liver Diseases and European Association for the Study of the Liver clinical practice guidelines suggest initial therapy with lactulose for the treatment of hepatic encephalopathy. Rifaximin (Xifaxan) is an effective add-on therapy to lactulose for prevention of recurrence.

IV. Treatment options for IBS-D include antidiarrheals, antibiotics, antispasmodics, antidepressants, and bile acid sequestrants. The American College of Gastroenterology gave moderate or weak recommendations for all IBS-D therapies due to poor quality of evidence and applicability to patient groups. Due to insufficient comparative evidence for efficacy, other treatment options provide a better value over rifaximin (Xifaxan). Of the antidepressants, tricyclic agents have

shown to slow intestinal transit; however, SSRI/SNRI agents have less published data and the data available is inconsistent in showing benefit in IBS.

V. Rifaximin (Xifaxan) will be authorized for a total of three courses per lifetime for IBS-D per FDA label. In clinical studies, 14-day repeat treatment courses were separated by 10 weeks.

Investigational or Not Medically Necessary Uses

I. Small Intestinal Bacterial Overgrowth (SIBO)
   A. Although likely an association exists between IBS-D and SIBO, the evidence linking a causal relationship between the two diagnoses is conflicting.
   B. Intestinal motility disorders and chronic pancreatitis are estimated to account for approximately 90 percent of cases of SIBO. Underlying etiology of SIBO should be addressed prior to pharmacologic therapy. Common causes of SIBO include: anatomic abnormalities; strictures, motility Issues, hypochlorhydria, immunodeficiency, chronic pancreatitis, cirrhosis, end stage renal disease, or medications (e.g., proton pump inhibitors, tricyclic antidepressants, opioids).
   C. Rifaximin (Xifaxan) use in adults with SIBO has not been evaluated in multicenter, prospective, randomized, placebo-controlled trials. Although five single-site, open-label, randomized controlled trials demonstrated a potential modest benefit of rifaximin (Xifaxan) use in adults with a SIBO, the studies were poorly designed, had a small sample size, and had minimal follow up.
   D. Gastroenterological Association Institute clinical guidelines for treatment of SIBO have not been established.

References

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Policy Implementation/Update:

Date Created	August 2015
Date Effective	August 2015
Last Updated	July 2019
Last Reviewed	08/2015; 04/2019, 07/2019

Action and Summary of Changes	Date
Criteria for the IBS-d indicated updated to require three prior therapies prior to payment consideration. Additionally, agents with low quality or conflicting data were removed from the list of conventional agents allowed for previous trial and failure. Rearrangement of criteria to include the most requested indication first.	07/2019
Updated to policy format, evidence for the investigational use of rifaximin (Xifaxan) in SIBO updated, addition of specialist involvement in prescribing for IBS-D, age criteria edited.	04/2019

riluzole (Rilutek®, Tiglutik®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP214

Description

Riluzole (Rilutek®, Tiglutik®) is an orally administered benzothiazole for the treatment of patients with amyotrophic lateral sclerosis (ALS).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
riluzole (Rilutek) *	50 mg tablet	Amyotrophic lateral sclerosis (ALS)	60 tablets/30 days
riluzole (Tiglutik)	50 mg/10 mL (5 mg/mL) oral suspension		600 ml/30 days

**Generic riluzole* is a formulary agent and does not require prior authorization

Initial Evaluation

I. Riluzole (Rilutek, Tiglutik) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. A diagnosis of **Amyotrophic lateral sclerosis (ALS); AND**
   D. Treatment with generic riluzole tablet has been ineffective, contraindicated, or not tolerated.

II. Riluzole (Rilutek, Tiglutik) are considered investigational when used for all other conditions, including but not limited to:
   A. Treatment-resistant depression
   B. Chorea in Huntington's 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.; **AND**

III. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
IV. Documentation of clinical benefit, including stabilization of disease and absence of unacceptable toxicity from the drug [e.g. hepatic injury, severe neutropenia, interstitial lung disease]; **AND**
V. Treatment with generic riluzole tablet has been ineffective, contraindicated, or not tolerated

Supporting Evidence

I. According to the American Academy of Neurology (AAN) two randomized controlled clinical trials and one cross-sectional study, show that multidisciplinary clinics specializing in ALS care are likely effective in several ways, which include improved quality of life and lengthened survival. The AAN guidelines recommend that specialized multidisciplinary clinical referral should be considered for patients with ALS to optimize health care delivery and prolong survival and may be linked to enhanced quality of life.
II. The safety and efficacy of riluzole (Rilutek®) in pediatric patients with amyotrophic lateral sclerosis (ALS) has not been established.
III. According to the American Academy of Neurology (AAN) practice parameter for the care of patients with ALS, riluzole is safe and effective for slowing disease progression to a modest degree in ALS. They therefore recommend that riluzole should be offered to slow disease progression in patients with ALS.

Investigational or Not Medically Necessary Uses

I. In a randomized, double-blind, placebo-controlled sequential trial that evaluated the efficacy and safety of adjunctive riluzole for treatment-resistant major depressive disorder (MDD), 104 participants were randomized in a 2:3:3 ratio to receive riluzole/riluzole, placebo/placebo and placebo/riluzole. The trial had two phases of 4 weeks each, and the primary endpoint was change in depression severity as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS), which did not show a statistically significant difference between riluzole and placebo.
II. Chorea is a hallmark of Huntington Disease (HD), along with cognitive decline and psychiatric impairment. The AAN guidelines for pharmacologic treatment of HD, notes two randomized controlled trials evaluating riluzole for chorea for HD using different doses (100 mg or 200 mg) and durations (8 weeks and 3 years). The first study (n=63) showed a statistically significant reduction in unified huntington's disease rating scale (UHDRS) in patients who received riluzole 200 mg/day (-2.2 ± 3.3, p 0.01); however, statistical significance was observed in those who received riluzole 100 mg/day [-0.2 ± 2.9; vs placebo (± 0.7 ± 3.4)]. In the second study (n=537), no statistically significant difference in UHDRS chorea scores at 3 years was observed between participants who received riluzole 50 mg twice daily and placebo. Although the guidelines recommend riluzole 200 mg/day with level B of evidence for HD chorea, there is modest evidence on the efficacy and safety of riluzole for chorea in HD.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria changed to policy format, added age requirement, specialist referral/prescription, step through generic riluzole tablet and renewal evaluation.	12/2020
Criteria created	07/2013

Policy Type: PA Pharmacy Coverage Policy: UMP207

Description

Ripretinib (Qinlock) is an orally administered tyrosine kinase inhibitor (TKI) that inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinase.

Length of Authorization

I. Initial: Three months

- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
ripretinib (Qinlock)	50 mg tablets	Gastrointestinal Stromal Tumor, advanced disease after treatment with three or more tyrosine kinase inhibitors, including imatinib	90 tablets/30 days

Initial Evaluation

I. Ripretinib (Qinlock) 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. Ripretinib (Qinlock) will be used as monotherapy (i.e., will not be used in combination with any other oncology therapy); **AND**
   D. A diagnosis of **Gastrointestinal Stromal Tumor (GIST)** when the following are met:
      1. Member has advanced (Stage III), unresectable or metastatic (Stage IV) disease; **AND**
      2. Member has previously progressed on, or after, **ALL** of the following:
         a. imatinib (e.g., Gleevec)
         b. sunitinib (Sutent)
         c. regorafenib (Stivarga)

II. Ripretinib (Qinlock) is considered investigational when used for all other conditions, including but not limited to:
   A. Third-line or prior treatment of gastrointestinal stromal tumor
   B. Advanced Systemic Mastocytosis or other hematologic malignancies
   C. Soft Tissue Sarcoma, outside of gastrointestinal stromal tumor
   D. Malignant Gliomas
   E. Melanoma
   F. Germ Cell, Penile Cancer

G. Non-Small Cell Lung Carcinoma (NSCLC)
H. Other Advanced Solid Tumor Cancers/Malignancies

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. Ripretinib (Qinlock) will be used as monotherapy (i.e., will not be used in combination with other oncologic medications); **AND**
IV. Member has experienced response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

I. Ripretinib (Qinlock) was evaluated in INVICTUS - a randomized (2:1), double-blind, placebo-controlled study in adults with advanced gastrointestinal stromal tumors. The trial included 129 subjects who had previously progressed on or after imatinib, sunitinib, and regorafenib, or had documented intolerance to any of these treatments despite dose modifications. Mutation status was collected but was not utilized as part of the inclusion criteria for this trial. Ripretinib (Qinlock) was evaluated as monotherapy, and use of ripretinib (Qinlock) in addition to other oncologic therapies has not been evaluated for safety and/or efficacy.
II. The primary efficacy endpoint was progression-free survival (PFS) and notable secondary endpoints included objective response rate (ORR), overall survival (OS), and quality of life (QOL). Ripretinib (Qinlock) showed statistically significant results in PFS compared to placebo [6.3 months vs. 1.0 months; HR 0.15; 95% CI 0.09-0.25; $p<0.001$]; however, there was not a statistically significant difference in ORR. Due to a hierarchal testing procedure of endpoints, overall survival and quality of life could not be formally tested for statistical significance given the insignificance of the ORR result.
III. The safety profile of ripretinib (Qinlock) is similar to that of other TKIs. The most common treatment-related treatment emergent adverse events (occurring in 20% or more of patients in the ripretinib group) during the INVICTUS trial included alopecia, myalgia, nausea, fatigue, palmar-plantar erythrodysesthesia (also known as hand-foot syndrome), and diarrhea. There are no contraindications to ripretinib (Qinlock); however, warnings and precautions include: palmar-plantar erythrodysesthesia syndrome, new primary cutaneous malignancies, hypertension, cardiac dysfunction, risk of impaired wound healing, and embryo-fetal toxicity. Ripretinib (Qinlock) was studied in adult patients age 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients. FDA-approval has only been granted for adult patients.
IV. Gastrointestinal Stromal Tumor (GIST) is a rare subtype of soft tissue sarcoma, thus a definitive diagnosis from a specialty provider is warranted.

V. NCCN Guidelines recommend ripretinib (Qinlock) as fourth-line therapy for the treatment of unresectable or metastatic GIST for those who have progressed after imatinib (Gleevec), sunitinib (Sutent), and regorafenib (Stivarga) with a Category 2A recommendation.

Investigational or Not Medically Necessary Uses

I. Ripretinib (Qinlock) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Third-line or prior treatment for Gastrointestinal Stromal Tumor
   B. Advanced Systemic Mastocytosis or other hematologic malignancies
   C. Soft Tissue Sarcoma
   D. Malignant Gliomas
   E. Melanoma
   F. Germ Cell, Penile Cancer
   G. Non-Small Cell Lung Carcinoma (NSCLC)
   H. Other Advanced Solid Tumor Cancers/Malignancies

References

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2. National Comprehensive Cancer Network. NCCN Guidelines: Soft Tissue Sarcoma . Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf Updated 5/28/2020.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

risdiplam (Evrysdi®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP208

Description

Risdiplam (Evrysdi) is an orally administered survival of motor neuron 2 (SMN2) splicing modifier.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
risdiplam (Evrysdi)	60 mg/80 mL (0.75 mg/mL) solution	Spinal Muscular Atrophy	240 mL /30 days

Initial Evaluation

I. Risdiplam (Evrysdi) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neuromuscular specialist; **AND**
   B. Member must have a diagnosis of **5q spinal muscular atrophy** confirmed by either homozygous deletion of the *SMN1* gene or dysfunctional mutation of the *SMN1* gene; **AND**
   C. Provider attests member does not require invasive ventilation or tracheostomy; **AND**
   D. Provider attestation that nusinersen (Spinraza) will not be used concurrently with risdiplam (Evrysdi); **AND**
   E. Provider attestation of ONE of the following:
      1. The member has not had treatment with onasemnogene abeparvovec-xioi (Zolgensma); **OR**
      2. If the member has had a history of treatment with onasemnogene abeparvovec-xioi (Zolgensma) and there has been clinical deterioration or poor response to onasemnogene abeparvovec-xioi (Zolgensma); **AND**
   F. Member must have ONE of the following SMA phenotypes:
      1. SMA I; **OR**
      2. SMA II with symptomatic disease (e.g., impaired motor function and/or delayed motor milestones); **OR**
      3. SMA III with symptomatic disease (e.g., impaired motor function and/or delayed motor milestones); **AND**
   G. Baseline documentation of at least ONE of the following motor function/milestone measures:
      1. Members less than two years of age:
         i. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), OR Hammersmith Infant Neurologic Exam (HINE); **OR**
      2. Members two years of age or older:

i. Motor Function Measure 32 (MFM32), Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale Expanded (HFMSE), OR Six-Minute Walk Test (6MWT).

II. Risdiplam (Evrysdi) is considered investigational when used for all other conditions, including but not limited to:
   A. Use in members with Type IV SMA
   B. Use in members with pre-symptomatic SMA
   C. Used in combination with nusinersen (Spinraza)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member has responded to therapy, defined as stability or improvement in net motor function/milestones, compared to pretreatment baseline as exemplified by at least ONE of the following:
   A. Members less than two years of age:
      1. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Infant Neurologic Exam (HINE), OR Bayley Scales of Infant Development–Third Edition (BSID-III) Item 22; **OR**
   B. Members two years of age or older:
      1. Motor Function Measure 32 (MFM32), Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale Expanded (HFMSE), OR Six-Minute Walk Test (6MWT); **OR**
   C. Provider attests that member has had a slowed rate of decline in the aforementioned measures compared to pretreatment rate.

Supporting Evidence

I. In clinical trials, the youngest patient to receive medication was two months of age, this, coupled with the median symptom onset of patients included was two months set the FDA-approved age at two months and older. While all dosing guidelines are for those two months and older, in SMA trials it is has been shown that patients who begin treatment earlier may have more favorable outcomes.
II. There are no specific contraindications or warnings and precautions to using risdiplam (Evrysdi).
III. Risdiplam (Evrysdi) was studied in two ongoing Phase 2/3 trials (FIREFISH and SUNFISH). FIREFISH studied patients with infantile-onset Type I SMA and SUNFISH studied patients with later-onset Type II and non-ambulatory Type III. Both studies required a confirmed diagnosis of 5q-autosomal recessive SMA prior to enrollment.
   - SMA is an autosomal recessive genetic disorder caused by mutations in chromosome 5q that lead to survival motor neuron (SMN) protein deficiencies. SMN protein from the SMN1 gene, located on chromosome 5, is expressed in all cells and is required for life. In order to develop SMA, an individual must inherit two faulty

SMN1 genes, one from each parent; however, the majority of mutations responsible for 5q-SMA are either deletions or gene conversions.

IV. FIREFISH is an open-label, two-part study designed to assess safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD). The study included 21 patients in Part One and 41 patients in Part Two aged one to seven months with Type I SMA. Patients requiring invasive ventilation or tracheostomy were excluded; therefore, there is no clinical trial data to show efficacy and safety in this patient population. The following endpoints were used: Bayley Scales of Infant Development–Third Edition (BSID-III) Item 22, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), and Hammersmith Infant Neurologic Exam (HINE).

- BSID-III is a clinical evaluation developed to help identify children with developmental delay who may require intervention services. The BSID-III consists of three areas of development: cognitive, language, and motor. Effectiveness was established based on the ability to sit without support for at least five seconds (as measured by Item 22). This scale is intended for pediatrics only and is not specific to SMA.
- CHOP-INTEND is a validated, 16-item, 64-point scale, designed to measure motor function for weak infants with Type I SMA and is intended for pediatrics only. It measures spontaneous upper and lower extremity movement, hand grip, head in midline with visual stimulation, hip adductors, rolling from legs and arms, shoulder and elbow flexion by itself and in addition to horizontal abduction, knee extension, hip flexion an foot dorsiflexion, head control, head/neck extension, and spinal incurvation. Each of the 16 items is graded on a scale of zero to four, with zero meaning no response and four meaning complete response.
- HINE-2 is an SMA-specific measurement, 8-item, 26-point scale, designed to measure motor skills in infants with SMA. A score of zero for items such as sitting, crawling, and walking is expected for Type I. It measures voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing, and walking.
- The primary efficacy outcome in FIREFISH Part One was dose determination for Part Two of the study, which was 0.2 mg/kg/day. The primary efficacy outcome in FIREFISH Part Two was the proportion of infants sitting without support for at least five seconds as assessed by the Gross Motor Scale of the BSID-III at Month 12, which was 29% (90% CI: 17.8 to 43.1%). Key secondary efficacy outcomes in FIREFISH Part One include BSID-III at Month 12, which was 33%; infants alive with no permanent ventilation, 90.5%; proportion of infants who require hospitalization, and 38% did not require hospitalization. Key secondary efficacy outcomes in FIREFISH Part Two include HINE-2, which was 78% ($p<0.0001$) while the proportion of patients who achieved at least four points on the CHOP-INTEND score was 90% ($p<0.0001$).

V. SUNFISH is a two-part randomized, placebo-controlled study designed to assess safety, tolerability, efficacy, PK, and PD. The study included 51 patients in Part One and 180 patients in Part Two aged two to 25 with Type II or III SMA. Patients in Part Two of SUNFISH were randomized. The following endpoints were used: Motor Function Measure 32 (MFM-32) and Revised Upper Limb Module (RULM).

- MFM-32 is a 32-item scale that measures motor function abilities that relate to daily functions. The total MFM-32 score is expressed as a percentage (range: zero to 100) of the maximum possible score, with higher scores indicating greater motor

function. This scale is suitable for assessing gross and fine motor skills in children and adult patients.

- RULM is a 19-item scorable scale used to assess motor performance of the upper limb in ambulatory and non-ambulatory patients with SMA. It tests proximal and distal motor functions of both upper limbs. The total score ranges from zero (all the items cannot be performed) to 37 (all the activities are achieved fully without any compensatory maneuvers). Each item is scored from zero to two: zero= unable, one=able with modification, two=able with no difficulty. RULM is applicable to both children and adults with SMA.
- The primary efficacy outcome in SUNFISH Part Two was the change from baseline to Month 12 in the MFM32 score in risdiplam (Evrysdi) vs. placebo, which was 1.36 (95% CI 0.61, 2.11) vs. -0.19 (-1.22, 0.84), with a difference from placebo of 1.55 (95% CI 0.30, 2.81, p=0.0156). Key secondary outcomes in SUNFISH Part Two include the proportion of patients with a 3-point or greater change from baseline to Month 12 in the MFM32 total score in risdiplam (Evrysdi) vs. placebo, which was 38.3% (28.9, 47.6) vs. 23.7% (12.0, 35.4), with a difference from placebo of 2.35 (1.01, 5.44), p-value=0.0469; change from baseline in total score of RULM at Month 12 in risdiplam (Evrysdi) vs. placebo of 1.61 (1.00, 2.22) vs. 0.02 (-0.83, 0.87), with a difference from placebo of 1.59 (0.55, 2.62), p-value=0.0469.

VI. While primary endpoint was measured at Month 12, patients showed improvement at Month 6. In FIREFISH Part Two, 38 of 41 infants surpassed responder threshold (≥4-point CHOP-INTEND improvement) at Month 6. Moreover, at Month 12, the same number of infants (38 of 41) achieved ≥4-point CHOP-INTEND improvement. SUNFISH Part Two had follow-up visits every five weeks and appeared to significantly show greater changes in MFM32 from baseline compared to placebo starting at week 16.

VII. Other acceptable motor measurements not measured in risdiplam (Evrysdi) trials, but are validated are the following: Hammersmith Functional Motor Scale Expanded (HFMSE) and Six-Minute Walk Test (6MWT)

- HFMSE is a 33-item scorable scale used to assess motor function in people with SMA Type II or Type III; this is intended for individuals older than 24 months of age. Each item is scored from zero (lowest item grade) to two (highest item grade), with a maximum score of 66. Higher scores indicate increased levels of ability. Scorable items include, but not limited to, plinth/chair sitting, long sitting, one to two hands to head in sitting, spine to side-lying, rolls prone to supine over right and left, rolls supine to prone over right and left, sitting to lying, props on forearms, lifts head from prone, prop on extended arms, lying to sitting, 4-point kneeling, crawling, and stepping.
- 6MWT is an objective evaluation of functional exercise capability in ambulatory patients with later-onset (Type II or Type III) SMA. This test is based on distance where the patient walks as far as possible in six minutes; test is performed on a linear 25-meter marked course.

VIII. The International Conference on the Standard of Care for Spinal Muscular Atrophy guidelines have not been updated to include risdiplam (Evrysdi) for the treatment of SMA.

IX. Per the Working Group for SMA-positive infants (comprised of 15 SMA experts), a pediatrician's expertise in child healthcare may be broad and not cover the unique features of a rare neuromuscular disorder; similarly, a general child neurologist may not specialize in the role of the neuromuscular system of the patient's symptomatology and diagnosis and may not have the knowledge to administer the specific tests being recommended here. A neuromuscular specialist would have the deepest knowledge of the clinical manifestations of SMA in order to detect the earliest symptomatology, in addition to experience with administering the highly sensitive assessments of motor neuron function and SMA specific motor function.

X. Nusinersen (Spinraza) is a chronic, intrathecally administered therapy. Use of risdiplam (Evrysdi) in patients previously treated with nusinersen (Spinraza) or onasemnogene abeparvovec-xioi (Zolgensma) is currently being studied (JEWELFISH trial). At this time, there is no evidence to suggest efficacy and safety concerns of risdiplam (Evrysdi) in patients previously treated with nusinersen (Spinraza) or onasemnogene abeparvovec-xioi (Zolgensma).

XI. Onasemnogene abeparvovec-xioi (Zolgensma) is a one-dose treatment and it is not a cure. Patients who previously received onasemnogene abeparvovec-xioi (Zolgensma) may continue to show signs and symptoms of SMA. Clinical deterioration is defined as, but not limited to, sustained decrease in CHOP-INTEND score over a period of six months (primary endpoint in the onasemnogene abeparvovec-xioi (Zolgensma) pivotal trial), increased frequency of breathing support (e.g., BiPAP machine at night, cough assist machine), and/or requirement of feeding tubes.

Investigational Uses

I. Risdiplam (Evrysdi) has not been FDA approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Use in members with Type IV SMA
      i. Risdiplam (Evrysdi) has not be studied in this population.
   B. Use in members with pre-symptomatic SMA
      i. Ongoing clinical trial in this setting (RAINBOWFISH)
   C. Use in combination with nusinersen (Spinraza)
      i. Risdiplam (Evrysdi) has not been studied as combination use with nusinersen.

Appendix

I. Table 1: risdiplam (Evrysdi) Adult and Pediatric Dosing Regimen by Age and Body Weight

Age and Body Weight	Recommended Daily Dosage
2 months to less than 2 years of age	0.2 mg/kg
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

roflumilast (Daliresp®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP105

Description

Roflumilast (Daliresp) is an oral phosphodiesterase 4 (PDE4) inhibitor to selectively inhibit a major cyclic-AMP (cAMP) metabolizing enzyme in the lung tissue.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Roflumilast (Daliresp)	250 mcg tablet	Severe chronic obstructive pulmonary disease (COPD) with chronic bronchitis and a history of exacerbation	30 tablets/30 days
	500 mcg tablet		30 tablets/30 days

Initial Evaluation

I. Roflumilast (Daliresp) may be considered medically necessary when the following criteria below are met:
   A. Member is diagnosed with severe COPD (GOLD 3 or 4; FEV_1 < 50% predicted) associated with chronic bronchitis; **AND**
   B. Member has a history of COPD exacerbations (at least one per year) that resulted in hospitalization; **AND**
   C. Member has tried and failed, or has a contraindication to triple therapy with: long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS); **AND**
   D. Member will be using this medication in combination with an inhaled corticosteroid (ICS)

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
II. The member is <u>not</u> 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; **AND**
IV. If the request is for a dose increase, the new dose does not exceed 500 mcg per day

Supporting Evidence

I. Roflumilast (Daliresp) is FDA approved for treatment in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.

II. Utilization of roflumilast (Daliresp) is reserved for members that have tried and failed a triple therapy including following active ingredients:
   - An Inhaled long-acting beta$_2$-agonist (LABA) [e.g. salmeterol, formoterol, indacaterol, olodaterol]
   - An inhaled long-acting muscarinic antagonist (LAMA) [e.g. tiotropium, umeclidinium, aclidinium, glycopyrrolate]
   - An inhaled corticosteroid (ICS) [e.g. fluticasone]

III. Per GOLD 2020 Guidelines, if patients treated with LABA/LAMA/ICS still have exacerbations, stopping inhaled corticosteroid (ICS) may be considered if there are adverse effects (such as pneumonia) or a reported lack of efficacy.

References

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Policy Implementation/Update:

Date Created	April 2018
Date Effective	April 2018
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	**Date**
Transition from criteria to policy: In this transition process, the following updates were made: further clarification around severe COPD definition, dose limit that it does not exceed 500 mcg per day if request is for a dose increase, supporting evidences were updated, and GOLD 2020 Report was updated.	11/2019
Criteria created	4/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP152

Description

Rucaparib (Rubraca) 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

Product Name	Dosage Form	Indication	Quantity Limit
rucaparib (Rubraca)	200 mg tablets	Maintenance for: recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer; Treatment for: advanced ovarian, fallopian tube, or primary peritoneal cancer	60 tablets/30 days
	250 mg tablets		
	300 mg tablets		

Initial Evaluation

I. Rucaparib (Rubraca) 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. Rucaparib (Rubraca) will be used as monotherapy; **AND**
   D. Member has not progressed on a prior PARP inhibitor (e.g., olaparib [Lynparza], niraparib [Zejula]) therapy; **AND**
   E. A diagnosis of one of the following:
      1. **Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer**; **AND**
         i. Provider is requesting for maintenance therapy; **AND**
         ii. Member has experienced disease progression on or after at least TWO or more prior platinum-based chemotherapy regimens (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
         iii. Member is in complete or partial response to their last platinum-based chemotherapy regimen (i.e., platinum sensitive); **AND**
         iv. Rucaparib (Rubraca) will be started within eight weeks of completion of the most the most recent platinum-based chemotherapy regimen; **OR**

v. Provider attests with supporting documentation that member's recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based chemotherapy regimen; **OR**

2. **Advanced ovarian, fallopian tube, or primary peritoneal cancer**; **AND**
   i. Provider is requesting for treatment therapy, and not maintenance therapy; **AND**
   ii. Member has been treated with two or more prior lines of chemotherapy; **AND**
   iii. Member has deleterious *BRCA* mutation (germline and/or somatic) confirmed by an FDA-approved compendia diagnostic for rucaparib (Rubraca).

II. Rucaparib (Rubraca) 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. Advance Solid Tumors
   E. Melanoma
   F. Pancreatic cancer
   G. 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 does not have evidence of disease progression.

Supporting Evidence

I. The safety and efficacy of rucaparib (Rubraca) in the setting of maintenance therapy for recurrent ovarian cancer was studied in a double-blind, multicenter trial (ARIEL3) where 564 adult patients with platinum-sensitive recurrent epithelial ovarian fallopian tube, or primary peritoneal cancer. The patients were randomized 2:1 rucaparib (Rubraca) 600 mg orally daily or matched placebo within 8 weeks of their last dose of platinum-based therapy. The major efficacy outcome was progression-free survival (PFS) assessed by investigator, which ARIEL 3 demonstrated a statistically significant improvement in PFS in the rucaparib (Rubraca) arm as compared to the placebo arm. In the

rucaparib (Rubraca) arm, the median PFS was 10.8 months compared to 5.4 months in the placebo arm with a hazard ratio (HR) of 0.36 and 95% CI (0.3, 0.45).

II. Therapy in the maintenance setting was initiated within eight weeks after completion of the last dose of platinum-based chemotherapy. The intent is that treatment is started within a reasonable timeframe consistent with a maintenance treatment plan (i.e. as close to 8 weeks as possible), but recognize that scheduling or other factors may impact the ability of a patient to start exactly within these first eight weeks.

III. The safety and efficacy of rucaparib (Rubraca) for the treatment of advanced ovarian cancer after two or more chemotherapies was studied in two multicenter, single-arm, and open-label trials with 106 adult patients that have advanced *BRCA*-mutant ovarian cancer who had progressed after two or more prior chemotherapies. The efficacy outcomes were objective response rate (ORR) and duration of response (DOR) assessed by the investigator and independent radiology review; the average ORR was 54% and the average DOR was 9.2 months.

IV. 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 rucaparib (Rubraca) in the following settings listed below:
   A. Used in combination with other chemotherapy or targeted therapy regimen.
   B. Breast Cancer
   C. Solid Tumors
   D. Prostate Cancer
      1. Efficacy of rucaparib (Rubraca) was investigated in an ongoing multi-center, single arm clinical trial (TRITON2) in patients with *BRCA*-mutated metastatic castration-resistant prostate cancer (mCRPC), who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. There were 115 patients with either germline or somatic *BRCA* mutations enrolled in TRITON2, of whom 62 patients had measurable disease at baseline. Patients received rucaparib (Rubraca) 600 mg orally twice daily along with concomitant GnRH analog or had prior bilateral orchiectomy. Objective response rate (ORR) and duration of response (DOR) were assessed in patients with measurable disease by blinded IRR and by the investigator protocol. An ORR of 43.5% (n= 27; 31.0-56.7) was reported for IRR evaluation of 62 patients with measurable disease, while DoR was not estimable given the lack of data maturity. Quality of clinical evidence is low due to open label, single-arm trial design and lack of measurable survival outcomes and patient quality of life related outcomes. Of note, as of October 2020, rucaparib (Rubraca) is being studied in a phase 3 trial for mCRPC with other therapeutic agent(s) as active comparator (TRITON3) and results for this study are not available. Of note, another PARP-inhibitor, olaparib (Lynparza) is FDA-approved for treatment of mCRPC in patients who progressed on previous chemotherapy. Olaparib (Lynparza) was approved for this indication based on an open label phase 3 trial, which reported

survival outcomes (rPFS and OS) and has a category 1 recommendation per NCCN guidelines for treatment of prostate cancer.

References

1. Rubraca [Prescribing Information]. Boulder, CO: Clovis Oncology, Inc. May 2020.
2. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib Maintenance Treatment for Recurrent Ovarian Carcinoma After Response to Platinum Therapy (ARIEL3): A Randomized, Double-blind, Placebo-controlled, Phase 3 Trial. *Lancet.* 2017 Oct 390(10106): 1949–1961.
3. Abida W, Patnaik A, Campbell D, et al. Rucaparib in Men with Metastatic Castration-Resistant Prostate Cancer Harboring a *BRCA1* or *BRCA2* Gene Alteration. J Clin Oncol. 2020 Aug 14: JCO2001035. doi: 10.1200/JCO.20.01035.

Policy Implementation/Update:

Action and Summary of Changes	**Date**
Updated supporting evidence for investigational use of rucaparib (Rubraca) for treatment of prostate cancer	11/2020
Criteria transition into policy with the following updates made: addition of supporting evidence and investigation section, broke out the different indications (treatment versus maintenance therapy), 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.	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP057

Split Fill Management*

Description

Ruxolitinib (Jakafi) is an orally administered Janus Associated Kinase (JAK) inhibitor of JAK1 and JAK2.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indications	Quantity Limit
ruxolitinib (Jakafi)	5 mg tablets	Intermediate or high-risk myelofibrosis Polycythemia vera	60 tablets/30 days *Quantity exceptions are not allowed. *The maximum number of ruxolitinib (Jakafi) tablets allowed is 60 tablets/30 days total if a combination of strengths is used
	10 mg tablets		
	15 mg tablets		
	20 mg tablets		
	25 mg tablets		
	5 mg tablets	Acute Graft-Versus-Host Disease Chronic Graft-Versus-Host disease	
	10 mg tablets		

***Dose optimization will be required if the prescribed dose is unable to be reached at a quantity of 60/30. Use of two strengths may be necessary to reach target dose. Quantity is subject to 30/30 if multiple tablet strengths are utilized, for a maximum total allowed quantity of 60 ruxolitinib (Jakafi) tablets per 30-day supply.**

Initial Evaluation

I. Ruxolitinib (Jakafi) 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 one of the following:
      1. **Intermediate-to-high-risk myelofibrosis (MF)** which includes primary MF, post-polycythemia vera MF, or post essential thrombocythemia MF; **OR**
      2. **Polycythemia vera**; **AND**

i. Treatment with hydroxyurea has been ineffective, contraindicated, or not tolerated; **OR**

3. Graft versus-host disease (GVHD), acute or chronic; AND

i. Member is 12 years of age or older; **AND**

ii. Documentation of moderate-to-severe GVHD (e.g., Grade 2 to 4 GVHD, OR Grade B to D); **AND**

iii. The member has had an inadequate response to steroids (e.g., prednisone, methylprednisolone, beclomethasone, budesonide).

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

A. Low risk myelofibrosis
B. Acute leukemia
C. COVID-19
D. Alopecia areata
E. Vitiligo
F. Glioma and glioblastoma
G. Hidradenitis suppurativa
H. Malignancy or cancer outside of myelofibrosis

Renewal Evaluation

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

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

III. A diagnosis of one of the following:

A. **Intermediate- to high-risk myelofibrosis (MF) OR polycythemia vera**; **AND**

1. Documentation of reduction in spleen volume; **OR**
2. Provider attestation of positive treatment response (e.g., improvement in symptoms, hematocrit control); **OR**

B. **Graft versus-host disease (GVHD), acute or chronic; AND**

1. Provider attestation of positive treatment response (e.g. reduction in symptoms associated with GVHD: gastrointestinal, ophthalmic, cutaneous, pulmonary).

Supporting Evidence

I. Length of authorization for initial approval is six months due to the clinical trial design, efficacy was evaluated at 24 weeks for all indications. Additionally, therapy beyond six months of treatment should be reserved for those where benefits outweigh the risks. If no treatment response is seen at six months, therapy should be tapered into discontinuation. Therapy should not be abruptly discontinued given the potential for symptom proliferation and exacerbation.

II. The FDA-approved conditions for this therapy require specialized and individualized care and monitoring; thus, a specialist prescriber, or consultation with a specialist, is required.

III. Treatment for MF is based on risk. For intermediate-to high risk MF, stem cell transplant is the recommended treatment option; however, in those ineligible for stem cell transplant, hydroxyurea, fedratinib (Inrebic), and ruxolitinib (Jakafi) are available treatment options. While hydroxurea may relieve splenomegaly and some symptoms of the condition (e.g., thrombocytosis, leukocytosis), it is thought to be less efficacious than other treatment options and may not be beneficial for major symptoms of the condition.

IV. Polycythemia vera treatment selection is also based on risk. Phlebotomy and/or low-dose aspirin are used in the management of low-risk disease. For high-risk disease, hydroxyurea is the preferred therapy given the extensive history of use, well-established safety profile, efficacy, and cost-effectiveness. Although busulfan has been used historically as a second-line therapy, because it has been associated with safety concerns such as cytopenia, pulmonary fibrosis, leukemia, and others, hydroxyurea remains the mainstay therapy. Ruxolitinib (Jakafi) is reserved for those that are not candidates for, or are refractory to, hydroxyurea, given the limited long-term safety and efficacy data. Additionally, for the treatment of polycythemia vera, ruxolitinib (Jakafi) is specifically FDA-approved after inadequate response or intolerance to hydroxyurea.

V. The FDA approval of ruxolitinib (Jakafi) in the setting of intermediate-to high-risk myelofibrosis was based on the results of two randomized Phase 3 trials. In Study 1, the primary endpoint was the proportion of participants achieving greater than, or equal to, a 35% reduction from baseline in spleen volume at Week 24. Secondary outcomes included proportion of patients achieving a 50% or greater reduction in Total Symptom Score from baseline to week 24. This was measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF), which incorporates abdominal discomfort, pain, night sweating, itching, bone and muscle pain, and early satiety. The study met statistical significance in all outcomes. In Study 2, the primary endpoint was the proportion of participants achieving greater than, or equal to, a 35% reduction from baseline in spleen volume at Week 48. This outcome was statistically significant.

VI. The FDA approval of ruxolitinib (Jakafi) in the setting of polycythemia vera was based on the result of a randomized, open-label, active-controlled Phase 3 study. The primary endpoint was the proportion of participants at Week 32 achieving hematocrit control in the absence of phlebotomy and spleen volume reduction. In the ruxolitinib (Jakafi) arm, 60% of the participants met the primary endpoint compared to 19% in the placebo arm. Participants must have had a resistance or intolerance to hydroxyurea.

VII. Graft-versus-host disease is a complication of allogenic hematopoietic 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.

VIII. 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. Glucocorticoids are the mainstay therapy; however, for those with glucocorticoid resistant disease, participation in clinical trials is recommended as there is currently no consensus on standard of care. Otherwise, therapies such as ruxolitinib (Jakafi) or ibrutinib (Imbruvica) are recommended. Therapy such as

mycophenolate, rituximab, etanercept (Enbrel), everolimus, and others have been used historically, but there is lack safety and efficacy data from clinical trials to support the use of these therapies.

IX. The FDA approval of ruxolitinib (Jakafi) in the setting of acute GVHD was based on the results of an open-label, single-arm, multicenter study in participants with steroid-refractory acute GVHD Grades II to IV that were 12 years of age or older. Therapy was evaluated up to 10 mg twice daily. The efficacy of ruxolitinib (Jakafi) was based on a Day-28 overall response rate (ORR) by the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria and the duration of response. The ORR was 57.1% with a median duration response of 16 days.

X. For chronic GVHD, ruxolitinib (Jakafi) was evaluated in a Phase 3, open-label, randomized trial against best available treatment (BAT). Patients were 12 years of age or older, steroid-refractory, and had moderate-to-severe disease. Outcomes were ORR, failure-free survival (FFS), and Lee Symptom Score. Ruxolitinib (Jakafi) was superior to BAT in all outcomes. Given the availability of objective and subjective positive outcomes in this condition, and lack of standard of care beyond glucocorticoids, there is moderate confidence that ruxolitinib (Jakafi) provides clinical value for this condition.

XI. To date, ruxolitinib (Jakafi) has not been shown to improve survival for any condition.

XII. The safety and efficacy of ruxolitinib (Jakafi), or any other JAK inhibitor has not been evaluated in patients under 12 years of age.

XIII. Split fill applies to ruxolitinib (Jakafi) given the high rates of treatment discontinuation due to adverse events, and the rates of dose reduction or interruption seen in clinical trials (e.g in the pivotal trial for aGVHD the rate of treatment discontinuation due to adverse events was 31%).

Investigational or Not Medically Necessary Uses

I. Ruxolitinib (Jakafi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Low risk myelofibrosis
   B. Acute leukemia
   C. COVID-19
   D. Alopecia areata
   E. Vitiligo
   F. Glioma and glioblastoma
   G. Hidradenitis suppurativa
   H. Cancer or malignancy outside of myelofibrosis

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

References

1. Jakafi [Prescribing Information]. Wilmington, DE: Incyte Corporation. May 2019.
2. Verstovsek, S, Mesa, RA, Gotlib, J, et al. Efficacy, safety and survival with ruxolitinib in patients with myelofibrosis: results of a median 2-year follow-up of COMFORT-I. Italy, 2013. p. 1865-71.
3. Verstovsek, S, Mesa, RA, Gotlib, J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. The New England journal of medicine. 2012 Mar 1;366(9):799-807. PMID: 22375971
4. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015;372(5):426-435. [PubMed 25629741]
5. Mesa RA, Gotlib J, Gupta V, et al. Effect of ruxolitinib therapy on myelofibrosis-related symptoms and other patient-reported outcomes in COMFORT-I: a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2013;31(10):1285-1292. [PubMed 23423753]
6. Verstovsek S, Mesa RA, Gotlib J, et al. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. J Hematol Oncol. 2017;10.
7. Jagasia M, Perales M-A, Schroeder MA, et al. Ruxolitinib for the treatment of steroid-refractory acute GVHD (Reach1): a multicenter, open-label phase 2 trial. Blood. 2020;135(20):1739-1749.
8. Wu H, Shi J, Luo Y, et al. Evaluation of Ruxolitinib for Steroid-Refractory Chronic Graft-vs-Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation. JAMA Netw Open. 2021;4(1):e2034750. doi:10.1001/jamanetworkopen.2020.34750.

Policy Implementation/Update:

Action and Summary of Changes	Date
Chronic graft vs. host disease indication added to policy. Update of qualifying prescribers and appropriate doses and quantities per indication. Removal of infection free requirement, check of unacceptable toxicity, and requirement for previous use of hydroxyurea in myelofibrosis.	06/2021
Addition of acute graft vs. host disease indication to renewal section.	01/2020
Criteria transitioned to policy. Added newly FDA approved indication of acute graft versus host disease. Remove diagnostic questions, interaction questions, lab value questions. Added requirement for previous use of hydroxyurea prior to coverage of Jakafi for the indication of polycythemia vera.	07/2019
Previous reviews	12/2014, 12/2012, 07/2012, 05/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP209

Description

Satralizumab-mwge (Enspryng) is an IL-6 monoclonal antibody subcutaneous injection.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
satralizumab (Enspryng)	120 mg/mL Prefilled Syringe	Neuromyelitis optica spectrum disorder (NMOSD)	**Initial**: 2 mL (pens) per 28 days for one fill **Maintenance**: 1 mL (pen) per 28 days

Initial Evaluation

I. Satralizumab (Enspryng) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
   C. Provider attestation the medication will not be used in combination with other biologic therapies (e.g., tocilizumab [Actemra], eculizumab [Soliris], inebilizumab [Uplinza]) used to treat inflammatory conditions; **AND**
   D. Documentation of a confirmed diagnosis of **neuromyelitis optica spectrum disorder (NMOSD)** when all of the following are met:
      1. The member is positive for anti-aquaporin-4 (AQP4) IgG antibodies (i.e., seropositive) supported by chart note documentation or laboratory results; **AND**
      2. The member has a history of one or more relapses requiring rescue or acute treatment (e.g., glucocorticoids, plasma exchange); **AND**
      3. Glucocorticoids, azathioprine, and/or mycophenolate will be used in combination with satralizumab (Enspryng); **OR**
         i. Treatment with ALL of the following has been ineffective, contraindicated, or not tolerated for long term maintenance therapy:
            i. Glucocorticoids
            ii. azathioprine
            iii. mycophenolate; **AND**

4. Treatment with rituximab (e.g. Rituxan) has been ineffective, contraindicated, or not tolerated

II. Satralizumab (Enspryng) is considered not medically necessary when criteria above are not met and/or when used for:
   A. NMOSD that is anti-quaporin-4 (AQP4) IgG antibody negative (i.e., seronegative)

III. Satralizumab (Enspryng) is considered investigational when used for all other conditions, including but not limited to:
   A. Rheumatoid or other forms of arthritis
   B. Cytokine release syndrome
   C. Arteritis

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 neurologist; **AND**
IV. Provider attestation the medication will not be used in combination with other biologic therapies (e.g., tocilizumab [Actemra], eculizumab [Soliris], inebilizumab [Uplinza]) used to treat inflammatory conditions; **AND**
V. Provider attestation of a positive response to therapy (e.g., stabilization of disease, relapse reduction, relapse-free)

Supporting Evidence

I. Satralizumab (Enspryng) is FDA-approved for NMOSD, a rare inflammatory disorder characterized by severe, immune-mediated attacks on the optic nerves and spinal cord. Hallmark features include optic neuritis attacks, transverse myelitis, unexplained hiccups, nausea, vomiting, and somnolence. Patients experience relapses that have varying degrees of recovery over weeks to months. NMOSD was historically considered as a form of multiple sclerosis (MS); however, MS therapies are often inefficacious in the setting of NMOSD and certain MS therapies may further exacerbate NMOSD. Thus, a definitive diagnosis from a specialty provider is warranted. The majority of patients are seropositive, and if test results show seronegative disease, patients should be retested or considered for a differential diagnosis. Seronegative disease is often treated similarly to seropositive NMOSD; however, biologic medications often lack efficacy in the seronegative population.
II. NMOSD is often treated acutely with high-dose IV glucocorticoids, and if refractory – plasma exchange. Once a definitive diagnosis is made, long-term therapy is recommended in all patients. Long-term therapies that are FDA-approved include eculizumab (Soliris) and inebilizumab (Uplinza), which are both provider administered products. Other therapies that

have been used historically and are often regarded as standard of care include glucocorticoids, azathioprine, mycophenolate, and rituximab (e.g., Rituxan). Additionally and increasingly, IV tocilizumab (Actemra) has been considered. The quality of data varies for these agents; however, all have shown positive response on relapse rates for seropositive NMOSD. The safety profile, is also further defined, given the longevity and extent of use in patients relative to satralizumab (Enspryng).

III. The efficacy and safety of satralizumab (Enspryng) was evaluated in two Phase 3, blinded, randomized, placebo-controlled trials, where treatment was administered at weeks zero, two, four, then four weeks thereafter. Population characteristics: seropositive and negative patients, majority female, an annualized relapse rate of 1.5 with at least one documented attack in the last 12 months, with a variety of treatment histories (e.g., glucocorticoids [GC], DMARDS, previous b-cell depleting therapy). Exclusions: history of anti-IL-6 therapy, alemtuzumab, total body irradiation, or bone marrow transplantation.

IV. Trial one evaluated satralizumab (Enspryng) monotherapy versus placebo, and trial two evaluated against placebo with both groups adding treatment to background immunosuppressive therapy (glucocorticoids, mycophenolate, azathioprine, and various combinations). The use of satralizumab (Enspryng) in addition to other biologic therapies (e.g., tocilizumab [Actemra], eculizumab [Soliris], inebilizumab [Uplinza]) has not been evaluated for safety and/or efficacy. Additionally, there is evidence to show that use of two biologic therapies concurrently has demonstrated increased risk of serious infection.

V. Adolescent patients were included in the second pivotal trial, ages 12 and older. There was a low number (n=7) enrolled and subgroup analyses did not show clinical efficacy. Although this analysis was likely underpowered, safety and efficacy in non-adult population remains unknown at this time and FDA-approval has been granted for adults only.

VI. In both trials there was a positive response on relapse rates in the seropositive (anti-aquaporin-4 [AQP4) antibody-positive) population. Of note, there was a lack of statistically significant efficacy in the seronegative population. Secondary outcomes evaluated medication efficacy on other symptom control, quality of life, and caregiver burden; however, they were not statistically significant. Medication success may be measured as a reduction in or freedom from relapses.

Investigational or Not Medically Necessary Uses

I. Satralizumab (Enspryng) did not show improvement in relapse rates in the seronegative NMOSD population. Given lack of efficacy and largely unknown safety profile for this therapy, use is not medically necessary at this time.

II. Satralizumab (Enspryng) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Rheumatoid or other forms of arthritis
   B. Cytokine release syndrome
   C. Arteritis
      i. IL-6 therapies (e.g., tocilizumab [Actemra] have been FDA-approved for the conditions listed above; however, use of satralizumab (Enspryng) for these conditions remains experimental and investigational.

References

1. Traboulsee A, Greenberg BM, Bennett JL, et al. Safety and efficacy of satralizumab monotherapy in neuromyelitis optica spectrum disorder: a randomised, double-blind, multicentre, placebo-controlled phase 3 trial. Lancet Neurol. 2020;19(5):402-412.
2. Yamamura T, Kleiter I, Fujihara K, et al. Trial of Satralizumab in Neuromyelitis Optica Spectrum Disorder. N Engl J Med. 2019;381(22):2114-2124.
3. Enspryng [Prescribing Information]. Genentech, Inc. San Francisco, CA. August, 2020.
4. Collongues N, Ayme-dietrich E, Monassier L, De seze J. Pharmacotherapy for Neuromyelitis Optica Spectrum Disorders: Current Management and Future Options. Drugs. 2019;79(2):125-142.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Select Insulin Products

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP058

Description

Insulins are subcutaneously administered to help manage diabetes mellitus.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
insulin aspart (Novolog)	U100 vial	Diabetes mellitus, type I and II	60 mL per 30 days
	U100 Flexpen		
	U100 PenFill (cartridge)		
insulin aspart	U100 vial		60 mL per 30 days
	U100 Flexpen		
	U100 PenFill (cartridge)		
insulin aspart (Novolog Mix 70/30)	U100 vial		60 mL per 30 days
	U10 Flexpen		
insulin aspart Mix 70/30	U100 vial		60 mL per 30 days
	U100 Flexpen		
insulin regular (Novolin R)	U100 vial		60 mL per 30 days
	U100 ReliOn		
insulin isophane; NPH (Novolin N)	U100 vial		60 mL per 30 days
	U100 ReliOn		
insulin isophane; NPH/regular (Novolin 70/30)	U100 vial		60 mL per 30 days
	U100 Flexpen		
	U100 Flexpen ReliOn		
	U100 ReliOn		
insulin aspart (Fiasp)	U100 vial		60 mL per 30 days
	U100 FlexTouch		
insulin human powder (Afrezza)	4 unit powder		1530 units per 30 days
	4 & 8 unit powder		630 units per 30 days
	60 x 4 unit & 30 x 8 unit powder		630 units per 30 days
	30 x 4 unit & 60 x 8 unit powder		1170 units per 30 days
	60 x 8 unit & 30 x 12 unit powder		900 units per 30 days
	90 x 4 unit & 90 x 8 unit powder		900 units per 30 days
	4, 8 &		720 units per 30 days

	12 unit powder		
	8 unit powder		810 units per 30 days
	12 unit powder		540 units per 30 days
	90 x 8 unit & 90 x 12 unit powder		630 units per 30 days
insulin glulisine (Apidra)	U100 vial		60 mL per 30 days
	U100 SoloStar		
insulin lispro (Humalog)	U100 vial		60 mL per 30 days
	U100 Junior KwikPen		
	U100 KwikPen		
	U200 KwikPen		
	U100 Pen		
Insulin lispro	U100 vial		60 mL per 30 days
	U100 Pen		
insulin lispro (Admelog)	U100 vial		60 mL per 30 days
	U100 SoloStar		
Insulin lispro-aabc (Lyumjev)	U100 vial		60 mL per 30 days
	U100 Kwikpen		
	U100 Junior Kwikpen		
	U100 Tempopen		
	U100 PenFill cartridge		
	U200 Kwikpen		
insulin lispro (Humalog mix 50/50)	U100 vial		60 mL per 30 days
	U100 KwikPen		
	U100 Pen		
insulin lispro (Humalog mix 75/25)	U100 vial		60 mL per 30 days
	U100 KwikPen		
	U100 Pen		
insulin isophane/regular (Humulin 70/30)	U100 vial		60 mL per 30 days
	U100 KwikPen		
	U100 Pen		
insulin isophane/regular (Humulin 50/50)	U100 vial		60 mL per 30 days
(insulin isophane; NPH) Humulin N	U100 vial		60 mL per 30 days
	U100 Kwikpen		
insulin regular (Humulin R)	U100 vial		60 mL per 30 days

Initial Evaluation

Novolog, Novolin, Fiasp, and their generic products are the preferred agents.

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

I. **Apidra, Afrezza, Humalog, Lyumjev, Humulin, insulin lispro, and other non-preferred products**, may be considered medically necessary when the following criteria below are met:
   A. Documented history of use with **one** of the preferred products:
      1. Novolog
      2. Novolin
      3. Fiasp
      4. generic insulin aspart; **AND**
   B. Documentation and clinical rationale of treatment failure with preferred Novolog, Novolin, Fiasp, or their generic products including **one** or more of the following**:**
      1. Trial of dose adjustments
      2. Trial of sliding scale
      3. Concentrated dosing required
      4. Half unit dosing required
      5. Documentation of other rationale of medical necessity for use of non-preferred insulin products

Renewal Evaluation

I. Member has received a previous prior authorization approval for the non-preferred insulin product through this health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, shortages on preferred insulin products, or otherwise.

Supporting Evidence

I. There is a lack of strong scientific evidence demonstrating benefit of use of non-preferred insulin products over preferred Novolog, Novolin, or Fiasp products.

References

1. Novolin Products [Prescribing Information]. Plainsboro, NJ: Novo Nordisk A/S. June 2019.
2. Novolog Products [Prescribing Information]. Plainsboro, NJ: Novo Nordisk A/S. June 2019.
3. Fiasp [Prescribing Information]. Plainsboro, NJ: Novo Nordisk A/S. June 2019.
4. Humalog Products [Prescribing Information]. Indianapolis, IN: Lilly USA, LLC. June 2019.
5. Humulin Products [Prescribing Information]. Indianapolis, IN: Lilly USA, LLC. June 2019.
6. Admelog [Prescribing Information]. Bridgewater, NJ: Sanofi-aventis U.S. LLC. June 2019.
7. Apidra [Prescribing Information]. Bridgewater, NJ: Sanofi-aventis U.S. LLC. June 2019.
8. Afrezza [Prescribing Information]. Danbury, CT: MannKind Corporation. June 2019.
9. Lyumjev [Prescribing Information]. Indianapolis, IN: Eli Lilly USA LLC. June 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of Lyumjev (insulin lispro-aabc) products	11/2020
Addition of generic insulin aspart products and update to renewal policy	01/2020
Conversion to policy format; addition of generic insulin lispro	06/2019
Inserted Fiasp products; removed long acting insulins to which this policy does not apply	01/2018
Included questions to ensure members is injecting more than 200 units per day for U500 formulations	09/2017
Afrezza and Apidra added to policy	06/2016
Criteria developed	04/2016

Policy Type: PA Pharmacy Coverage Policy: UMP067

Description

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

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
testosterone undecanoate (Jatenzo)	158 mg tablets	Primary hypogonadism; hypogonadotropic hypogonadism	120 capsules/30 days
	198 mg tablets		120 capsules/30 days
	237 mg capsules		60 capsules/30 days
testosterone undecanoate (Aveed)	750 mg/ 3 mL intramuscular solution		3 mL/28 days
testosterone (Striant)	30 mg buccal system		60 buccal systems/ 30 days
testosterone (Androderm)	2 mg/24 hour patch		60 patches/30 days
	4 mg/24 hour patch		30 patches/30 days
testosterone 1% (AndroGel, Testim, Vogelxo)	25mg/2.5gm gel		300 g/30 days
	50 mg/5gm gel		300 g/30days
	1.25 g/actuation gel pump		300 g/30 days
testosterone 1.62% (AndroGel, Vogelxo)	20.25 mg/ 1.25 gm gel packet		150 g/30 days
	40.5 mg/2.5gm gel packet		150 g/30 days
	20.25 mg/ actuation gel pump		150 g/30 days

testosterone cypionate (Depo-testosterone)	100mg/ mL intramuscular injection		8 mL/28 days
testosterone cypionate (Depo-testosterone)	200mg/ mL intramuscular injection		4 mL/28 days
testosterone (Axiron)	30 mg actuation roll-on solution		110 mL /30 days
testosterone (Xyosted)	50 mg/ 0.5 mL subcutaneous solution autoinjector		5 mL/28 days
	75 mg/0.5 mL subcutaneous solution autoinjector		5 mL/28 days
	100 mg/ 0.5 mL subcutaneous solution autoinjector		4 mL/28 days
testosterone Cypionate 2% (Fortesta)	10mg/ actuation gel		120 g /30 days
methyltestosterone (Methitest)	10 mg tablet or capsule		Men: 150 tablets/ 30 days Women: 600 tablets/ 30 days

Initial Evaluation

I. Testosterone (Branded) may be considered medically necessary when the following criteria are met:
   A. A diagnosis of one of the following:
      1. **Gender dysphoria**; **OR**
      2. **Primary or Secondary Hypogonadism defined as one of the following**;
         i. Primary hypogonadism (testicular failure) due to Klinefelter syndrome (KS), cryptorchidism, orchiectomy, vanishing testes syndrome, chemotherapy affecting or radiation to the testes, testicular trauma, torsion, infectious orchitis, HIV infection, anorchia syndrome, or myotonic dystrophy; **OR**
         ii. Secondary hypogonadism (pituitary-hypothalamic hypogonadism) as caused by hypothalamic or pituitary tumor, iron overload syndromes,

idiopathic hypogonadotropic hypogonadism, hyperprolactinemia, head trauma, or pituitary surgery or radiation; **AND**

iii. Two sub-normal testosterone concentration levels taken on two separate mornings while fasting; **AND**

iv. Treatment with **all** of the following has been ineffective, contraindicated, or not tolerated**:**

a. Generic injectable testosterone; **AND**

b. Generic topical testosterone; **AND**

v. Member is male; **AND**

vi. Age is 18 years old or greater; **AND**

vii. Member does **not**:

a. Plan to conceive; **OR**

b. Have breast or prostate cancer; **OR**

c. Have palpable prostate nodule or induration; **OR**

d. Have a prostate-specific antigen level greater than 4 ng/mL, a prostate-specific antigen greater than 3 ng/mL combined with a high risk of prostate cancer; **OR**

e. Have testosterone levels within the normal range

II. Testosterone is considered not medically necessary when used for all other conditions, including

A. Men with low testosterone concentration and without clinical symptoms and signs consistent with testosterone deficiency. The routine assessment of testosterone level in the absence of hypogonadal symptoms is not advised.

B. Men with a single, sub-normal testosterone concentration that is not repeatable per the U.S. Endocrine Society.

C. Men with symptoms of hypogonadism, however, present with testosterone level within normal range.

III. Testosterone is considered investigational when used for all other conditions, including but not limited to:

A. Age-related hypogonadism

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

B. Men with type 2 diabetes mellitus with low testosterone for the purpose of improving glycemic control

C. For the healing of fracture

D. Functional uterine bleed

E. Treatment of weight loss unrelated to HIV-wasting

Renewal Evaluation

I. A previously approved prior-authorization for a branded testosterone product.

Supporting Evidence

I. Per the 2018 AUA guidelines, diagnosis of hypogonadism should be confirmed prior to initiating testosterone replacement therapy. Testosterone levels should be drawn ideally between 8 and 10 AM while fasting due to the diurnal fluctuation of testosterone and its sensitivity to glucose ingestion. A separate, confirmatory measurement is recommended.

II. Thirty percent of men with an initial testosterone concentration in the hypogonadal range can have a measurement within the normal range on repeat measurement.

III. The Endocrine Society strongly advises against "trial periods" of testosterone in men with a single sub-normal testosterone concentration and vague symptoms of deficiency.

IV. The benefit of increasing testosterone concentration has only been shown in patients with organic hypogonadism due to disorders of the hypothalamus, pituitary or testes.

V. In patients within normal range, or have low testosterone concentration due to age, obesity, or otherwise, the benefit of increased testosterone has not been shown. Rather, in this patient population with low testosterone and an intact gonadal system, increasing testosterone is associated with an increase of certain health risks, including cardiovascular disease. Due to this, the FDA has required manufacturers to label testosterone products warning of the increased risk for heart attack and stroke.

VI. To discriminate between primary and secondary hypogonadism, a measurement of serum luteinizing hormone (LH) and follicle-stimulation hormone (FSH) concentrations is required.
   - Primary: testicular failure; usually associated with high LH and FSH
   - Secondary: pituitary and/or hypothalamic dysfunction; usually associated with low LH and FSH

VII. Lower limit of the normal total testosterone (TT) to the CDC standard in healthy, non-obese young men is 264 ng/dL (9.2 nmol/L).

VIII. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the use of oral testosterone undecanoate (Jatenzo) or topical testosterone products in women.

IX. A randomized trial showed that use of testosterone undecanoate (Jatenzo) resulted in an increase in systolic and diastolic blood pressure by an average of 4.9 mmHg and 2.5 mmHg, respectively.
   - Increases in hematocrit and heart rate were also noted, leading to an increased risk of major adverse cardiac events (MACE), limiting dose frequency to twice daily.

X. Testosterone replacement therapy is subject to abuse at doses higher than recommended for approved indications and in combination with other anabolic androgenic steroids. Abuse-related adverse events include cardiac arrest, myocardial infarction, hypertrophic cardiomyopathy, congestive heart failure, hepatotoxicity, and serious psychiatric complaints.

XI. Payment consideration for oral methyltestosterone is reserved for members who have tried and failed injectable testosterone. Testosterone enanthate injectable is approved for use in females that have 1-5 years postmenopausal advanced inoperable metastatic breast cancer, in premenopausal women who have benefited from oophorectomy with hormone responsive tumors, OR in delayed puberty in males. Topical formulations of testosterone are not indicated for use in women and pediatrics.

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Policy Implementation/Update:

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

Action and Summary of Changes	**Date**
Change to policy format; added supplementary evidence section; updated references	07/2018
Add methyltestosterone to table; removed DDID column	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP086

Split Fill Management*

Description

Selinexor (Xpovio) is an oral nuclear export inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
selinexor (Xpovio)	80 mg tablet twice weekly carton	Relapsed or refractory multiple myeloma (MM)	1 carton (32 tablets)/28 days
	100 mg tablet once weekly carton		1 carton (20 tablets)/28 days
	80 mg tablet once weekly carton		1 carton (16 tablets)/28 days
	60 mg tablet once weekly carton		1 carton (12 tablets)/28 days
	40 mg tablet once weekly carton		1 carton (8 tablets)/28 days
	60 mg tablet twice weekly carton	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	1 carton (24 tablets)/28 days
	40 mg tablet twice weekly carton		1 carton (16 tablets)/28 days

Initial Evaluation

I. Selinexor (Xpovio) 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. Not used in combination with any other oncology therapy unless outlined below; **AND**
   D. A diagnosis of **multiple myeloma** when **ONE** of the following are met:
      1. The provider attests to the following:
         i. The member has received ONE, but no more than THREE previous therapies; **AND**
            a. Previous treatments included at least one of the following medications:
               i. Bortezomib (Velcade)

ii. Carfilzomib (Kyprolis)
iii. Ixazomib (Ninlaro)
iv. Daratumumab (Darzalex)
v. Immunomodulatory agent (e.g., lenalidomide, pomalidomide); **AND**

b. Selinexor (Xpovio) will be used in combination with bortezomib (Velcade) AND dexamethasone; **OR**

ii. The member has received **FOUR** or more previous therapies; **AND**

a. Refractory to ALL of the following medications:

i. TWO proteasome inhibitors (e.g., bortezomib, carfilzomib)
ii. TWO immunomodulatory medications (e.g., lenalidomide, pomalidomide)
iii. An anti-CD38 monoclonal antibody (e.g., daratumumab); **AND**

b. Selinexor (Xpovio) will be used in combination with dexamethasone.

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

A. Multiple myeloma when given as part of a quadruplet ("quad") regimen
B. Diffuse large B-cell lymphoma

Renewal Evaluation

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

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

II. Clinical documentation of response to treatment such as stabilization or improvement in disease or symptoms; **AND**

III. Provider attests to the following:

A. The member has received ONE, but no more than THREE previous therapies; **AND**

1. Selinexor (Xpovio) will be used in combination with bortezomib (Velcade) AND dexamethasone; **OR**

B. The member has received **FOUR** or more previous therapies; **AND**

1. Selinexor (Xpovio) will be used in combination with dexamethasone.

Supporting Evidence

I. As of February 2021, selinexor (Xpovio) has three FDA-approved indications:

- In combination with bortezomib and dexamethasone in adult patients with multiple myeloma who have received at least one prior therapy
- In combination with dexamethasone in adult patients with multiple myeloma who have previously received at least four prior therapies and whose disease is refractory to at

least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (penta-refractory)

- Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

II. Multiple myeloma (MM)

- Selinexor (Xpovio) is indicated for use in two different multiple myeloma settings: (1) received at least one prior therapy (*BOSTON trial*) and (2) received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody *(STORM trial*).
- Selinexor (Xpovio) for treatment in the setting of penta-refractory MM was approved via the accelerated approval pathway, and continued approval was contingent upon verification and description of clinical benefit in confirmatory trials. Results from the BOSTON trial confirmed continued approval for use in the setting of penta-refractory MM.
    i. **STORM**: Phase 2, open-label trial of 79 patients in combination with dexamethasone only. No other oncolytic therapies were included in the drug regimen. Patients included were previously treated with glucocorticoids, an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb **and** refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.
        1. The primary endpoint was objective response rate (ORR), which occurred in 21%. Secondary outcomes included progression free survival (PFS) and overall survival (OS), which resulted in 2.3 and 9.3 months, respectively.
        2. The safety profile is as follows: Sixty percent of patients in the trial experienced grade 3-4 adverse events including thrombocytopenia, anemia, and neutropenia. Additionally, other serious adverse events occurred such as febrile neutropenia, serious infections, and fatal serious bleeding.
        3. Selinexor (Xpovio) has not been sufficiently studied in the penta-refractory setting with further clinical evaluation of safety and efficacy needed to confirm a net health benefit and place in therapy for this medication.
    ii. **BOSTON**: Phase 3, randomized, open-label trial of 402 patients in combination with bortezomib and dexamethasone (N= 195 SEL-BTZ-Dex) compared to a combination with bortezomib and dexamethasone only (N=207 BTZ-Dex). Patients included had received one to three previous different regimens for multiple myeloma. Patients who previously received proteasome inhibitors (mono- or combination therapy) were required to have had at least a partial response and at least a 6-month interval since their last proteasome inhibitor therapy, with no history of discontinuation of bortezomib due to Grade 3+ AEs.
        1. The primary efficacy endpoint was progression free survival (PFS), which was 13.93 months in the SEL-BTZ-Dex arm versus 9.46 months in the BTZ-Dex arm. Key secondary endpoints were overall survival (OS), which was not reached in the SEL-BTZ-Dex arm versus 25 months in the BTZ-Dex arm; overall response rate (ORR) of 76.4% in the SEL-BTZ-Dex arm versus 62.3% in the BTZ-Dex arm; duration of response (DoR) of 20.3 months in the SEL-BTZ-

Dex arm versus 12.9 months in the BTZ-Dex arm; time to response (TTR) of 1.1 months in the SEL-BTZ-Dex arm versus 1.4 months in the BTZ-Dex arm.

2. Safety results were analyzed in all patients who received at least one dose of the study drug (N=195 SEL-BTZ-Dex, N=204 BTZ-Dex). The most common adverse events (≥20% incidence) included thrombocytopenia, anemia, nausea, fatigue, decreased appetite, diarrhea, peripheral neuropathy, weight loss, asthenia, cataract, and vomiting. Selinexor (Xpovio) showed an 81% treatment discontinuation rate: 21% due to adverse events versus 16% in the BTZ-Dex arm.

- Recommended dosage for MM:
  i. In combination with bortezomib and dexamethasone is selinexor (Xpovio) 100 mg taken orally once weekly on Day 1 of each week until disease progression or unacceptable toxicity.
  ii. In combination with dexamethasone is selinexor (Xpovio) 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.
- As of February 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for previously treated multiple myeloma has included selinexor (Xpovio) in combination with bortezomib and dexamethasone as "Other Recommended Regimens" (Category 1 recommendation). Additionally, NCCN recommends selinexor (Xpovio) in combination with dexamethasone as "Useful in Certain Circumstances" for patients with relapsed/refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (Category 2A recommendation).

III. Diffuse large B-cell lymphoma (DLBCL)

- **SADAL**: Phase 2, an open-label, single-arm, multi-cohort trial of 127 patients with de novo DLBCL or DLBCL transformed from previously diagnosed indolent lymphoma, previously treated with two to five lines of therapy and progressed after, or were not candidates for autologous stem-cell transplantation were included. Previous systemic regimens permitted included at least one course of anthracycline-based chemotherapy (unless contraindicated due to cardiac dysfunction, in which case, other active drugs such as etoposide, bendamustine, or gemcitabine were given) and at least one course of anti-CD20 immunotherapy such as rituximab. Low dose dexamethasone (4 mg) was permitted as it does not show anti-lymphoma activity. FDA approval was based on the overall response rate (ORR).
  i. The primary efficacy endpoint was overall response rate (ORR), which occurred in 28%, and the secondary endpoint was duration of response (DoR), which was 9.3 months. Based on analysis of this clinical trial data, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as, the lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy has not yet been confirmed.

ii. Safety results were analyzed in all patients who received at least one dose of selinexor (Xpovio) (N=125). The most common adverse events (≥20% incidence) included thrombocytopenia, nausea, fatigue, anemia, decreased appetite, diarrhea, constipation, neutropenia, weight loss, vomiting, pyrexia, and asthenia. There are no specific contraindications to selinexor (Xpovio); however, warnings and precautions include: thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, serious infection, neurological toxicity, and embryo-fetal toxicity. Selinexor (Xpovio) showed a 93% treatment discontinuation rate: 63% due to disease progression, 10% withdrawal by patient, 7% death, 6% physician decision, and 7% due to adverse events.

- Selinexor (Xpovio) for treatment in the setting of DLBCL received accelerated approval from the FDA based on ORR and DoR. Continued approval for this drug may be contingent upon verification of clinical benefit in confirmatory trials. There is a Phase 2/3 trial underway to assess rituximab + gemcitabine + dexamethasone + platinum (R-GDP) with or without selinexor (Xpovio) in patients with relapsed/refractory diffuse large B-cell lymphoma.
- Recommended dosage for DLBCL:
  i. Selinexor (Xpovio) 60 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.
- As of February 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for B-cell lymphomas has included selinexor (Xpovio) as third-line and subsequent treatment with a Category 2A recommendation.

Investigational or Not Medically Necessary Uses

I. Selinexor (Xpovio) has not been sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Quadruple ("quad") regimen
      i. Although triplet regimens remain the standard of care for multiple myeloma, 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.
   B. Diffuse large B-cell lymphoma
      i. Refer to SADAL trial information under Supporting Evidence

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

Appendix

Table 1: Classification of Medications used for Multiple Myeloma

Proteasome Inhibitors	Immunomodulatory Agents	Monoclonal Antibodies	Histone Deacetylase Inhibitors	B-cell Maturation Antigen-Directed Antibody	Chemotherapy
• bortezomib • carfilzomib • ixazomib	• thalidomide • lenalidomide • pomalidomide	• elotuzumab • daratumumab • isatuximab-irfc	• panobinostat	• belantamab mafodotin-blmf	• cyclophosphamide • doxorubicin • cisplatin • etoposide • melphalan • bendamustine

Table 2: Selinexor (Xpovio) Dosage Reduction Steps for Adverse Reactions

	MM In combination with Bortezomib and Dexamethasone	**MM In combination with Dexamethasone**	**DLBCL**
Recommended Starting Dosage	100 mg once weekly	80 mg Days 1 and 3 of each week (160 mg total per week)	60 mg Days 1 and 3 of each week (120 mg total per week)
First Reduction	80 mg once weekly	100 mg once weekly	40 mg Days 1 and 3 of each week (80 mg total per week)
Second Reduction	60 mg once weekly	80 mg once weekly	60 mg once weekly
Third Reduction	40 mg once weekly	60 mg once weekly	40 mg once weekly
Fourth Reduction	Permanently discontinue	Permanently discontinue	Permanently discontinue

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added split fill management, length of authorization. Updated quantity limits to include 40 mg tablet once weekly carton, as well as DLBCL dosage forms. Updated penta-refractory MM indication from E/I to allow criteria coverage. Added criteria coverage for new MM indication of at least one prior therapy. Added new DLBCL indication and quad-regimen for MM as E/I. Added additional supporting evidence to include more details surrounding all three indications. Added "Table 1: Classification of Medications used for Multiple Myeloma" and "Table 2: Selinexor (Xpovio) Dosage Reduction Steps for Adverse Reactions" under Appendix.	02/2021
Policy created	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP192

Split Fill Management*

Description

Selpercatinib (Retevmo) is an orally administered kinase inhibitor of RET.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
selpercatinib (Retevmo)	40 mg capsules	RET Fusion-Positive Non-Small Cell Lung Cancer RET-Mutant Medullary Thyroid Cancer	180 capsules/30 days
	80 mg capsules	RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory	120 capsules/30 days

Initial Evaluation

I. Selpercatinib (Retevmo) is considered investigational when used for all indications, including but not limited to Non-Small Cell Lung Cancer and Thyroid Cancer.

Renewal Evaluation

I. N/A

Supporting Evidence

I. RET, a transmembrane receptor protein, is present at the surface of several tissue types. Alterations include fusions and point mutations – both are oncogenic drivers. Selpercatinib (Retevmo) is the first FDA-approved therapy that targets RET alterations specifically.

II. Selpercatinib (Retevmo) is a kinase inhibitor of RET. It is FDA-approved for adults with metastatic RET fusion-positive non-small-cell lung cancer (NSCLC), advanced or metastatic RET-mutant medullary thyroid cancer (MTC) in patients age 12 years and older, and advanced or

metastatic RET fusion-positive thyroid cancer who are radioactive iodine (RAI)-refractory in patients age 12 years and older.

III. RET fusion-positive NSCLC, advanced or metastatic: First-line treatment options include cabozantinib (Cometriq®) or vandetanib (Caprelsa®) (not FDA-approved for lung cancer) or combinations of platinum-based chemotherapy, anti-PD-1/PD-L1 therapy, pemetrexed, and bevacizumab. In the second-line setting, additional options include various immunotherapy and chemotherapy treatments (e.g., taxanes, gemcitabine).

IV. RET-mutant MTC, advanced or metastatic: Systemic treatment may be warranted for high volume, symptomatic or progressive MTC. General treatment options include cabozantinib (Cometriq) or vandetanib (Caprelsa).

V. RET fusion-positive thyroid cancer: In persistent/recurrent or metastatic disease, radioactive iodine (RAI) is recommended. In those not amenable to RAI, general treatment options include lenvatinib (Lenvima®) or sorafenib (Nexavar®).

VI. Selpercatinib (Retevmo) is being evaluated in one Phase 1/2, open-label, multi-cohort, single-arm trial in patients with RET abnormal, advanced solid tumors Interim results showed potential antitumor activity, based on objective response rate (ORR), in the three FDA-approved settings. Additional outcomes: progression-free survival (PFS) and overall survival (OS) at 12 months.

- RET fusion-positive NSCLC: Patients were advanced or metastatic, progressed on platinum-based chemotherapy or were systemic treatment naïve. Over half of pretreated patients also received anti-PD1/PD-L1 therapy (n=58).
- RET-mutant MTC: 98% had metastatic disease, and patients were previously treated with cabozantinib (Cometriq) and/or vandetanib (Caprelsa), or were treatment naïve to both. Ten patients were previously treated with platinum chemotherapy or anti-PD1/PD-L1 therapy.
- RET fusion-positive TC: Patients were not amenable to RAI therapy, and may have been treated with lenvatinib (Lenvima) and/or sorafenib (Nexavar), or were naïve to both.

Clinical Efficacy in Pretreated Patients			
Outcome	**RET Fusion+ NSCLC (n=105)**	**RET-Mutant MTC (n=55)**	**RET Fusion-Positive TC (n=19)**
ORR (n)	67 (64%)	38 (69%)	15 (79%)
CR (n)	2 (2%)	5 (9%)	1 (5%)
PR (n)	65 (62%)	33 (60%)	14 (74%)
PFS (months)	16.5 (13.7-NE)	NE	20 (9.4-NE)
OS, 12 months (%)	88%	87%	NR
Clinical Efficacy in Treatment-Naïve Patients			
Outcome	**RET Fusion+ NSCLC (n=39)**	**RET-Mutant MTC (n=88)**	**RET Fusion-Positive TC (n=8)**
ORR (n)	33 (85%)	64 (73%)	8 (100%)
CR (n)	0	10 (11%)	1 (12.5%)
PR (n)	33 (85%)	54 (61%)	7 (87.5%)
PFS (months)	NE	23.6 (NE-NE)	NE
OS, 12 months (%)	NR	NR	NR

VII. Selpercatinib (Retevmo) was FDA-approved under the accelerated approval pathway based on ORR. Continued approval may be contingent upon verification and description of clinical benefit

in confirmatory trials. This therapy is being evaluated in multiple other clinical Phase 2 and Phase 3 trials. The quality of the evidence is considered low at this time given the open-label trial design and lack of comparator arm. Given the observational data, medication efficacy remains uncertain. Additionally, the medication has an unfavorable safety profile.

VIII. As of June 2020, safety data are based on a pooled population in 702 patients, 65% were exposed for six months or greater, and 34% were exposed for over one year. Ninety-five percent of patients received 160 mg twice daily.

IX. Warnings and precautions: hepatotoxicity, hypertension, QT interval prolongation, hemorrhagic events, hypersensitivity, impaired wound healing and embryo-fetal toxicity. There are no contraindications. Serious adverse reactions occurred in 33% of patients. The most frequent was pneumonia. Fatal adverse reactions occurred in 3% of individuals due to sepsis (n=1), cardiac arrest (n=3), respiratory failure (N=3).

X. Common adverse reactions (≥25%): increase liver enzymes, laboratory abnormalities (≥25% each, glucose, leukocytes, albumin, calcium, creatinine, alkaline phosphatase, platelets, cholesterol, sodium), dry mouth, diarrhea, hypertension, fatigue, edema, rash, constipation. Permanent discontinuation due to adverse reactions occurred in 5%, dose interruptions in 42%, and dose reduction in 31% of patients.

Investigational or Not Medically Necessary Uses

I. Selpercatinib (Retevmo) 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.*

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP193

Split Fill Management*

Description

Selumetinib (Koselugo) is a mitogen-activated protein kinase (MEK) inhibitor for both MEK 1 and 2 that inhibits the phosphorylation of extracellular signal related kinase (ERK) and reducing neurofibroma numbers, volume, and proliferation.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
selumetinib (Koselugo)	10 mg capsules	Neurofibromatosis type 1 (NF1)	120 capsules/30 days
	25 mg capsules		

Initial Evaluation

I. Selumetinib (Koselugo) may be considered medically necessary when the following criteria are met:
   A. Member is between two and 18 years of age; **AND**
   B. Medication is prescribed by, or in consultation with, a neurosurgeon or neurologist; **AND**
   C. Documentation of baseline comprehensive ophthalmic assessments; **AND**
   D. Documentation of baseline assessment of left ventricular ejection fraction (LVEF); **AND**
   E. Member has NOT experienced disease progression (increase in tumor size or tumor spread) while on a MEK inhibitor [e.g., binimetinib (Mektovi®), cobimetinib (Cotellic®), trametinib (Mekinist®)]; **AND**
   F. A diagnosis of **Neurofibromatosis type 1 (NF1)** when the following are met:
      1. Member has inoperable and symptomatic plexiform neurofibromas (PN); **AND**
      2. Symptoms affect quality of life (e.g. pain, impaired physical function, compression of vital organs, respiratory impairment, visual dysfunction, and neurological dysfunction); **AND**
      3. Diagnosis confirmed by genetic testing; **OR**
         i. Member meets at least one criterion:
            a. Six or more light brown spots (café-au-lait macule – CALMs) equal to, or greater than, 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in post pubertal patient; **OR**

b. Freckling in the axillary or inguinal regions (Crowe sign); **OR**
c. Optic glioma (OPG); **OR**
d. Two or more iris hamartomas (Lisch nodules – dome-shaped gelatinous masses developing on the surface of the iris); **OR**
e. A distinctive osseous lesion, such as sphenoid wing dysplasia or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis; **OR**
f. A first-degree relative (parent, sibling, or child) with NF1.

II. Selumetinib (Koselugo) 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 response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
IV. Member has **NOT** exhibited ophthalmic toxicity (e.g. blurred vision, photophobia, cataracts, or ocular hypertension) nor experienced a decrease of 10% or more below baseline in LVEF during treatment.

Supporting Evidence

I. The safety and efficacy of selumetinib (Koselugo) in pediatric patients two years of age or older with NF1 who have inoperable PN was established in the SPRINT trial (a phase II, open-label, single arm, multicenter clinical trial).
II. Patients older than 18 years of age are being studied in a phase 2, open label, single site clinical trial, with the primary outcome being to determine an objective response rate. The study is still ongoing and therefore has no published safety and efficacy data to support the use in adult patients (those 18 years of age or older).
III. NF1 is a multifaceted disease state and selumetinib (Koselugo) has a complex dosing regimen and safety profile; therefore, it should be prescribed by, or in consultation with, a specialist in the treatment and management of NF1.
IV. Cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) of 10% or more below baseline, occurred in 23% of the 74 pediatric patients who received selumetinib (Koselugo) in the clinical trial. The safety and efficacy, of use in those with a history of impaired LVEF or a baseline ejection fraction that is below the institutional LLN, has not been established.
V. Blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 pediatric patients receiving selumetinib (Koselugo). Blurred vision resulted in dose interruption in 2.7% of patients. Ocular toxicity resolved in 82% of 11 patients. Comprehensive ophthalmic assessments

prior to initiating, and at regular intervals during treatment, for new or worsening visual changes is recommended.

VI. There is no published data from a head-to-head study between selumetinib (Koselugo) and other MEK inhibitors [e.g., binimetinib (Mektovi®), cobimetinib (Cotellic®), trametinib (Mekinist®)] to show effectiveness for the treatment of pediatric patients two years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).
There is no data to show one MEK inhibitor could overcome common mechanisms of resistance of MEK inhibitors.

VII. The safety and efficacy of selumetinib (Koselugo) was evaluated in patients with NF1 who have inoperable (defined as a PN that could not be completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN) and symptomatic [defined as PNs that may located around the orbit, face, upper and lower limbs, back, thorax, abdomen, neck brachial plexus and/or lumbosacral plexus, which result in clinical symptoms such as disfigurement, motor dysfunction (weakness and restricted range of motion), pain, respiratory impairment, visual dysfunction, and neurological dysfunction] PNs.

VIII. Per the American Academy of Pediatrics, National Institutes of Health (NIH) consensus development conference regarding NF1, to establish a diagnosis of NF1, two out of seven criteria have to have been met: **1.** Six or more light brown spots on skin (café-au-lait macule – CALMs) equal to, or greater than, 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in post pubertal patient. **2.** Two or more neurofibromas of any type or 1 plexiform neurofibroma. **3.** Freckling in the axillary or inguinal regions (Crowe sign). **4.** Optic glioma (OPG). **5**. Two or more iris hamartomas (Lisch nodules – dome-shaped gelatinous masses developing on the surface of the iris). **6**. A distinctive osseous lesion, such as sphenoid wing dysplasia (partial or complete absence of the greater wing of the sphenoid) or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis (unsuccessful spinal fusion). **7.** A first-degree relative (parent, sibling, or child) with NF1

   A. NF1 genetic testing may be performed for purposes of diagnosis, but if a child fulfills diagnostic criteria for NF1, molecular genetic confirmation is usually unnecessary. Molecular diagnosis of NF1 is available based on DNA analysis for a pathogenic variant in the NF1 gene. Only 4 genotype-phenotype correlations have been established (deletion of the entire NF1 gene, specific 3-base deletion in exon 22, Amino acid substitution at codon 1809, some missense or splicing variants are associated with "spinal NF1,").

Investigational or Not Medically Necessary Uses

I. Selumetinib (Koselugo) has not been FDA-approved, or sufficiently studied for safety and efficacy for other conditions except neurofibromatosis type 1 (NF1) with inoperable PNs.

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

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP020

Description

Sildenafil (Revatio), and tadalafil (Adcirca) are phosphodiesterase type 5 (PDE5) inhibitors.

Length of Authorization

- Initial: Length of benefit
- Renewal: Not applicable

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
sildenafil (Revatio)	20 mg tablets	Raynaud's phenomena	90 tablets/30 days	095712
	10 mg/mL	Pulmonary arterial hypertension	224 mL/30 days (2 bottles)	185438, 185439
tadalafil (Cialis)	2.5 mg tablets	Benign prostatic hyperplasia	30 tablets/30 days	133138, 133126
	5 mg tablets			085041, 085008
	20 mg tablets	Pulmonary arterial hypertension	60 tablets/30 days	095039, 083319
tadalafil (Adcirca)	20 mg tablets	Pulmonary arterial hypertension	60 tablets/30 days	144282, 143348
tadalafil (Alyq)	20 mg tablets	Pulmonary arterial hypertension	60 tablets/30 days	205589

Initial Evaluation

I. Medication contained in this policy may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      1. **Pulmonary arterial hypertension (PAH)**; **AND**
         i. The medication is prescribed by or in consultation with a specialist (e.g., pulmonologist, cardiologist); **AND**
         ii. The patient is classified as having World Health Organization (WHO) Functional Class II-IV symptoms; **AND**
         iii. The request is for generic sildenafil tablets or generic tadalafil tablets; **OR**
            a. The request is for Revatio tablets or Adcirca and both generic sildenafil and generic tadalafil are found to be ineffective, not tolerated, or contraindicated; **OR**

b. The request is for generic sildenafil oral suspension 10 mg/mL, and the member is unable to swallow oral tablets; **OR**
    i. The request is for Revatio oral suspension 10 mg/mL, and the generic has been ineffective, not tolerated, or containdicated; **OR**

2. **Benign prostatic hyperplasia (BPH); AND**
    i. At least one alpha-1 blocker AND one 5-alpha-reductase inhibitor medication have been ineffective, not tolerated, or both are contraindicated
        a. Examples of 5-alpha reductase inhibitors: dutasteride, finasteride
        b. Examples of alpha-1 blockers: alfuzosin, doxazosin, silodosin, tamsulosin, terazosin; **AND**
    ii. Generic tadalafil 2.5 or 5 mg tablets are requested (please note, no other medications addressed in this policy are covered for BPH); **OR**
3. **Raynaud's disease/phenomena; AND**
    i. Generic sildenafil 20mg has been prescribed at a maximum quantity of 90 tablets per 30-day supply (please note, no other medications in this policy are covered for Raynaud's); **AND**
    ii. Treatment with a dihydropyridine calcium channel blocker (e.g., nifedipine, amlodipine, isradipine, felodipine) or diltiazem has been ineffective, not tolerated, or is contraindicated; **OR**
        a. Generic sildenafil 20mg tablets will be used in combination with a calcium channel blocker or diltiazem as additional treatment.

II. Medications listed in this policy are considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
    A. Erectile dysfunction.

III. Medications listed in this policy are considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
    A. Traumatic brain injury
    B. Hypertension, not of the pulmonary atrial type
    C. Heart failure and/or other cardiovascular or central nervous system conditions, disorders, or diseases
    D. Oncologic conditions
    E. Encephalopathy
    F. Cirrhosis

Renewal Evaluation

I. Renewal criteria; Not applicable, approval allowed for length of benefit.

Supporting Evidence

I. Pulmonary arterial hypertension: Pulmonary hypertension (PH) specific therapy is directed at the PH itself rather than the underlying cause of PH. Patients with persistent PH with World Health Organization (WHO) functional class II, III, or IV despite treatment of the underlying cause of PH should be evaluated for PH specific therapy. Group I patients should be observed and treated for the contributing factors. As of 2019, preferential treatments for group II-III patients include tadalafil plus other agents, and group IV should be treated with IV agents or double or triple combination therapy regimen that may or may not include tadalafil or sildenafil. Therapy is individualized to the patient and there are several suitable agents outside of sildenafil or tadalafil.

II. Benign prostatic hyperplasia (BPH): common treatment for BPH include alpha-1 adrenergic antagonists, 5-alpha-reductase inhibitors, anticholinergic agents, and phosphodiesterase-5 (PED-5) inhibitors. As of 2019, it was recommended that those with mild disease should be considered for an alpha-1 adrenergic antagonist. This is due to 5-alpha-reductase inhibitors requiring long-term treatment for efficacy (six to twelve months of treatment required prior to symptom improvement); however, it shall be noted that some patients will experience hypotension with alpha-1-adrenergic antagonists. Alternative options beyond these two classes include anticholinergic agents and PDE-5 inhibitors.

III. Raynaud phenomenon (RP): An exaggerated vascular response to cold temperature or emotional stress. This is manifested clinically by sharply demarcated color changes of the skin. Attacks occur commonly in the hands but may also occur in the toes, and attacks may cause symptoms such as numbness, clumsiness of the hand, aches, pains, or a feeling of pins and needles. Initial management of RP includes avoidance of triggers and vasoconstricting medications (e.g., nasal decongestants, amphetamines, ephedra, stimulants, triptans, ergotamines), as well as smoking cessation.

IV. Initial pharmacologic management of RP is recommended with calcium channel blockers of the dihydropyridine type. Amlodipine is preferred, but other such as nifedipine may be used. Other agents, such as PED-5 medications (e.g., sildenafil, tadalafil, vardenafil) may be considered with calcium channel blockers are contraindicated or not tolerated.

Investigational or Not Medically Necessary Uses

I. Erectile dysfunction treatment is deemed medically necessary by the plan and is excluded from coverage.

II. All of the aforementioned indications, conditions, diseases listed in the experimental/investigational section and treated with medications in this policy are being evaluated in clinical trials. Safety and efficacy have not yet been determined.

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Policy Implementation/Update:

Date Created	April 2015
Date Effective	April 2015
Last Updated	May 2019
Last Reviewed	06/15, 03/18, 05/19

Action and Summary of Changes	Date
Creation of policy from prior authorization criteria. Opened up criteria to allow for generic sildenafil and tadalafil for BPH and PAH due to generic availability.	05/2019
Updated PAH questions to remove contraindication questions, assess function classification of staging and trial and failure of generic sildenafil. Aligned with commercial PAH criteria. Added clinical note of Raynaud phenomena.	03/2018

simvastatin (Zocor®) 80 mg

UMP POLICY

Uniform Medical Plan

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP106

Description

Simvastatin (Zocor) is an orally administered 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor used to reduce LDL-C and prevent cardiovascular events.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Simvastatin (Zocor)	80 mg tablets	Prevention of cardiovascular events/cardiovascular disease and reduce the risk of atherosclerotic cardiovascular disease, homozygous familial hypercholesterolemia	30 tablets/30 days

Initial Evaluation

I. **Simvastatin 80 mg (Zocor)** may be considered medically necessary when the following criteria below are met:
   A. Member has been established and stabilized on the 80 mg dose for a duration of 12 or more months without evidence of muscle toxicity (e.g. myopathy, rhabdomyolysis) within the past 12 months.

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; **AND**
III. Member has not experienced symptoms of muscle toxicity (e.g. myopathy, rhabdomyolysis).

Supporting Evidence

I. In 2011, the FDA issued a dose limitation on simvastatin 80 mg stating that it should not be started in new patients and should only be used in patients who have been taking this dose for 12 months or more without evidence of muscle injury (myopathy). Furthermore, 2018 AHA/ACC guidelines note simvastatin 80 mg/day is not recommended due to increased risk of myopathy. If patient is unable to achieve LDL-C goal with simvastatin 40 mg/day, switch to a high-intensity statin.

II. The SEARCH trial was a seven-year, randomized, double-blind study that compared the efficacy and safety of simvastatin 80 mg versus simvastatin 20 mg, with or without vitamin B12 and folate in survivors of myocardial infarction.

- Incidence of major vascular events between the simvastatin 80 mg group and simvastatin 20 mg group was 24.5% vs 25.7%, respectively (95% CI 0.88, 1.01, p=0.10).
- 0.9% of patients in the simvastatin 80 mg group experienced myopathy versus 0.02% in the simvastatin 20 mg group. Risk for myopathy and rhabdomyolysis was highest in the first 12 months of therapy.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updates to wording of initial criteria in efforts to clarify policy intent	05/2021
Criteria transitioned to policy with supporting evidence section added.	10/2019
New criteria	01/2017

Policy Type: PA/SP Pharmacy Coverage Policy: UMP186

Description

Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) are orally administered metabolites of the neurotransmitter GABA that act as central nervous system depressants with an unknown mechanism of action.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
sodium oxybate (Xyrem)	500 mg/mL	Narcolepsy with cataplexy; Narcolepsy with excessive daytime sleepiness in patients greater than 7 years of age	540 mL/30 days
calcium, magnesium, potassium, sodium oxybates (Xywav)	500mg/mL		540 mL/30 days

Initial Evaluation

I. **Sodium oxybate (Xyrem)** may be considered medically necessary when the following criteria are met:
   A. Member is seven years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a sleep specialist, psychiatrist, or neurologist; **AND**
   C. Not used in combination with sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate); **AND**
   D. Confirmation the member does <u>not</u> have a succinic semialdehyde dehydrogenase deficiency; **AND**
   E. Provider attestation the member does not have a history of substance abuse; **AND**
   F. A diagnosis of one of the following:
      1. **Narcolepsy with cataplexy**; **AND**
         i. Confirmation of cataplexy defined as episodes of sudden loss of muscle tone; **AND**
         ii. Symptoms have been present for at least three months; **AND**
         iii. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving); **OR**
      2. **Narcolepsy with excessive daytime sleepiness**; **AND**

i. Confirmation of diagnosis with a sleep study (including polysomnography and multiple sleep latency test); **AND**
ii. Symptoms have been present for at least three months; **AND**
iii. For members that are 18 years of age or older, treatment with ALL of the following has been ineffective, contraindicated, or not tolerated:
    a. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**
    b. Solriamfetol (Sunosi); **AND**
iv. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving)

II. **Calcium, magnesium, potassium, sodium oxybates (Xywav)** may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(F) above have been met; **AND**
B. Treatment with pitolisant (Wakix) has been ineffective, contraindicated, or not tolerated; **AND**
C. The member has an FDA labeled contraindication or intolerance to Xyrem; **OR**
1. The member is sensitive to sodium intake due to at least one of the following:
i. Heart failure
ii. Hypertension
iii. Impaired renal function; **AND**
2. Provider attestation member has tried and can no further reduce dietary salt intake via other means (i.e. salt restricted diet, others)

III. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) are considered investigational when used for all other conditions, including but not limited to:
A. Fibromyalgia
B. Idiopathic hypersomnia
C. Insomnia

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 in cataplexy attacks, improvement in ability to complete activities of daily living, improvement in ability to stay awake); **AND**
IV. Medication will not be used in combination with sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate);

Supporting Evidence

I. The American Academy of Sleep Medicine does not make any recommendations on preferring any agents over one another. Other guidance on the treatment of narcolepsy, recommends modafinil and armodafinil as first-line treatment options, stimulants as second-line options due to their adverse event profile, and sodium oxybate (Xyrem) as a third-line option due to its adverse event profile and requirement for a REMS program. Guidelines have not been updated to include calcium, magnesium, potassium, sodium oxybates (Xywav) at this time.

II. The REMS program only allows certified prescribers and pharmacies to dispense sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav). Prescribers must screen each patient for a history of alcohol or substance abuse, sleep-related breathing disorders, compromised respiratory function, depression or suicidality, and concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents.

III. Patients included in clinical trials had a history of narcolepsy for three months or greater and had chronic narcolepsy that was ongoing.

IV. For the treatment of narcolepsy with cataplexy, sodium oxybate (Xyrem) was evaluated in two randomized, double-blind, placebo-controlled, multicenter, parallel-group trials with a total of 191 patients. Over 80% of patients in these trials were on stimulants as background therapy. The primary efficacy endpoint was the median change from baseline in cataplexy attacks. The baseline number of cataplexy attacks was 20 and 23 for the placebo group and Xyrem 9g group, respectively. Trial one had a reduction of 16 attacks per week in the 9g treatment group and 4 attacks per week in the placebo group ($p=0.0016$). Trial two was a randomized withdrawal trial, and the placebo group had 21 attacks within two weeks, while the sodium oxybate (Xyrem) group had zero attacks within two weeks ($p<0.001$).

V. For the treatment of narcolepsy with excessive daytime sleepiness, sodium oxybate (Xyrem) was evaluated in two randomized, double-blind, placebo-controlled trials with a total of 450 patients. The primary efficacy endpoint for trial three was the change from baseline in the Epworth Sleepiness Scale (EPSS). Sodium oxybate (Xyrem) had a -2 and -5 median change from baseline at week 8 for the 6g and 9g treatment groups, and both groups had statistically greater reductions than the placebo group ($p<0.001$). The primary efficacy endpoint for trial four was the change from baseline in the Maintenance of Wakefulness Test (MWT). Sodium oxybate (Xyrem) had a mean change from baseline of 0.6 compared to -2.7 for placebo at week 8 ($p<0.001$).

VI. For the treatment of narcolepsy with cataplexy and excessive daytime sleepiness, sodium oxybate (Xyrem) was evaluated in one double-blind, placebo-controlled, randomized-withdrawal trial with 106 pediatric patients. Patients included in this study were seven to 16 years of age. The primary efficacy endpoints were the change in the frequency of cataplexy attacks and EPSS. The median change from baseline in the number of cataplexy attacks per week was 0.3 for sodium oxybate (Xyrem) compared to 12.7 for placebo ($p<0.0001$). The median change in the EPSS was zero for sodium oxybate (Xyrem) and three for placebo ($p=0.0004$).

VII. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) are contraindicated in patients taking sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate), and in patients with a succinic semialdehyde dehydrogenase deficiency. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) have serious side effects such as, central nervous system depression, abuse and misuse, respiratory

depression and sleep-disordered breathing, depression and suicidality, parasomnias, other psychiatric reactions (e.g. anxiety, hallucinations, psychosis), and elevates salt content (use with caution in patients that have heart failure, hypertension, or renal impairment).

VIII. Solriamfetol (Sunosi) is FDA-approved for the treatment of excessive daytime sleepiness associated with OSA and narcolepsy in adults.

IX. The efficacy and safety of solriamfetol (Sunosi) was established in two Phase 3, multi-center, double-blind, placebo-controlled, randomized trials of fair quality that evaluated the use of solriamfetol (Sunosi) in patients with excessive daytime sleepiness associated with OSA (n=459) or either type I or type II narcolepsy (n=231). Solriamfetol (Sunosi) demonstrated a change in MWT of 7.7 minutes from baseline, and a change in EPSS of -3.8 from baseline, at week 12 ($p<0.0001$) for both endpoints against placebo.

X. The efficacy and safety of calcium, magnesium, potassium, sodium oxybates (Xywav) was established in a Phase 3, multi-center, double-blind, placebo-controlled, randomized trial that evaluated the use of calcium, magnesium, potassium, sodium oxybates (Xywav) in patients with narcolepsy with cataplexy. Patients were all transitioned to the use of calcium, magnesium, potassium, sodium oxybates (Xywav) and optimized regardless of prior anti-cataplectic therapy or being naïve to treatment (n=201). Once optimized, efficacy was confirmed in the double blind, randomized withdrawal period (DB RWP) of this trial. During the DB RWP, outcomes showed a statistically significant worsening of cataplexy symptoms in patients on placebo when compared to those in the calcium, magnesium, potassium, sodium oxybates (Xywav) arm. The safety profile in pediatric patients with Xywav is expected to be similar to that of adult patients treated with Xywav and to that of pediatric patients treated with Xyrem.

XI. Pitolisant (Wakix) is FDA-approved for the treatment of cataplexy or excessive daytime sleepiness in adults with narcolepsy. The efficacy of pitolisant (Wakix) was established in three randomized controlled trials (HARMONY I, I bis, and III), and one open-label, single-arm, long term safety & efficacy trial, in a total of 468 patients with excessive daytime sleepiness. The use of pitolisant (Wakix) in the treatment of narcolepsy with cataplexy was established in HARMONY CTP with supporting evidence in HARMONY I.

- In HARMONY I (n = 95): The primary efficacy outcome was the change in the Epworth Sleepiness Scale (ESS) score after eight weeks. Pitolisant (Wakix) 35.6 mg demonstrated a statistically greater reduction in the ESS score compared to placebo (change of -3.1 points [-5.73, -0.46]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.
- HARMONY I bis (n = 165): The primary efficacy outcome was the change in the ESS score and compared pitolisant (Wakix) 17.4 mg vs. placebo. Pitolisant (Wakix) demonstrated statistically significant reduction in the ESS score compared to placebo (change of -2.12 points [-4.10, -0.14]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.
- HARMONY III (n = 102): Efficacy was a secondary endpoint and was measured by the change in the ESS score from baseline to one year. The mean decrease in ESS scores was -4.6 ± 0.59 (-5.82, -3.44).
- HARMONY CTP (n = 106): The primary efficacy outcome was the change in the average number of cataplexy attacks per week as documented by patient diaries.

The cataplexy ratio rate was 0.51 (0.44-0.60, p<0.0001) for pitolisant (Wakix) compared to placebo.

XII. There are no direct head-to-head studies comparing pitolisant (Wakix), solriamfetol (Sunosi), sodium oxybate (Xyrem), and calcium, magnesium, potassium, sodium oxybates (Xywav) to establish superior safety or efficacy of one product over the other. However, there are substantial cost differences between products despite not having any evidence of improved clinical efficacy or safety.

XIII. Outside of salt content, there is no clinical difference between sodium oxybate (Xyrem), and calcium, magnesium, potassium, sodium oxybates (Xywav). Sodium oxybate (Xyrem) is the plan's preferred product over calcium, magnesium, potassium, sodium oxybates (Xywav). Medical necessity of treating with Xywav over Xyrem is limited to members with comorbidities that place them at increased sensitivity to their daily sodium intake (e.g., heart failure, hypertension, impaired renal function). However, allowance of Xywav does not negate the need for the member to continue reduction of dietary salt intake and is not a means of a convenience option for those unwilling to reduce dietary salt intake.

Investigational or Not Medically Necessary Uses

I. Sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Fibromyalgia
   B. Idiopathic hypersomnia
   C. Insomnia

References

1. Xyrem [Prescribing Information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. October 2018.
2. SUNOSI [Prescribing Information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. October 2019.
3. Scammell TE. Treatment of narcolepsy in adults. UpToDate Inc. https://www.uptodate.com. (Accessed on April 27, 2020.)
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5. Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30(12):1705-11.
6. XyremREMS. Xyrem REMS Program. https://www.xyremrems.com/. Accessed April 27, 2020.
7. Xywav [Prescribing Information]. Palo Alto, CA: Jazz Pharmaceuticals, Inc. July 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated route of approval of Xywav to require trial of Wakix; updated language around trial of Xyrem prior to Xywav to require member has a FDA labeled contraindication or intolerance to Xyrem OR member is sensitive to sodium intake and provider attests dietary salt intake cannot be reduced further. Updates to supporting evidence.	04/2021
Removed need to trial and fail stimulates prior to use with Xyrem for Narcolepsy with excessive daytime sleepiness	01/2021
Update to add new to market Xywav with requirement to trial and fail or demonstrate contraindication or intolerance to Xyrem. Updated clinical trial background on Xywav.	10/2020

Transitioned from criteria to policy. Included information on: • Requirement to be prescribed by or in consultation with a sleep specialist, psychiatrist, or neurologist • Confirmation of diagnosis for narcolepsy • Requirement for chronic narcolepsy defined as three-month history • Requirement that member has functional impairment for activities of daily living • Updated requirements for trial and failure to one stimulant, and modafinil or armodafinil, and Sunosi	05/2020
Policy created	02/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP060

Description

Solriamfetol (Sunosi) is a dopamine and norepinephrine reuptake inhibitor (DNRI).
Pitolisant (Wakix) is a histamine-3 receptor antagonist/reverse agonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
solriamfetol (Sunosi)	75 mg tablets	Excessive sleepiness associated with either OSA or narcolepsy	60 tablets/30 days
	150 mg tablets		30 tablets/30 days
pitolisant (Wakix)	4.45 mg tablets	Excessive daytime sleepiness associated with narcolepsy or narcolepsy with cataplexy	14 tablets/7 days
	17.8 mg tablets		60 tablets/30 days

Initial Evaluation

I. Solriamfetol (Sunosi) and pitolisant (Wakix) 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 sleep specialist, psychiatrist, or neurologist; **AND**
   C. Use will **not** be in combination with sodium oxybate (Xyrem) or calcium, magnesium, potassium, sodium oxybates (Xywav); **AND**
   D. A diagnosis of one of the following:
      1. **Excessive daytime sleepiness; AND**
         i. **Narcolepsy without cataplexy; AND**
            a. Treatment with the following has been ineffective, contraindicated, or not tolerated:
               i. Stimulant (e.g., methylphenidate, amphetamine, etc.); **AND**
               ii. Modafinil or armodafinil; **AND**
               iii. If the request is for pitolisant (Wakix): Treatment with solriamfetol (Sunosi) has been ineffective, contraindicated, or not tolerated; **OR**

ii. **Obstructive sleep apnea (OSA)**; **AND**
    a. The request is for solriamfetol (Sunosi); **AND**
    b. The member has current or prior use of a primary OSA therapy (e.g., CPAP, mandibular advancement device or surgical intervention); **AND**
    c. Treatment with modafinil or armodafinil has been ineffective, contraindicated, or not tolerated

2. **Narcolepsy <u>with cataplexy</u>; AND**
    i. The request is for pitolisant (Wakix); **AND**
    ii. Confirmation of cataplexy defined as episodes of sudden loss of muscle tone; **AND**
    iii. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving).

II. Solriamfetol (Sunosi) and pitolisant (Wakix) are considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
    1. Excessive sleepiness associated with Parkinson's Disease or glioblastoma
    2. Shift work sleep disorder (SWSD)
    3. Attention-deficit/hyperactivity disorder (ADHD)
    4. Fatigue not related to narcolepsy or OSA

A. Solriamfetol (Sunosi)
    1. Major depressive disorder
    2. Steinert myotonic dystrophy syndrome

B. Pitolisant (Wakix)
    1. Excessive daytime sleepiness associated with obstructive sleep apnea

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 in cataplexy attacks, improvement in ability to complete activities of daily living, improvement in ability to stay awake)

Supporting Evidence

I. Solriamfetol (Sunosi) is FDA-approved for the treatment of excessive daytime sleepiness associated with OSA and narcolepsy in adults.
II. The efficacy and safety of solriamfetol (Sunosi) was established in two Phase 3, multi-center, double-blind, placebo-controlled, randomized trials of fair quality that evaluated the use of

solriamfetol (Sunosi) in patients with excessive daytime sleepiness associated with OSA (n=459) or either type I or type II narcolepsy (n=231).

III. In clinical trials, patients with OSA were required to be stable for greater than one month on primary OSA therapy (e.g. CPAP, mandibular advancement device, or surgical intervention) prior to use of solriamfetol (Sunosi).

IV. Stimulants such as amphetamine have not been studied in OSA.

V. Current guidelines for patients with excessive sleepiness associated with narcolepsy recommend modafinil or armodafinil as first-line treatment options. Stimulants are recommended as second line therapy.

VI. The current FDA maximum dose for solriamfetol (Sunosi) is 150 mg per day. Although doses of 300 mg were studied, the 300 mg dose was not approved due to tolerability concerns.

VII. Pitolisant (Wakix) is FDA-approved for the treatment of excessive daytime sleepiness in adults with narcolepsy. Pitolisant (Wakix) is the only agent for the treatment of narcolepsy that is not scheduled at this time. Pitolisant (Wakix) was studied in three randomized controlled trials, and one open-label, single-arm, long term safety & efficacy trial, in a total of 468 patients with EDS. HARMONY I and I bis included modafinil as an active comparator to pitolisant (Wakix).

VIII. HARMONY I (n = 95): The primary efficacy outcome was the change in the Epworth Sleepiness Scale (ESS) score after eight weeks. Pitolisant (Wakix) 35.6 mg demonstrated a statistically greater reduction in the ESS score compared to placebo (change of -3.1 points [-5.73, -0.46]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score. The ESS score has been commonly used in standard practice and was originally validated through a study in 1991.

IX. HARMONY I bis (n = 165): The primary efficacy outcome was the change in the ESS score and compared pitolisant (Wakix) 17.4 mg vs. placebo. Pitolisant (Wakix) demonstrated statistically significant reduction in the ESS score compared to placebo (change of -2.12 points [-4.10, -0.14]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.

X. HARMONY CTP (n = 106): The primary efficacy outcome was the change in the average number of cataplexy attacks per week as documented by patient diaries. The cataplexy ratio rate was 0.51 (0.44-0.60, $p<0.0001$) for pitolisant (Wakix) compared to placebo.

XI. HARMONY III (n = 102): Efficacy was a secondary endpoint and was measured by the change in the ESS score from baseline to one year. The mean decrease in ESS scores was -4.6 ± 0.59 (-5.82, -3.44).

XII. Pitolisant (Wakix) has a noted contraindication for patients with severe hepatic impairment, as well as a warnings and precaution for QTc prolongation. Common side effects were headache, insomnia, irritability, anxiety, and nausea. Less common side effects of musculoskeletal pain, upper respiratory tract infection, heart rate increase, hallucinations, abdominal pain, sleep disturbance, and decreased appetite were also noted.

XIII. There are no direct head-to-head studies comparing pitolisant (Wakix) and solriamfetol (Sunosi) to establish superior safety or efficacy of one product over the other; however, pitolisant (Wakix) is significantly more costly than solriamfetol (Sunosi) despite not having any evidence of improved clinical efficacy or safety.

XIV. The use of pitolisant (Wakix) in the treatment of narcolepsy with cataplexy was established in HARMONY CTP with supporting evidence in HARMONY I. Primary outcomes of HARMONY CTP

evaluated weekly rate of cataplexy (WRC) while HARMONY I, Daily Rate of Cataplexy (DRC) was evaluated as a secondary endpoint to support the use in cataplexy. Secondary outcomes of DRC in HARMONY I showed a significant improvement DRC.

Investigational or Not Medically Necessary Uses

I. Solriamfetol (Sunosi) and pitolisant (Wakix) currently have no evidence supporting efficacy or safety in the following conditions:
   A. Shift work sleep disorder (SWSD)
   B. Attention-deficit/hyperactivity disorder (ADHD)
   C. Fatigue not related to narcolepsy or OSA
   D. Excessive sleepiness associated with Parkinson's Disease
II. Solriamfetol (Sunosi) has not been studied in the following indications:
   A. Major depressive disorder
   B. Steinert myotonic dystrophy syndrome
III. Pitolisant (Wakix) is currently being studied for use in excessive daytime sleepiness in patients with obstructive sleep apnea, however, there is currently a lack of sufficient safety and efficacy information to support use in this condition.

References

1. SUNOSI (solriamfetol) tablets, for oral use. Prescribing Information. Palo Alto, CA. Jazz
2. Thorpy M, Shapiro C, Mayer G, et al. A Randomized Study of Solriamfetol for Excessive Sleepiness in Narcolepsy. Annals of Neurology. 2019; 85:359-370.
3. Schweitzer PK, Rosenberg R, Zammit GK, Gotfried M, Chen D, Carter LP et al. Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3): A Randomized Controlled Trial. Am J Respir Crit Care Med. 2018 Dec 6. doi: 10.1164/rccm.201806-1100OC.
4. Wakix (pitolisant) [Prescribing Information]. Harmony Biosciences, LLC: Plymouth Meeting, PA. August 2019.
5. Wakix (pitolisant) [Formulary Dossier]. Harmony Biosciences, LLC: Plymouth Meeting, PA. September 2019.
6. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomized trial. Lancet Neurol. 2013; 12: 1068–75.
7. Dauvilliers Y, Arnulf I, Szakacs Z, et al. Long-term use of pitolisant to treat patients with narcolepsy: Harmony III Study. Sleep. 2019.
8. Szakacs Z, Dauvilliers Y, Mikhaylov V, et al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomized, double-blind, placebo-controlled trial. Lancet Neurol. 2017; 16: 200–07.
9. Dauvilliers Y, Bassetti C, Lammers GJ, et al. Pitolisant versus placebo or modafinil in patients with narcolepsy: a double-blind, randomised trial. Lancet Neurol. 2013;12(11):1068-1075.
1. Zoltan Szakacs, Yves Dauvilliers, et. al. Safety and efficacy of pitolisant on cataplexy in patients with narcolepsy: a randomised, double-blind, placebo-controlled trial (HARMONY CTP). Lancet Neurol 2017; 16: 200–07

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to include new indication for Wakix use in patients with narcolepsy with cataplexy.	12/2020
Updated policy to require trial and failure of solriamfetol (Sunosi) prior to approval of pitolisant (Wakix) for narcolepsy.	06/2020

Addition of pitolisant (Wakix) information for coverage including: experimental/investigational, coverage for narcolepsy, quantity limits, and evidence base.	09/2019
New policy for solriamfetol (Sunosi).	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP153

Split Fill Management*

Description

Sonidegib (Odomzo) is an orally administered Hedgehog pathway inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
sonidegib (Odomzo)	200 mg capsule	Basal cell carcinoma of the skin, locally advanced	30 capsules/30 days

Initial Evaluation

I. Sonidegib (Odomzo) 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. Sonidegib (Odomzo) will not be used in combination with any other oncologic medication; **AND**
   D. A diagnosis of **locally advanced basal cell carcinoma (BCC)** when the following are met:
      1. Basal cell carcinoma has recurred or progressed after radiation or surgery, unless both are contraindicated; **AND**
      2. The member has not progressed on any other oncologic medication (e.g., has not progressed on vismodegib [Erivedge]); **AND**
      3. Provider attestation that the member, either male or female, has been counseled on the teratogenicity and embryo-fetal toxicity risks with sonidegib (Odomzo).

II. Sonidegib (Odomzo) is considered investigational when used for all other conditions, including but not limited to:
   A. Metastatic basal cell carcinoma
   B. Acute leukemia
   C. Breast cancer
   D. Medulloblastoma
   E. Multiple myeloma
   F. Myelofibrosis

G. Prostate cancer
H. Breast cancer
I. Ovarian cancer
J. Graft versus host disease
K. Pancreatic cancer
L. Lung cancer
M. Hepatocellular carcinoma

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. Sonidegib (Odomzo) is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
IV. A diagnosis of **locally advanced basal cell carcinoma**; **AND**
   A. Clinical response to therapy, such as improvement or stabilization of disease, or decrease or stabilization of tumor size or spread; **AND**
   B. Provider attestation that the member, either male or female, has been counseled on the teratogenicity and embryo-fetal toxicity risks with sonidegib (Odomzo).

Supporting Evidence

I. The safety and efficacy of sonidegib (Odomzo) was evaluated in a single, double-blind, single-drug trial. Those included had a diagnosis of locally advanced basal cell carcinoma (laBCC), and 144 adult subjects were randomized (2:1) to receive sonidegib (Odomzo) 800 mg or 200 mg daily. To be included in the trial, subjects were required to have lesions for which radiotherapy was contraindicated or inappropriate (e.g., limitations due to tumor location), that had recurred after radiotherapy, had unresectable disease in which surgical resection would result in substantial deformity, or that had recurred after prior surgical resection. The primary outcome was objective response rate (ORR) which was determined by a blinded central review committee according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). A secondary measure was duration of response (DoR). The ORR was 56% (CI 43-68), and consisted of three (5%) complete responders, and 34 (52%) partial responders. The median duration of response was 26.1%; however, due to the single-drug nature of the trial, these results should be interpreted with caution.
II. There were 128 subjects randomized to sonidegib (Odomzo) 800 mg daily. There was a lack of further benefit over the 200 mg dose relative to the safety profile.
III. Sonidegib (Odomzo) carries a black box warning for embryo-fetal death or severe birth defects when administered to a pregnant woman. It is noted in the medication label that pregnancy be ruled out prior to initiating therapy. Those of reproductive potential should use contraception during treatment and for at least 20 months following the last dose. Males carry of risk of

exposure through semen; thus, the package label recommends use of condoms with female partners during medication exposure and for at least eight months after the last dose.

IV. Vismodegib (Erivedge) is FDA-approved for adults with metastatic and locally advanced basal cell carcinoma. Erivedge has an overlapping indication with sonidegib (Odomzo), and if disease progression has occurred on or after one of these therapies, there is currently insufficient evidence regarding safety and/or efficacy of the other. One published piece of literature evaluated sonidegib (Odomzo) in those that were resistant to vismodegib (Erivedge); however, this trial included only nine subjects all of which showed no response to sonidegib (Odomzo) or were not evaluable for safety and/or efficacy. Available evidence disfavors use of sequential Hedgehog pathway inhibitors.

Investigational or Not Medically Necessary Uses

I. There is currently insufficient evidence to support safety and/or efficacy of sonidegib (Odomzo) in the following settings:
   A. Metastatic basal cell carcinoma
   B. Acute leukemia
   C. Breast cancer
   D. Medulloblastoma
   E. Multiple myeloma
   F. Myelofibrosis
   G. Prostate cancer
   H. Breast cancer
   I. Ovarian cancer
   J. Graft versus host disease
   K. Pancreatic cancer
   L. Lung cancer
   M. Hepatocellular 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

1. Odomzo [Package Insert]. Cranbury, NJ. Sun Pharmaceutical Industries, Inc. 2017.
2. Burness CB, Scott LJ. Sonidegib: A Review in Locally Advanced Basal Cell Carcinoma. Target Oncol. 2016;11(2):239-46.
3. Danial C., Sarin K. Oro A., et al. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. Clin Cancer Res. 2016;22: 1325-1329.

Policy Implementation/Update:

Date Created	October 2015
Date Effective	November 2015
Last Updated	November 2019
Last Reviewed	November 2019

Action and Summary of Changes	Date
Prior authorization transitioned to policy. Addition of age edit, clarification and addition of requirements regarding previous therapies and use of sonidegib (Odomzo) monotherapy. Renewal duration increased for six to 12 months.	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP061

Description
AlphaNine SD, BeneFix, Ixinity, Mononine, and Rixubis are standard 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 (prophylaxis); 6 months (on-demand)

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
AlphaNine SD, coagulation factor IX (human)	500, 1000, 1500 IU	**Control and prevention of bleeding episodes:** Up to 100 IU/kg; Repeat dose after 12 hours as needed for three to five days. Major hemorrhages may require treatment for up to ten days	**Control and prevention of bleeding episodes:** Up to the number of doses requested every 28 days
BeneFIX, coagulation factor IX (recombinant)	250, 500, 1000, 2000, 3000 IU	**Control and prevention of bleeding episodes and perioperative management*:** Up to 100 IU/dL; Consider repeat dose after 12 to 24 hours as needed for seven to ten days	**Control and prevention of bleeding episodes and perioperative management:** Up to the number of doses requested every 28 days
Ixinity, coagulation factor IX (recombinant)	250, 500, 1000 IU	**Control and prevention of bleeding episodes δ:** Up to 100 IU/dL, doses every 12 to 24 hours on days two through 14 until healing is achieved **Perioperative Management δ:** • *Minor*: Up to 80 IU/dL pre- and post-operative; Repeat every 24 hours on days one through five, depending on type of procedure • *Major*: Up to 80 IU/dL pre-op; Post-op: Up to 60 IU, dosed every 8 to 24 hours on days one through three, or up to 50 IU/dL dosed every 8 to 24 hours on days four through six, or up to 40 IU/dL dosed every 8 to 24 hours on days seven through 14	**Control and prevention of bleeding episodes:** Up to the number of doses requested every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
MonoNine, coagulation	500, 1000 IU	**Control and prevention of bleeding episodes and perioperative management:**	**Control and prevention of bleeding episodes and perioperative management:**

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
factor IX (human)		• Minor spontaneous hemorrhage prophylaxis: Up to 30 IU/kg for one dose. Repeat in 24 hours if necessary • Major trauma or surgery: Up to 75 IU/kg, dosed every 18 to 30 hours depending on T ½ and measured factor IX levels. Continue for up to ten days depending on nature of insult	Up to the number of doses requested every 28 days
Profilnine SD, factor IX complex	500, 1000, 1500 IU	**Control and prevention of bleeding episodes€:** Up to 50 IU/dL for a single dose. Daily infusions are generally required **Perioperative Management:** Up to 50 IU/kg every 16 to 24 hours for seven to ten days until healing is achieved.	**Control and prevention of bleeding episodes:** Up to the number of doses requested every 28 days **Perioperative Management:** Up to the number of doses requested every 28 days
Rixubis, coagulation factor IX (recombinant)	250, 500, 1000, 2000, 3000 IU	**Control and prevention of bleeding episodes ν:** Up to 100 IU/dL every 12 to 24 hours for seven to ten days, until bleeding stops and healing is achieved **Routine Prophylaxis:** • < 12 years: Up to 80 IU/kg twice weekly • ≥ 12 years: Up to 60 IU/kg twice weekly **Perioperative Management ν:** Up to 100 IU/dL every 8 to 24 hours for seven to ten days, until bleeding stops and healing is achieved	**Control and prevention of bleeding episodes:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • < 12 years: Up to 672 IU/kg every 28 days • ≥ 12 years: Up to 504 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested every 28 days

‡Allows for +5% to account for assay and vial availability

* One unit per kilogram body weight increases the circulating Factor IX level by 1% (IU/dL). Adult: Number of Factor IX IU required = body wt (kg) x Desired increase in Plasma Factor IX (%) x 1.3 IU/kg; Pediatric (<15 years): Number of Factor IX IU required = body wt (kg) x Desired increase in Plasma Factor IX (%) x 1.4 IU/kg

δ One IU per kg body weight increases the circulating activity of factor IX by 0.98 IU/dL

Initial dose: required factor IX units (IU) = body weight (kg) x desired factor IX increase (% of normal IU/dL) x reciprocal of observed recovery (IU/kg per IU/dL)

Maintenance dose: Depends upon the type of bleed or surgery, clinical response, and the severity of the underlying factor IX deficiency

€ One unit per kilogram body weight increases the circulating Factor IX level by 1% (IU/dL). Number of Factor IX IU required = body wt (kg) x Desired increase in Plasma Factor IX(percent) x 1.0 IU/kg

ν One IU per kilogram body weight increases the circulating activity of factor IX by 0.7 IU/dL for patients < 12 years of age and 0.9 IU/dL for patients ≥ 12 years of age. Initial dose = body wt (kg) x desired factor IX increase (percent of normal or IU/dL) x reciprocal of observed recovery (IU/kg per IU/dL)

Initial Evaluation

I. Standard 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)** the following are met:
      1. Treatment is prescribed by or in consultation with a hematologist; **AND**
      2. Use of standard half-life factor IX is planned for one of the following indications:
         i. On-demand treatment and control of bleeding episodes **AND** the number of factor IX units requested does not exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
         ii. Perioperative management of bleeding; **OR**
         iii. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
            a. Member has severe hemophilia B (defined as factor IX level of <1%); **OR**
            b. Member has had more than one documented episode of spontaneous bleeding; **AND**
      3. 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**
      4. 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. Standard 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 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 standard half-life factor IX products in any other condition.

References

1. AlphaNine SD [package insert]. Los Angeles, CA; Grifols Biologicals Inc.; January 2013.
2. BeneFIX [package insert]. Philadelphia, PA; Wyeth Biopharma; June 2017.
3. Ixinity [package insert]. Winnipeg, Manitoba, Canada. Cangene Corporation; December 2018.
4. Mononine [package insert]. Kankakee, IL; CSL Behring LLC; April 2016.
5. Rixubis [package insert]. Westlake Village, CA; Baxalta US Inc.; May 2018
1. National Hemophilia Foundation. Hemophilia A. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed July 5, 2019.
2. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
3. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	**Date**
New policy created for standard half-life factor products	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP062

Description

Advate, Afstyla, Hemofil M, Kogenate FS, Koate DVI, Kovaltry, Novoeight, Nuwiq, Recombinate, and Xyntha are standard half-life factor VIII products for the treatment and prevention of bleeding in patients with hemophilia A.

Length of Authorization

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

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
Advate, antihemophilic factor (recombinant)	250, 500, 1000, 1500, 2000, 3000, 4000 IU	**On-demand Treatment:** Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:** • Up to 40 IU/kg every other day (3 to 4 times weekly) or every third day **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 50 IU/kg within one hour before surgery; Repeat every 12 to 24 hours as needed until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 60 IU/kg preoperative to achieve 100% activity; Repeat every 8 to 24 (every 6 to 24 hours for patients under the age of six) hours to keep factor VIII activity in desired range until healing is complete	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** Up to 672 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Afstyla, antihemophilic factor	250, 500, 1000, 1500,	**On-demand Treatment:** Up to 50 IU/kg every 8 to 24 hours until bleeding is resolve	**On-demand Treatment:** Up to the number of doses requested every 28

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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.

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
(recombinant), single chain	2000, 2500, 3000 IU	**Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg two to three times per week • <12 years: Up to 50 IU/kg two to three times per week. More frequent or higher dosing may be required to account for the higher clearance in this age group. **Perioperative Management:** • *Minor* (e.g. tooth extraction): Up to 30 IU/kg every 24 hours for at least one day until healing is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 50 IU/kg every 8 to 24 hours until adequate wound healing, then continue therapy for at least another seven days	**Routine Prophylaxis:** • ≥12 years: Up to 630 IU/kg every 28 days • <12 years: Up to 630 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Hemofil M, antihemophilic factor (human)	250, 500, 1000, 1700 IU	**On-demand Treatment** δ**:** Up to 100 IU/dL; Repeat every 8 to 24 hours until the bleeding threat is resolved **Perioperative Management** δ**:** • *Minor* (e.g. tooth extraction): A single infusion of up to 80 IU/dL plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat dose every 8 to 24 hours depending on state of healing	**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
Koate DVI, antihemophilic factor (human)	250, 500, 1000 IU	**On-demand Treatment** δ**:** Up to 100 IU/dL every 8 to 12 hours until bleeding threat is resolved **Perioperative Management** δ**:** For major surgical procedures, the factor VIII level should be raised to	**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

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit[‡]
		approximately 100% by giving a preoperative dose of 50 IU/kg. Repeat infusions may be necessary every 6 to 12 hours initially, and for a total of 10 to 14 days until healing is complete. The intensity of factor replacement therapy required depends on the type of surgery and postoperative regimen employed. For minor surgical procedures, less intensive treatment schedules may provide adequate homeostasis.	
Kogenate FS, antihemophilic factor (recombinant), formulated with sucrose	250, 500, 1000, 2000, 3000 IU	**On-demand Treatment** [δ]**:** Up to 50 IU/kg every 8 to 12 hours until bleeding is resolved **Routine Prophylaxis:** • Adults: Up to 25 IU/kg three times per week • Children: Up to 25 IU/kg every other day **Perioperative Management** [δ]**:** • *Minor* (e.g. tooth extraction): Up to 30 IU/kg every 12 to 24 hours until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 50 IU/kg preoperative to achieve 100% activity; Repeat every 6 to 12 hours to keep factor VIII activity in desired range until healing is complete	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • Adults: Up to 315 IU/kg every 28 days • Children: Up to 368 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Kovaltry, antihemophilic factor (recombinant)	250, 500, 1000, 2000, 3000 IU	**On-demand Treatment** [δ]**:** Up to 100 IU/dL every 8 to 24 hours until bleeding is resolved **Routine Prophylaxis:** • ≥12 years: Up to 40 IU/kg two or three times per week • ≤ 12 years: Up to 50 IU/kg twice weekly, three times weekly, or every other day	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 504 IU/kg every 28 days • ≤12 years: Up to 735 IU/kg every 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		Perioperative Management δ**:** • *Minor* (e.g. tooth extraction): Up to 60 IU/dL every 24 hours until healing is achieved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until adequate wound healing is complete, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL)	**Perioperative Management:** Up to the number of doses requested for 28 days
Novoeight, antihemophilic factor (recombinant)	250, 500, 1000, 2000, 3000 IU	**On-demand Treatment** δ**:** Up to 100 IU/dL every 8 to 24 hours until resolution of bleed (approximately seven to ten days) **Routine Prophylaxis:** • ≥12 years: Up to 50 IU/kg three times per week or up to 40 IU/kg every other day • ≤ 12 years: Up to 60 IU/kg three times weekly or up to 50 IU/kg every other day **Perioperative Management** δ**:** • *Minor* (e.g. tooth extraction): Up to 60 IU/dL every 12 to 24 hours until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until adequate wound healing is complete, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL)	**On-demand Treatment:** Up to the number of doses requested every 28 days **Routine Prophylaxis:** • ≥12 years: Up to 630 IU/kg every 28 days • ≤12 years: Up to 756 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Nuwiq, antihemophilic factor (recombinant)	250, 500, 1000, 2000, 2500, 3000, 4000 IU	**On-demand Treatment** δ**:** Up to 100 IU/dL every 8 to 24 hours until bleeding risk is resolved	**On-demand Treatment:** Up to the number of doses requested every 28 days

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		Routine Prophylaxis: • ≥12 years: Up to 40 IU/kg every other day • ≤ 12 years: Up to 50 IU/kg every other day or three times per week **Perioperative Management**[δ]**:** • *Minor* (e.g. tooth extraction): Up to 40 IU/dL every 12 to 24 hours until bleeding is resolved • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until adequate wound healing, then continue therapy for at least another seven days to maintain factor VIII activity of 30-60% (IU/dL)	**Routine Prophylaxis:** • ≥12 years: Up to 588 IU/kg every 28 days • ≤12 years: Up to 735 IU/kg every 28 days **Perioperative Management:** Up to the number of doses requested for 28 days
Recombinate, antihemophilic factor (recombinant)	250, 500, 1000, 1500, 2000 IU	**On-demand Treatment**[δ]**:** Up to 100 IU/dL every 8 to 24 hours until bleeding threat is resolved **Perioperative Management**[δ]**:** • *Minor* (e.g. tooth extraction): Up to 80 IU/dL as a single infusion plus oral antifibrinolytic therapy within one hour is sufficient in approximately 70% of cases • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours depending on state of healing	**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
Xyntha, antihemophilic factor (recombinant)	250, 500, 1000, 2000 IU	**On-demand Treatment**[δ]**:** Up to 100 IU/dL every 8 to 24 hours until bleeding threat is resolved **Perioperative Management**[δ]**:** • *Minor* (e.g. tooth extraction): Up to 60 IU/dL for 3 to 4 days or until adequate hemostasis is	**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

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit‡
		achieved. For tooth extraction, a single infusion plus oral antifibrinolytic therapy within 1 hour may be sufficient • *Major* (e.g. intracranial, intra-abdominal, or intrathoracic, or joint- replacement): Up to 100 IU/dL pre- and post-operative; Repeat every 8 to 24 hours until threat is resolved, or in the case of surgery, until adequate local hemostasis and wound healing are achieved	

‡Allows for +5% to account for assay and vial availability

δ Dose (IU/kg) = Desired factor VIII rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL); *Expected Factor VIII rise (% of normal) = 2 x administered IU/body weight (kg)*

Initial Evaluation

I. Standard 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 standard 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**
      3. 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**
      4. 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. Standard 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 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 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:
   - 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 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 standard half-life factor VIII products in any other condition.

References

1. Advate [package insert]. Westlake Village, CA; Baxalta US Inc. May 2018.
2. Afstyla [package insert]. Kankakee, IL; CSL Behring, LLC; April 2017.
3. Hemofil M [package insert]. Westlake Village, CA; Baxalta US Inc. June 2018.
4. Koate DVI [package insert]. Research Triangle Park, NC; Grifols Therapeutics Inc.; August 2012.
5. Kogenate FS [package insert]. Whippany, NJ. Bayer HealthCare LLC; May 2016.
6. Novoeight [package insert]. Bagsvaerd, Denmark; Novo Nordisk; November 2018.
7. NUWIQ [package insert]. Elersvagen, Sweden; Octapharma AB; July 2017.
8. Recombinate [package insert]. Westlake Village, CA; Baxalta US Inc. June 2018.
9. Kovaltry [package insert]. Whippany, NJ; Bayer HealthCare LLC; March 2016
10. National Hemophilia Foundation. Hemophilia A. Available from: https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders/Hemophilia-A. Accessed July 5, 2019.
11. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
12. UpToDate, Inc. Hemophilia A and B: Routine management including prophylaxis. UpToDate [database online]. Last updated February 11, 2019.

Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	Date
New policy created for standard half-life factor products	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP063

Description

Stiripentol (Diacomit) is an orally administered anticonvulsant with direct effects mediated through the GABAa receptor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
stiripentol (Diacomit)	250 mg capsules	Dravet syndrome	180 capsules/30 days	179386
	500 mg capsules		180 capsules/30 days	179387
	250 mg powder for oral suspension		180 packets/30 days	179389
	500 mg powder for oral suspension		180 packets/30 days	179390

Initial Evaluation

I. Stiripentol (Diacomit) 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 **Dravet Syndrome** when the following are met:
      i. History of use of clobazam (Onfi); **AND**
      ii. History of use of valproate (Depakote) unless documentation of contraindication or intolerance; **AND**
      iii. Use in combination with clobazam (Onfi); **AND**
      iv. Use in combination with valproate (Depakote) unless documentation of contraindication or intolerance;

II. Stiripentol (Diacomit) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Epileptic encephalopathies associated with SCN1A mutations
   B. Other non-FDA approve seizure disorder
   C. Primary Hyperoxaluria
   D. Stiripentol (Diacomit) as monotherapy
   E. Use in combination with cannabidiol (Epidiolex)

Renewal Evaluation

I. Documentation of treatment benefit with use of stiripentol (Diacomit) indicated by reduction in generalized tonic-clonic or clonic seizures; **AND**
II. Ongoing use of clobazam (Onfi) and valproate (Depakote) unless documentation of contraindication or intolerance

Supporting Evidence

I. Stiripentol (Diacomit) was studied in two Phase III, multicenter, randomized, placebo-controlled trials with on-going use of clobazam and valproate and demonstrated lack of disease management on clobazam and valproate without stiripentol (Diacomit).
II. The use of stiripentol (Diacomit) has not been studied as monotherapy or in combination with anticonvulsant regimens that do not contain clobazam and valproate.

Investigational or Not Medically Necessary Uses

I. Epileptic encephalopathies associated with SCN1A mutations
    A. Ongoing clinical trials in this setting
II. Other non-FDA approve seizure disorder
    A. Ongoing clinical trials in this setting
III. Primary Hyperoxaluria
    A. Ongoing clinical trials in this setting
IV. Stiripentol (Diacomit) as monotherapy
    A. Stiripentol (Diacomit) has not been studied as monotherapy in Dravet syndrome. Package label also notes lack of clinical data to support the use as monotherapy
V. Use in combination with cannabidiol (Epidiolex)
    A. Stiripentol (Diacomit) has not been studied as combination use with cannabidiol.

References

1. Diacomit [Prescribing Information]. Redwood City, CA: Biocodex, Gentilly, France. August 2018.
2. Stiripentol (Diacomit): For Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Apr. 3, RESULTS. Available from: https://www.ncbi.nlm.nih.gov/books/NBK349320/
3. Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet. 2000 Nov 11;356(9242):1638–1642.

Policy Implementation/Update:

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

Action and Summary of Changes	Date

Policy Type: PA/SP Pharmacy Coverage Policy: UMP154

Split Fill Management*

Description

Sunitinib (Sutent) is an orally administered tyrosine kinase inhibitor targeting multiple receptors

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
sunitinib (Sutent)	12.5 mg capsule	Gastrointestinal stromal tumor, after disease progression on or intolerance to imatinib; Neuroendocrine pancreatic tumor, locally advanced or metastatic; Renal cell carcinoma, adjuvant following nephrectomy in patients at high risk of recurrence; Renal cell carcinoma, advanced	28 capsules/42 days for all indications except neuroendocrine pancreatic tumor 28 capsules/28 days for pancreatic neuroendocrine tumor
	25 mg capsule		
	37.5 mg capsule		
	50 mg capsule		

Initial Evaluation

I. Sunitinib (Sutent) 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. Sunitinib (Sutent) will <u>not</u> be used in combination with other oncolytic medications (i.e., will be used as monotherapy); **AND**
   D. A diagnosis of one of the following:
      1. **Gastrointestinal stromal tumor (GIST)**; **AND**
         i. The member has tried and failed imatinib (Gleevec) due to progression of disease or intolerability; **OR**
      2. **Pancreatic neuroendocrine tumor (pNET)**; **AND**

i. The member has unresectable, locally advanced (stage III), or metastatic (stage IV) disease; **OR**

3. Renal cell carcinoma (RCC); AND

i. Disease is advanced (stage III) or metastatic (stage IV)

II. Sunitinib (Sutent) is considered not medically necessary when criteria above are not met and/or when used for:

A. Adjuvant treatment for renal cell carcinoma

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

A. Angiosarcoma
B. Breast cancer
C. Colorectal cancer
D. Central nervous system cancers
E. Neuroendocrine tumors other than those of pancreatic origin
F. Gastric cancer
G. Lung cancer
H. Soft tissue sarcoma
I. Thyroid carcinoma
J. Osteosarcoma
K. Cholangiocarcinoma
L. Adenoid cystic carcinoma

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. Sunitinib (Sutent) is prescribed by, or in consultation with an oncologist; **AND**
IV. Clinical documentation of response to treatment, such as stabilization of disease or decrease in tumor size or spread**.**

Supporting Evidence

I. Sunitinib (Sutent) was evaluated for gastrointestinal stromal tumor (GIST) in a randomized, double-blind, placebo-controlled trial in adults that had previously progressed on imatinib (Gleevec) or were intolerant to therapy. Outcomes included time-to-tumor progression (TTP), progression-free survival (PFS), and objective response rate (ORR) and were statistically significant in favor of sunitinib (Sutent). At the time of disease progression, treatment was unblinded and those originally on placebo were allowed to crossover to open-label sunitinib

(Sutent). At the final analysis overall survival (OS) was not statistically different between the treatment arms.

II. A second study of sunitinib (Sutent) for GIST was conducted as an open-label, single-arm trial in adults that had previously progressed on, or had intolerance to, imatinib (Gleevec). Five of the 55 subjects included had a partial response to therapy (9.1%, CI 3-20%).

III. For renal cell carcinoma (RCC), sunitinib (Sutent) was evaluated in a randomized trial versus IFN-a in treatment-naïve RCC. The outcomes evaluated were PFS and ORR, both of which were statistically significant in favor of sunitinib (Sutent).

IV. In the adjuvant treatment setting for RCC, sunitinib (Sutent) was evaluated in a randomized, double-blind, placebo-controlled trial adults with high risk of recurrence following nephrectomy. Subjects were required to have clear cell histology. Subjects were treated for nine cycles maximum. The primary outcome was disease-free survival (DFS) which was statistically significant in favor of sunitinib (Sutent). Overall survival was a secondary endpoint; however, data was not mature at time of analysis and the medication is associated with a significant safety profile.

V. For pancreatic neuroendocrine tumors (pNET), sunitinib (Sutent) was evaluated in a randomized, double-blind, placebo-controlled trial in adults with unresectable disease. The Independent Data Monitoring Committee was terminated early which may have led to an overestimate of the PFS. The outcomes of PFS and ORR were statistically significant in favor of sunitinib (Sutent); however, OS data was not mature at time of analysis. In a follow up analysis at five years a statistical significant different in OS was not demonstrated; however, this may have been confounded by crossover.

VI. Sunitinib has not been evaluated for safety and/or efficacy in pediatric patients. The dosing for sunitinib (Sutent) outside of pancreatic neuroendocrine tumors, is four weeks on two weeks off. A maximum of nine 6-week cycles of therapy for adjuvant RCC has been evaluated and FDA-approved for adjuvant RCC. This is approximately 13 months of therapy total.

Investigational or Not Medically Necessary Uses

I. Adjuvant treatment for renal cell carcinoma
   A. Following 1 year of treatment with sunitinib (Sutent), patients experienced a 1 year improvement in disease free survival compared to placebo; however, there was no improvement in overall survival. Sunitinib (Sutent) is associated with significant toxicity and patients experienced a decline in quality of life while on treatment compared to placebo. NCCN has listed adjuvant sunitinib (Sutent) as a Category 3 recommendation, as there is still no clear role for adjuvant systemic therapy in this setting. Observation or clinical trials are still considered the standard of care given the lack of clinically meaningful supportive data for systemic therapy in the adjuvant setting.

II. Sunitinib (Sutent) has not been sufficiently studied for safety or efficacy and/or is currently being evaluated in clinical trials for the following indications:
   A. Angiosarcoma
   B. Breast cancer
   C. Colorectal cancer
   D. Central nervous system cancers

E. Neuroendocrine tumors other than those of pancreatic origin
F. Gastric cancer
G. Lung cancer
H. Soft tissue sarcoma
I. Thyroid carcinoma
J. Osteosarcoma
K. Cholangiocarcinoma
L. Adenoid cystic 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

1. Sutent [Prescribing Information]. New York, NY. Pfizer Labs. May 2019.
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3. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007;356(2):115-24.
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Policy Implementation/Update:

Date Created	March 2012
Date Effective	March 2012
Last Updated	November 2019
Last Reviewed	01/2018, 11/2019

Action and Summary of Changes	**Date**
Prior authorization criteria transitioned to policy format. Addition of age edit, monotherapy requirements, and clarification of renal cell carcinoma uses.	11/2019
Review of adjuvant RCC setting	01/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP064

Description
Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) are orally administered transthyretin stabilizers.

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

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
tafamidis meglumine (Vyndaqel)	20 mg capsules	Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis	120 capsules/30 days	206608
tafamidis (Vyndamax)	61 mg capsules		30 capsules/30 days	206614

Initial Evaluation

I. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) may be considered medically necessary when the following criteria below are met:
   A. Member 18 years or older; **AND**
   B. Medication is prescribed by or in consultation with a neurologist or cardiologist; **AND**
   C. Tafamidis meglumine (Vyndaqel) or tafamidis (Vyndamax) will not be used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [i.e. inotersen (Tegsedi), patisiran (Onpattro)]; **AND**
   D. A diagnosis of **cardiomyopathy of wild type (ATTRwt-CM) or hereditary transthyretin-mediated amyloidosis (hATTR-CM)** when the following are met:
      1. Confirmed transthyretin-mediated amyloidosis by one of the following:
         i. Documented presence of amyloid deposit by biopsy; **OR**
         ii. Presence of transthyretin precursor protein confirmed by scintigraphy (i.e. radiotracer 99m technetium pyrophosphate (99mTc-PYP))

      AND
      2. History of heart failure; **AND**
      3. Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm; **AND**
      4. New York Heart Association (NYHA) functional class I-III; **AND**
      5. No prior history of liver or heart transplantation

II. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) is considered <u>not medically necessary</u> when used for all other conditions, including but <u>not limited to</u>:

A. Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in members with NYHA functional class IV

III. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) is considered investigational when used for all other conditions, including but not limited to:
   A. Polyneuropathy of hereditary transthyretin-mediated amyloidosis (ATTR-PN) or familial amyloid polyneuropathy (FAP)
   B. Primary (light chain) amyloidosis

Renewal Evaluation

I. Member has previously received treatment with tafamidis meglumine (Vyndaqel) or tafamidis (Vyndamax); **AND**
II. Documentation that the patient has experienced a positive clinical response therapy (e.g., reduced cardiovascular hospitalizations, improved quality of life, slowing of disease progression, etc.); **AND**
III. No prior history of liver or heart transplantation; **AND**
IV. New York Heart Association (NYHA) functional class I-III; **AND**
V. Tafamidis meglumine (Vyndaqel) or tafamidis (Vyndamax) will not be used in combination with other agents for the treatment of transthyretin-mediated amyloidosis [i.e. inotersen (Tegsedi), patisiran (Onpattro)].

Supporting Evidence

I. Tafamidis meglumine (Vyndaqel) and tafamidis (Vyndamax) are transthyretin stabilizers FDA approved for the treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization.
II. Vyndamax (tafamidis) was developed for patient convenience. Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) are not substitutable on a per-mg basis.
III. Tafamidis meglumine (Vyndaqel) was studied in a phase 3, multicenter, international, randomized, double-blind, placebo-controlled study in 441 patients with wild type or hereditary ATTR-CM (ATTR-ACT trial). The trial met its primary endpoint, demonstrating a significant reduction ($p=0.0006$) in all-cause mortality and frequency of cardiovascular-related hospitalizations ($p<0.0001$) in the pre-specified pooled tafamidis meglumine (Vyndaqel) 20-mg and 80-mg groups versus placebo at 30 months. Tafamidis meglumine (Vyndaqel) also showed a lower rate of decline in distance for the 6-minute walk test and lower rate of decline in the Kansas City Cardiomyopathy Questionnaire Overall Summary score (KCCQ-OS). Of note, subgroup analysis of patients identified as NYHA class III at baseline did not show a reduction in all-cause mortality or cardiovascular related hospitalizations. In the NYHA class III patients, cardiovascular related hospitalizations were actually higher among patients receiving tafamidis meglumine (Vyndaqel) than those receiving placebo.
IV. NYHA Classification - The Stages of Heart Failure:

- Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
- Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- Class III - Marked limitation in activity due to symptoms. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain. Comfortable at rest.
- Class IV - Severe limitations. Inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

V. Patients included in the pivotal trial had a history of heart failure, evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness > 12 mm, and confirmed transthyretin-mediated amyloidosis by documented presence of amyloid deposit by biopsy and/or presence of transthyretin precursor protein confirmed by scintigraphy.

VI. Nuclear scintigraphy is a newer, less invasive diagnostic method thought to improve the diagnosis rate of ATTR-CM. Though use of this diagnostic tool may be limited, due to the specialized nature of the protocol and the skill needed for interpretation of the results. There are two radiolabeled phosphonates that have been studied most in this setting, ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP) in the US and ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) in Europe. In the US, the radiotracer 99m technetium pyrophosphate, or ^{99m}Tc-PYP, is not FDA-approved for the diagnosis of ATTR-CM, but it is increasingly used by the medical community.

VII. Patients were excluded if they had NYHA Class IV heart failure, primary amyloidosis, or a history of liver or heart transplantation.

- Primary amyloidosis was excluded as this diagnosis is considered emergent and entails a different treatment approach consisting of chemotherapy.
- Before the availability of tafamidis the management of ATTR-CM consisted of symptomatic treatment of heart failure symptoms and liver and/or heart transplantation. Orthotopic liver transplant (OLT) is one of the most established, potentially curative treatment options for some patients with ATTR-CM, specifically patients with early-stage hATTR. Orthotopic heart transplant (OHT), alone or in combination with OLT, may be a therapeutic option for select patients with ATTR-CM.
- Tafamidis meglumine (Vyndaqel) is designed to target the underlying disease process in ATTR-CM through inhibition of the TTR tetramer dissociation. This forms the rationale for the use of tafamidis meglumine to slow disease progression. The progressive nature of the disease underscores the importance of early diagnosis and suggests tafamidis meglumine treatment may be most beneficial when initiated in early stages of the disease when heart failure is less severe and may be more easily reversed compared with later stages. Disease-modifying treatments, such as tafamidis meglumine (Vyndaqel) may be less effective once amyloid deposition has caused irreversible organ damage.

VIII. Tafamidis meglumine (Vyndaqel) was studied as monotherapy. There is no data on the use of combination therapy with other medications indicated for different types of amyloid disease.

IX. Within the pivotal trial results, a greater proportion of patients in the tafamidis meglumine group either improved upon or remained at their respective NYHA baseline classification compared with patients in the placebo group.

Investigational or Not Medically Necessary Uses

I. Cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis in members with NYHA functional class IV
   A. In the ATTR-ACT trial, patients with NYHA Class IV were excluded from the pivotal trial. The progressive nature of the disease underscores the importance of early diagnosis and suggests tafamidis meglumine treatment may be most beneficial when initiated in early stages of the disease when heart failure is less severe and may be more easily reversed compared with later stages. Disease-modifying treatments, such as tafamidis meglumine (Vyndaqel) may be less effective once amyloid deposition has caused irreversible organ damage.

II. Polyneuropathy of hereditary transthyretin-mediated amyloidosis or familial amyloid polyneuropathy (FAP)
   A. Coelho et al. 2012 reported no significant changes in patients with early-stage V30M transthyretin familial amyloid polyneuropathy (TTR-FAP) as coprimary endpoints were not met in the ITT population.
   B. The US FDA did not approve tafamidis meglumine (Vyndaqel) use in FAP during a filing in 2012, due to limited efficacy data. The agency requested the completion of a second efficacy study to establish substantial evidence of effectiveness prior to an approval.

III. Primary (light chain) amyloidosis
   A. In the pivotal trial (ATTR-ACT), patients with primary amyloidosis were excluded. Primary amyloidosis is caused by a bone marrow disorder. Treatment consists of chemotherapy or bone marrow transplant.

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Policy Implementation/Update:

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

Action and Summary of Changes	**Date**

Policy Type: PA Pharmacy Coverage Policy: UMP065

Description

Talazoparib (Talzenna) is an orally administered poly (ADP-ribose) polymerase (PARP) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: Twelve months

Quantity limits

talazoparib (Talzenna)	Indication	Quantity Limit	DDID
0.25 mg capsules	BRCA-mutated breast cancer, locally advanced or metastatic	90 capsules/30 days	204472
1 mg capsules		30 capsules/30 days	204473

Initial Evaluation

I. Talazoparib (Talzenna) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Talazoparib (Talzenna) has been prescribed by, or in consultation with a specialist in oncology; **AND**
   C. Talazoparib (Talzenna) will be used as monotherapy; **AND**
   D. Member has not had documented disease progression on prior PARP inhibitor therapy; **AND**
   E. A diagnosis of locally advanced (stage III) or metastatic (stage IV) breast cancer when the following are met:
      1. Documented deleterious (pathogenic) or suspected deleterious (likely pathogenic) germline BRCA mutation as determined by BRCA testing; **AND**
      2. Documented HER2-negative disease; **AND**
      3. Prior treatment with an anthracycline (e.g., doxorubicin) and/or a taxane (e.g. paclitaxel) was ineffective, unless contraindicated; **AND**
      4. If treated with prior platinum chemotherapy, disease is not platinum refractory (i.e., progression of disease within 8 weeks of platinum discontinuation); **AND**
      5. Member has received no more than three previous cytotoxic regimens for advanced breast cancer (stage III or stage IV); **AND**
      6. For hormone receptor positive (HR+) disease, member has had progression of disease on prior endocrine therapy, unless the patient is considered inappropriate for endocrine therapy

II. Talazoparib (Talzenna) is considered investigational when used for all other conditions, including but not limited to:
   A. When used in combination with any other chemotherapy or targeted therapy
   B. Early-stage breast cancer
   C. Ovarian cancer, fallopian tube, and peritoneal cancer
   D. Lung cancer
   E. Prostate cancer

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

I. Talazoparib (Talzenna) is FDA-approved for the treatment of adults with germline BRCA mutated, HER2-negative locally advanced or metastatic disease.
II. The efficacy and safety of talazoparib (Talzenna) monotherapy was demonstrated in an open-label trial (EMBRACA) which enrolled adult patients that had a deleterious or suspected deleterious germline BRCA1/2 mutation detected by testing with BRACAnalysis.
III. Patients in the EMBRACA study had received no more than three previous cytotoxic regimens for advanced breast cancer, and they had received previous treatment with a taxane, an anthracycline, or both, unless contraindicated.
IV. Previous neoadjuvant or adjuvant platinum-based therapy was allowed, provided the patient had a disease-free interval for at least six months after the last dose. Patients were excluded if they had disease progression while receiving platinum chemotherapy for advanced breast cancer (i.e., progression of disease within approximately eight weeks after the last dose).
V. Patients included in the study had no more than three prior therapies in the advanced breast cancer setting. More than two therapies in other settings (e.g. neoadjuvant, adjuvant) do not apply.
VI. Although prior endocrine-based therapy was not required in the EMBRACA trial, 90.4% of patients had progressed on endocrine-based therapy before being treated with talazoparib (Talzenna), and 100% had received prior chemotherapy for HR+ disease. The standard treatment approach for HR+ disease is to first target the hormone pathway (unless considered inappropriate), then consider single agent chemotherapy or PARP inhibitor if there is progression on endocrine-based therapy.
VII. The National Comprehensive Cancer Network (NCCN) breast cancer guideline lists the PARP inhibitors [talazoparib (Talzenna) and olaparib (Lynparza)] as Category 1 options for previously treated recurrent or metastatic HER2-negative germline BRCA mutated breast cancer.

Investigational or Not Medically Necessary Uses

I. The efficacy and safety of talazoparib (Talzenna) in combination with other chemotherapy or immunotherapy agents has not been evaluated. Talazoparib (Talzenna) is indicated as monotherapy.
II. There is no evidence to support the use of a subsequent PARP inhibitor following progression of disease on another PARP inhibitor.
III. Due to its mechanism of action, there is interest in using talazoparib (Talzenna) in other cancers such as ovarian cancer, prostate cancer, and lung cancer; however, studies are still ongoing and use outside of BRCA mutated breast cancer is considered investigational.
IV. Additionally, there is a lack of evidence supporting the use of talazoparib (Talzenna) in early breast cancer (e.g., neoadjuvant treatment).

References

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Policy Implementation/Update:

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

Action and Summary of Changes	Date

Policy Type: PA/SP Pharmacy Coverage Policy: UMP215

Description

Tasimelteon (Hetlioz, Hetlioz LQ) is an agonist of melatonin MT1 and MT2 receptors which are thought to be involved in the control of circadian rhythms.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tasimelteon (Hetlioz)	20 mg capsules	Non 24-Hour Sleep-Wake Disorder; Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)	30 capsules/30 days
tasimelteon (Hetlioz LQ)	4 mg/mL oral suspension	Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)	0.7 mg/kg*
			158 ml bottle**

* for members weighing 28kg or less
** for members weighing more than 28kg

Initial Evaluation

I. Tasimelteon (Hetlioz, Hetlioz LQ) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, a neurologist, sleep specialist, or psychiatrist; **AND**
   B. Treatment with melatonin (for at least three months continuously) has been ineffective, contraindicated, or not tolerated; **AND**
   C. A diagnosis of **Non-24-hour sleep-wake disorder (N24HSWD)** when the following are met:
      1. Member is 18 years of age or older; **AND**
      2. Member has a diagnosis of total blindness in both eyes without light perception; **AND**
      3. Provider has documented progressively shifting sleep-wake times with sleep diaries and/or actigraphy for at least 14 days; **AND**
      4. Treatment with at least TWO of the following groups has been ineffective or not tolerated, or **all** are contraindicated:
         i. benzodiazepines (eg. flurazepam, lorazepam, temazepam)
         ii. non-benzodiazepines (eg. doxepin, eszopiclone, zaleplon)
         iii. melatonin agonist (eg. ramelteon); **OR**

D. A diagnosis of **Nighttime sleep disturbances in Smith-Magenis Syndrome (SMS)** when the following are met:
    1. Genetic testing has identified a heterozygous deletion of 17p11.2; **OR**
        i. A heterozygous pathogenic variant involving RAI1; **AND**
    2. Request is for tasimelteon (Hetlioz) capsules; **AND**
        i. Member is 16 years of age or older; **OR**
    3. Request is for tasimelteon (Hetlioz LQ) oral solution; **AND**
        i. Member is between three and 15 years of age; **AND**
        ii. Current weight provided in documentation

II. Tasimelteon (Hetlioz, Hetlioz LQ) is considered investigational when used for all other conditions, including but not limited to:
    A. Sighted individuals with non-24-hour sleep-wake disorder
    B. Non-24-hour sleep-wake disorder in blind individuals with light perception
    C. Jet lag disorder
    D. Major depressive disorder

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. longer duration of nighttime sleep, more alert during the day]

Supporting Evidence

I. The safety and efficacy of tasimelteon (Hetlioz) has been established in two phase III, placebo-controlled, randomized, double-blind studies (SET and RESET) in totally blind adult patients without light perception in both eyes and with a diagnosis of non-24-hour sleep-wake disorder.
    - Patients were randomized to receive tasimelteon 20mg or placebo every 24 hours at a fixed clock time one hour before target bedtime.
    - Primary outcome measure for the SET study of the proportion of entrained patients assessed in the intention-to-treat population assessed from 6-sulphatoxymelatonin (aMT6s) rhythms for 4 weeks starting from day 14, was met by eight (20%) of 40 patients in the tasimelteon group, compared with one (3%) of 38 patients in the placebo group.
    - Primary outcome measure for the RESET study of the proportion of maintenance of entrainment (aMT6s) has been met by nine (90%) of ten patients in the tasimelteon group, whereas only two (20%) of ten patients withdrawn to placebo, maintained entrainment.

- Entrained is the synchronization or alignment of the internal biological clock rhythm, including its phase and period, to external time cues, such as the natural dark-light cycle.
- Duration of nighttime sleep was improved by 28 minutes and the duration of daytime napping was reduced by 27 minutes, while each worsened when treatment was withdrawn.

II. There is a lack of randomized clinical trial data to show safety and efficacy of tasimelteon (Hetlioz) in pediatric patients with the diagnosis of N24SWD. Although the SMS indication is approved in pediatric patients – very few pediatric patients (N=11) have actually received the medication, thus, use for N24HSWD in those under 18 years of age would be considered experimental.

III. Per the American Academy of Sleep Medicine Clinical Practice Guideline, a diagnosis of N24SWD requires at least 14 days of documentation of progressively shifting sleep-wake times with sleep diaries and/or actigraphy.

IV. The exogenous melatonin (0.5-10 mg) has been shown to entrain the free-running circadian rhythms of some blind subjects. The American Academy of Sleep Medicine has identified three studies in their guideline. Melatonin was administered either one hour prior to preferred bedtime, or at a fixed clock hour (21:00), for a period of 26–81 days (one to three months). The entrainment rate (12 of 18) found in the current meta-analysis of melatonin treatment in N24SWD was 67%. Due to the lack of head-to-head trials there is no clinical trial data to show that one therapy is superior to the other.

V. The safety and efficacy of tasimelteon (Hetlioz) for Nighttime Sleep Disturbances in SMS has been established a pivotal phase 2/3, nine-week, double-blind, randomized, placebo-controlled, two-period crossover study in 14 adults and 11 pediatric patients.
- Patients 16 years of age and older received 20 mg capsules, and pediatric patients three years to 15 years of age received a weight-based dose of oral suspension.
- The primary endpoints in were nighttime total sleep time [assessed via daily diary total nighttime sleep duration (DDTST)] and nighttime sleep quality from a parent/guardian-recorded diary (DDSQ). The efficacy comparisons for nighttime sleep quality and total sleep time were based on the 50% of nights with the worst sleep quality and the 50% of nights with the least nighttime sleep in each 4-week period.
- Compared to placebo, treatment with tasimelteon (Hetlioz) resulted in a statistically significant improvement in the 50% worst nights' sleep quality. Although improvement on the 50% worst total nighttime sleep time numerically favored tasimelteon (Hetlioz) treatment, the difference was not statistically significant.

Primary Efficacy Measures	Treatment Group	LS Meana (SE)	Placebo-subtracted Difference (95% CI)
Average of 50% Worst Daily Nighttime Sleep Quality*	HETLIOZ (n=25)	2.8 (0.15)	0.4 (0.1, 0.7)
	Placebo (n=25)	2.4 (0.15)	-
Average of 50% Worst Daily	HETLIOZ (n=25)	7.0 (0.26)	0.3 (-0.0, 0.6)
	Placebo (n=25)	6.7 (0.26) -	-

Nighttime Total Sleep Time, hours			

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval unadjusted for multiplicity.
[a] LS Means are the model-based averages based on the 50% worst days per 4-week period.
[b] Difference (drug minus placebo) in least-squares means.
* Endpoint on which HETLIOZ was statistically significant different from placebo after controlling for multiple comparisons.

VI. The recommended dosage of tasimelteon (Hetlioz LQ) oral suspension for the treatment of nighttime sleep disturbance in SMS pediatric patients three to 15 years of age is by body weight. For patients with 28 kg or less the recommended dose is 0.7 mg/kg and for patients who weigh more than 28kg the recommended dose is 20 mg one hour before bedtime.

VII. Smith-Magenis syndrome (SMS) is a developmental disorder that affects many parts of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems. Most people with SMS have a deletion of genetic material in each cell from a specific region of chromosome 17. Although this region contains multiple genes, researchers believe that the loss of one particular gene, RAI1, is responsible for most of the features of the condition. In most of these cases, the deletion is not inherited, occurring randomly during the formation of eggs or sperm, or in early fetal development.

- The diagnosis of SMS is established in a proband with suggestive clinical features and one of the following on molecular genetic testing: A heterozygous deletion of 17p11.2 or heterozygous pathogenic variant involving RAI1. When the phenotypic findings suggest the diagnosis of SMS, molecular genetic testing approaches can include chromosomal microarray analysis, single-gene testing, or use of a multigene panel.

VIII. Recent studies have attributed the sleep disturbance in SMS to a primary disturbance of the circadian clock, with RAI1 functioning as a positive regulator of Circadian Locomotor Output Cycles Kaput (CLOCK) transcription, a key component of the mammalian circadian oscillator. Additionally, disrupted melatonin secretion has been noted with moderate to high levels of daytime salivary melatonin observed in SMS patients.

IX. As patients with SMS typically display a diurnal rather than nocturnal peak in melatonin secretion, exogenous melatonin has been used nocturnally to supplement the typical biological melatonin secretion. By adding an exogenous melatonin dose prior to bedtime, a nocturnal rise in melatonin levels can assist in increasing the biological propensity to sleep. Given the very limited experience of tasimelteon (Hetlioz) in pediatric populations, the safety and efficacy profile are largely unknown. Melatonin has a more established safety and efficacy profile and should be considered for use prior to tasimelteon (Hetlioz).

Investigational or Not Medically Necessary Uses

I. Tasimelteon (Hetlioz) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Sighted individuals with non-24-hour sleep-wake disorder and non-24-hour sleep-wake disorder in blind individuals with light perception
      i. There no published clinical trial data to show safety and efficacy and support the use of tasimelteon (Hetlioz) in these patient populations.
   B. Jet lag disorder

i. A phase II, randomized, double blind proof of concept study to evaluate the effects of tasimelteon and placebo in travelers with jet lag disorder with the primary outcome measure of changes in sleep after transmeridian travel measured by nighttime sleep parameters

ii. A randomized, double-blind, placebo-controlled, parallel design study evaluating the effects of tasimelteon compared to placebo on jet lag type insomnia enrolled 320 healthy adult patients. Tasimelteon treatment increased Total Sleep Time in the first 2/3 of the night (primary endpoint) by 60.3 min (95%CI 44.0 to 76.7, P < 0.0001) and whole night TST by 85.5 min (95% CI 64.3 to 106.6, P < 0.0001), improved next day alertness, next day sleepiness, and shortened latency to persistent sleep by −15.1 min (95% CI −26.2 to −4.0, P = 0.0081).

iii. Jet Lag was induced by an immediate phase advance of the sleep-wake cycle in a sleep clinic, rather than jet travel in the eastward direction.

iv. There isn't robust safety and efficacy data to support the use of tasimelteon (Hetlioz) in the treatment of the jet lag disorder.

C. Major Depressive Disorder (MDD)

i. A randomized, parallel, double-masked, placebo-controlled, multicenter outpatient study comparing tasimelteon with placebo with 507 enrolled participants (MAGELLAN) followed by a 52-week open label extension.

- The primary outcome measure was change from baseline to endpoint at week 8 using the total score of Hamilton Depression Rating Scale (HAM-D) was not met.
- The clinical trial showed insufficient efficacy and limited safety data.

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Policy Implementation/Update:

Action and Summary of Changes	Date

• Added new indication of Nighttime Sleep Disturbances in SMS
• Added a new formulation, the tasimelteon (Hetlioz LQ) oral solution
• New criteria added for the indication of N24HSWD:
  ○ Treatment with melatonin (for at least three months continuously) has been ineffective, contraindicated or not tolerated
  ○ Member has a diagnosis of total blindness in both eyes without light perception
  ○ Provider has documented progressively shifting sleep-wake times with sleep diaries and/or actigraphy for at least 14 days
  ○ Treatment with at least TWO alternatives has been ineffective or not tolerated, or all are contraindicated: benzodiazepines (eg. flurazepam, lorazepam, temazepam), or non-benzodiazepines (eg. doxepin, eszopiclone, zaleplon) or melatonin agonist (eg. ramelteon)
• Criteria removed from the indication of N24HSWD:
  ○ Member has no hepatic impairment or mild to moderate hepatic impairment
  ○ Member is not on concurrent strong CYP3A4 inducers or CYP1A2 inhibitors
Criteria updated to policy format
	12/2020

Criteria created	04/2014

Policy Type: PA/SP Pharmacy Coverage Policy: UMP184

Split Fill Management*

Description

Tazemetostat (Tazverik) is an orally administered inhibitor of methyltransferase, EZH2.

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tazemetostat (Tazverik)	200 mg tablets	Epithelioid sarcoma, advanced or metastatic, not eligible for resection; Follicular lymphoma, relapsed or refractory, EZH2 mutation-positive, in that that have received at least two therapies; Follicular lymphoma, relapsed or refractory, in those with no satisfactory alternative therapy	240 tablets/30 days

Initial Evaluation

I. Tazemetostat (Tazverik) is considered investigational when used for all conditions, including but not limited to:
   A. Epithelioid sarcoma
   B. Non-Hodgkin lymphoma, including follicular lymphoma

Renewal Evaluation

I. N/A

Supporting Evidence

I. Background: Epithelioid sarcoma is a very rare cancer of the soft tissue, generally seen in younger populations (average age of 27). This aggressive condition is known for recurrence, spread to locoregional lymph nodes, and eventually distant metastases. Common sites of origin include fingers, hands, forearms, feet, and other limbs. First-line management is typically surgery, with local recurrence necessitating amputation in many cases. Although, not specifically FDA-approved for epithelioid sarcoma, there are several systemic therapies used in the metastatic setting. Often, anthracycline based regimens (e.g., doxorubicin with or without ifosfamide), gemcitabine, pazopanib (Votrient), doxetaxel, sunitinib (Sutent), dacarbazine, epirubicin, and temozolomide.

II. Efficacy: Tazemetostat (Tazverik) was approved on data from a Phase 2 trial. Pooled data from two cohorts, five and six (n=62, n=44), were used to support the approval. Seventy-seven percent of patients had prior surgery and 61% had prior chemotherapy. Primary outcomes included objective response rate (ORR) assessed every eight weeks and progression-free survival (PFS). Secondary endpoints were duration of response (DOR), disease control rate (DCR) and overall survival (OS). The pooled data showed an objective response rate of 13% (CR 1.6%, PR 11%). Duration of response was 12.8 months (3.5-24 months). Pooled data for progression-free survival (PFS), disease control rate (DCR) and overall survival (OS) were not reported for the pooled data; however, for Cohort 5 PFS was 23.7 weeks, DCR was 21%, and OS was 82 weeks.

III. Safety: There are no contraindications for tazemetostat (Tazverik); however, there is a warning for development of secondary malignancies, such as T-cell lymphoblastic lymphoma, myelodysplastic syndrome, and acute myeloid leukemia. Six out of 668 treated patients had developed secondary malignancy as of quarter May 2019. Common (≥ 20%) adverse reactions noted from the trial included: fatigue, nausea, decreased appetite, vomiting and constipation. One patient in the clinical trial discontinued therapy due to adverse events, 34% required a dose interruption, and there were not deaths from treatment. Tazemetostat (Tazverik) has significant drug interactions with CYPP450 inhibitors and inducers, and there is a warming for embryo fetal toxicity and lactation. Due to the limited number of subjects treated and short duration of use, the safety profile of tazemetostat (Tazverik) is largely unknown at this time.

IV. The quality of the evidence is low given the Phase 2, open-label, single-arm trial. The primary endpoints have not been correlated with clinically meaningful outcomes such as improvement in morbidity, mortality or symptom relief, and results have not been confirmed in other studies. Additionally, due to the limited number of subjects treated, the safety profile is highly unknown. Coupled with the low rates of response, there is uncertain usefulness of tazemetostat (Tazverik) at this time.

V. Tazemetostat (Tazverik) was approved under the accelerated approval pathway and orphan drug designation. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

VI. Follicular lymphoma (FL), is an indolent form of NHL that arises from B-lymphocytes. Treatment is dependent on stage, or histologic grade of condition, and may include the following: radiation therapy, immunotherapy, and chemotherapy. In the space of relapsed or refractory to two prior therapies, the PI3K inhibitors are recommended per NCCN (e.g., copanlisib, duvelisib, idelalisib), as well as selinexor.

VII. Tazemetostat (Tazverik) for FL was evaluated for safety and efficacy in one open-label, single-arm, Phase 2 trial at 800 mg twice daily. There were 99 patients included in the trial , 45 of which were EZH2 mutated, and 54 were EZH2 wild type. Patients were adults with confirmed FL (grade 1-3b), relapsed or refractory to two or more standard systemic therapies, with life expectancy of three months or more, and adequate organ function. Some patients had up to five or more previous therapies, and up to 59% were rituximab refractory, up to 28% were double refractory, and up to 29% had hematopoietic stem cell transplant.

VIII. Tazemetostat (Tazverik) was approved under the accelerated approval pathway for FL based on objective response rate, duration or response, and progression free survival. Continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials. Treatment emergent adverse events (TEAE) occurred in 99% of patients, and serious AE occurred in 27%. The most common serious AE being sepsis, physical health deterioration, and anemia. Other notable serious AE were neutropenia, pancytopenia, global amnesia, arrhythmia, and myelodysplastic syndrome. Dose reductions due to adverse events as well as dose interruptions occurred at rates of 27%, and 8% of patients permanently discontinued due to AE. One case of AML was reported, and four patients died within 30 days of the last dose of study drug. The study investigators deemed these not related to treatment.

IX. Given the observational nature of the data, true medication safety and efficacy is unknown. Open-label, single-arm trials are insufficient for determining cause and effect of treatment. Additionally, ORR, DoR, and PFS have not been correlated with clinically meaningful outcomes such as improvement in quality of life, symptom control, or overall survival.

Investigational or Not Medically Necessary Uses

I. There is a lack of high-quality data from randomized controlled trials to indicate the safety and efficacy of tazemetostat (Tazverik) in the following indications:
   A. Soft tissue sarcoma, including epithelioid sarcoma
   B. Non-Hodgkin lymphoma, including follicular lymphoma
   C. Other types of lymphoma, including but not limited to mediastinal, B-Cell, Mantle-Cell, Marginal Zone,
   D. Rhabdoid tumors
   E. Mesothelioma
   F. Kidney, bladder, urothelial cancers
   G. Hepatocellular carcinoma

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

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Policy Implementation/Update:

Action and Summary of Changes	Date
Indication of Follicular Lymphoma reviewed and supporting evidence added to policy	01/2021
Policy created	05/2020

teduglutide (Gattex®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP066

Description

Teduglutide (Gattex) is a subcutaneously administered recombinant synthetic glucagon like peptide 2 (GLP-2) analog.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
teduglutide (Gattex)	5 mg vial kit (one vial)	Short Bowel Syndrome (SBS)	1 vial/1 day	177513
	5 mg vial kit (30 vial)		30 vials/30 days	

Initial Evaluation

I. Teduglutide (Gattex) may be considered medically necessary when the following criteria below are met:
   A. Member is one year of age or older and weighs more than 10 kg; **AND**
   B. Teduglutide (Gattex) has been prescribed by, or consultation with a specialist in gastroenterology; **AND**
   C. A diagnosis of **Short Bowel Syndrome**; **AND**
      1. Member dependence on parenteral nutrition/intravenous support for at least 12 months; **AND**
      2. Member dependence on parenteral nutrition at least three times a week; **AND**
      3. Laboratory assessment within the last six months of bilirubin, alkaline phosphatase, lipase and amylase to rule out gallbladder, biliary tract or pancreatic disease; **AND**
      4. Colonoscopy within the last 6 months to rule out colorectal polyps or small bowel neoplasia in adult members; **OR**
      5. Fecal occult blood testing in children and adolescents within the last 6 months; **AND**
         i. Documentation of a follow-up colonoscopy for any positive fecal occult blood test

II. Teduglutide (Gattex) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:

A. Crohn's disease
B. Enterocutaneous Fistula (ECF)
C. Gastric emptying

Renewal Evaluation

I. Clinical documentation of response to therapy as demonstrated by:
   A. Decrease in volume of parenteral or intravenous nutritional support; **OR**
   B. Decrease in number of days of parenteral or intravenous nutritional support; **AND**
II. Colonoscopy performed within the last 12 months to rule out colorectal polyps or small bowel neoplasia upon first renewal, and, no less than every five years; **AND**
III. Bilirubin, alkaline phosphatase, lipase, and amylase laboratory assessment to rule out gallbladder, biliary tract or pancreatic disease within the last six months.

Supporting Evidence

I. Teduglutide (Gattex) is FDA approved for treatment adults and pediatric patients 1 year of age or older with Short Bowel Syndrome (SBS) who are dependent on parenteral support.
II. The pivotal trial included patients with SBS who were dependent on parenteral nutrition/intravenous support for at least 12 months and at least 3 times per week.
III. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for an increased dosing frequency. The higher dose treatment arm did not demonstrate a statistically significant difference when compared to placebo.
IV. Colonoscopies should be completed again 1 year after treatment then no less frequently than every 5 years to evaluate for polyps and gastrointestinal malignancies.
V. Lab assessments are recommended every 6 months to evaluate for gallbladder, biliary tract and pancreatic disease.

Investigational or Not Medically Necessary Uses

I. Crohn's Disease
   A. Phase II clinical trials have evaluated teduglutide for the treatment of Crohn's disease.
   B. Clinical concerns for the safety of teduglutide in patients with Crohn's disease include neoplastic growth, intestinal obstruction and biliary and pancreatic disease.
   C. Large, well-controlled clinical trials are needed to demonstrate benefit of use of teduglutide in patients with Crohn's Disease.
II. Clinical trials are ongoing in the following indications:
   A. Enterocutaneous Fistula (ECF)
   B. Gastric emptying

References

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Policy Implementation/Update:

Date Created	May 2013
Date Effective	May 2013
Last Updated	August 2013
Last Reviewed	05/2013, 09/2013, 06/2019

Action and Summary of Changes	**Date**
Created new policy format. Addition of new FDA approved indication in pediatric population.	06/2019

tegaserod (Zelnorm®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA Pharmacy Coverage Policy: UMP087

Description

Tegaserod (Zelnorm) is an orally administered serodonin-4 (5-HT4) receptor agonist.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
tegaserod (Zelnorm)	6 mg tablets	Irritable bowel syndrome with constipation	60 tablets/30 days	077781

Initial Evaluation

I. Tegaserod (Zelnorm) may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older AND is less than 65 years of age; **AND**
   B. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
   C. A diagnosis of **irritable bowel syndrome with constipation (IBS-C)** when the following are met:
      1. The member does not have current or historical cardiovascular disease; **AND**
      2. The member is female; **AND**
      3. The member has had an inadequate response to the ALL of the following:
         i. Dietary modifications (e.g., removal of offending foods, increased fiber intake) AND increased physical activity; **AND**
         ii. At least one osmotic laxative (e.g., polyethylene glycol); **AND**
         iii. lubiprostone (Amitiza); **AND**
         iv. One of the following: linaclotide (Linzess) OR plecanatide (Trulance); **OR**
            a. The member is contraindicated to all of these therapies

II. Tegaserod (Zelnorm) is considered <u>not medically necessary</u> when criteria above are not met and/or when used for:
   A. Irritable bowel syndrome with constipation in males

III. Tegaserod (Zelnorm) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Idiopathic chronic constipation
   B. Opioid or other drug induced constipation
   C. Gastroesophageal reflux disease (GERD)

Renewal Evaluation

I. The member is 18 years of age or older AND the member is less than 65 years of age; **AND**
II. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
   A. **A diagnosis of irritable bowel syndrome with constipation (IBS-C)**; **AND**
      1. The member does not have a history of, or established, cardiovascular disease; **AND**
      2. The member has experienced a response to treatment (e.g., increase in rate of bowel movements)

Supporting Evidence

I. Tegaserod (Zelnorm), a serotonin-4 (5-HT4) receptor agonist. It is FDA-approved and indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) in women < 65 years. It was originally approved in 2002, for short-term treatment of women with IBS-C; however, it was withdrawn from the market in 2007 due to an unfavorable cardiovascular (CV) suicidal ideation and behavior (SI/B) safety profile.
II. Efficacy to support reintroduction of tegaserod (Zelnorm) was based on evidence established at the time of original approval. No new evidence on efficacy was added. Tegaserod (Zelnorm) was evaluated in three multicenter, double-blind, placebo-controlled, 12-week trials of 2,470 women that had at least a three-month history of IBS-C. Response rate (RR) was the primary outcome, and was based on subjective response on a five parameter scale measured each week indicating: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. Responders within a month were classified as those with complete relief or considerable relief for at least two of the four weeks, or somewhat relieved for all of the four weeks. Tegaserod (Zelnorm) had superior response rates compared to placebo ranging from 6 to 28%. Secondary outcomes of pain, discomfort and bloating were evaluated on six-to-seven point intensity scale. Positive response, defined as at least a 1-point reduction, was measured to be 1-10% superior for tegaserod (Zelnorm) for abdominal pain or discomfort and 4-11% for bloating. The baseline bowel movement rate averaged 3.8 per week, and increased to 6 per week for tegaserod (Zelnorm) and 5.5 for placebo.
III. Tegaserod (Zelnorm) is contraindicated in those with established CV history, renal impairment, hepatic impairment, bowel obstruction, gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions. In regards to CV disease, the product label specifically indicates: myocardial infarction, stroke, transient ischemic attach, angina. Warnings and precautions include CV ischemic events, major adverse CV events (MACE), ischemic colitis, volume depletion with diarrhea, and SI/B. Common adverse effects (≥ 2%) include headache, abdominal pain, nausea, diarrhea, flatulence, dyspepsia, and dizziness. Approval of tegaserod (Zelnorm) reintroduction was supported by a complete safety review by the FDA and FDA-assembled Gastrointestinal Drugs Advisory Committee (GIDAC). Retrospective analyses of pooled data from 18,645 patients in 29 placebo-controlled trials in various disease states of at least four weeks duration were included. The imbalance in CV events was measured to be 0.1% for tegaserod (Zelnorm) versus 0.01% in placebo. There was one death, attributed to suicide, during the trial. The member has a history of mild depression. The rate of SI/B is measured to be 0.07% for tegaserod (Zelnorm) vs. 0.02% for placebo.

IV. First-line treatment options include dietary modifications, increased fiber intake and physical activity. Adjunctive pharmacotherapy includes over-the-counter osmotic laxatives. When lifestyle modifications and osmotic laxatives fail to produce sufficient relief of constipation, further pharmacologic therapy with lubiprostone (Amitiza), linaclotide (Linzess), or plecanatide (Trulance), may be warranted. Due to the limited efficacy and concerning safety profile, tegaserod (Zelnorm) shall be reserved for those that have exhausted other treatment options.

Investigational or Not Medically Necessary Uses

I. Irritable bowel syndrome with constipation (IBS-C) in males
   A. Two randomized, placebo-controlled, double-blind trials of 288 men did not show differences in efficacy of tegaserod (Zelnorm) versus placebo. This information is stated in the product labeling.

II. Clinical trials are underway, but have not yet been completed to provide insight to safety and efficacy of tegaserod (Zelnorm) in the following settings:
   A. Idiopathic chronic constipation
   B. Opioid or other drug induced constipation
   C. Gastroesophageal reflux disease (GERD)

References

1. Zelnorm [Prescribing Information]. Sloan Pharma/WorldMeds LLC. Louisville, KY. 2019.
2. Black CJ, Burr NE, Ford AC. Relative Efficacy of Tegaserod in a Systematic Review and Network Meta-analysis of Licensed Therapies for Irritable Bowel Syndrome with Constipation. Clin Gastroenterol Hepatol. 2019.
3. Vakil N, Laine L, Talley NJ, et al. Tegaserod treatment for dysmotility-like functional dyspepsia: results of two randomized, controlled trials. Am J Gastroenterol. 2008;103(8):1906-19.
4. Weinberg D.S., Smalley W. Heidelbaugh J.J., et al. American Gastroenterological Association institute guidelines on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014;144: 1146-1148.
5. Chandar AK. Diagnosis and treatment of irritable bowel syndrome with predominant constipation in the primary-care setting: focus on linaclotide. Int J Gen Med. 2017;10:385-393.
6. Clinicaltrials.gov

Policy Implementation/Update:

Date Created	August 2019
Date Effective	November 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

telotristat ethyl (Xermelo®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP155

Description

Telotristat ethyl (Xermelo) is an orally administered tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
telotristat ethyl (Xermelo)	250 mg tablets	Carcinoid Syndrome Diarrhea	84 tablets/28 days

Initial Evaluation

I. Telotristat ethyl (Xermelo) 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, oncologist or gastroenterologist; **AND**
   C. Telotristat ethyl (Xermelo) will be used in combination with a somatostatin analog therapy (e.g., octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]); **AND**
   D. A diagnosis of **carcinoid syndrome diarrhea** when the following are met:
      1. Clinical documentation of significant diarrhea (≥ 4 bowel movements per day on average); **AND**
      2. Treatment with a somastatin analog therapy (e.g. octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]) has not been effective after at least 3 months of therapy, was not tolerated, or is contraindicated.

II. Telotristat ethyl (Xermelo) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Carcinoid syndrome without diarrhea
   B. Biliary Tract Cancer
   C. Pancreatic Cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has exhibited improvement or stability of disease symptoms defined by a decrease in overall average bowel movements per week from baseline; **AND**
IV. Telotristat ethyl (Xermelo) will be used in combination with a somatostatin analog therapy (e.g., octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]).

Supporting Evidence

I. The safety and efficacy for telotristat ethyl (Xermelo) was studied in a 12-week double-blind, placebo-controlled, randomized, multicenter trial in adult patients with well differentiated metastatic neuroendocrine tumor and carcinoid syndrome diarrhea who were having between 4 to 12 daily bowel movements despite the use of SSA therapy at a stable dose for at least 3 months. The primary efficacy outcome was the change from baseline in the number of daily bowel movements averaged over the 12-week treatment period; in the telotristat ethyl (Xermelo) arm, there was a reduction of -1.4 bowel movements per day compared to -0.6 in the placebo arm with $p<0.001$.

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:
   A. Carcinoid syndrome without diarrhea
   B. Biliary Tract Cancer
   C. Pancreatic Cancer/Other Neuroendocrine Tumors (NETs)

References

1. Xermelo [Prescribing Information]. Woodlands, TX: Lexicon Pharmaceuticals, Inc. February 2017.
2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines®): Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors). Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine_blocks.pdf

Policy Implementation/Update:

Date Created	11/2019
Date Effective	December 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

temozolomide (Temodar®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP163

Description

Temozolomide is an alkylating agent that undergoes rapid nonenzymatic conversion to the reactive compound 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be caused primarily by alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine which leads to DNA double strand breaks and apoptosis.

Length of Authorization

- Initial: Three months
- Renewal: Six months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
temozolomide (Temodar)	5 mg capsules	All indications	Maximum 200 mg/m^2/day
	20 mg capsules		
	100 mg capsules		
	140 mg capsules		
	180 mg capsules		
	250 mg capsules		
Provider Administered Agents*			
temozolomide (Temodar)	100 mg vial	All indications	Maximum 200 mg/m^2/day

**Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit.*

Initial Evaluation

I. Temozolomide (Temodar) may be considered medically necessary when treatment with generic temozolomide 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; **AND**

II. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

References

1. Temodar (temozolomide) [Prescribing Information]. Whitehouse Station, NJ: Merck & Co. October 2017.

Policy Implementation/Update:

Action and Summary of Changes	Date
• Removed generic temozolomide from the policy • Removed indication-specific criteria	03/2020
Updated to policy format	12/2019
Previous reviews	03/2016
Policy created	05/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP221

Split Fill Management*

Description

Tepotinib (Tepmetko) is an orally administered tyrosine kinase inhibitor (TKI) that targets mesenchymal-epithelial transition (MET).

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tepotinib (Tepmetko)	225 mg tablets	Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping	60 tablets/30-day supply

Initial Evaluation

I. **Tepotinib (Tepmetko)** 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. Tepotinib (Tepmetko) is a tyrosine kinase inhibitor that targets mesenchymal-epithelial transition (MET) and is currently being evaluated in Non-Small Cell Lung Cancer (NSCLC) that contains a mutation that leads to MET exon 14 skipping. The clinical trial dose is 500 mg orally once daily.

II. Tepotinib (Tepmetko) is the second therapy FDA-approved for this specific NSCLC mutation, joining capmatinib (Tabrecta). Other therapies that have been utilized in this setting include crizotinib (Xalkori), platinum-based doublet chemotherapy with or without bevacizumab, and/or immunotherapy (e.g., pembrolizumab); however, available data to support efficacy in this population is limited, and response to therapy is generally poor.

III. Place in therapy is likely to be in the advanced or metastatic setting based on the population being evaluated in the clinical trial, and may be utilized as first-line in these stages; however, given the limited safety and efficacy data to support its use, other therapies may be considered prior to tepotinib (Tepmetko). As of October 2020, the NCCN treatment guidelines had not yet included tepotinib (Tepmetko). Tepotinib (Tepmetko) is mentioned in the ESMO treatment guideline as a treatment option for this population, alongside capmatinib (Tabrecta) and investigational agent savolitinib.

IV. The pivotal trial for tepotinib (Tepmetko) is the VISION trial, which is an open-label, Phase 2, multi-cohort, single-arm, ongoing trial. Patients with MET exon 14 skipping mutations or MET-amplified disease across various treatment settings (e.g., treatment naïve vs. pretreated) were included in the trial. Patients were negative for EGFR mutations or ALK rearrangements, and those with brain metastases were allowed. Ninety-nine patients are being evaluated for efficacy, and the safety profile is based on 152 patients. The average patient age was 74 years, 97% had metastatic disease, 43% were treatment native in the advanced/metastatic setting, 33% received one prior therapy, and 11% had two or more prior therapies. Japanese patients were excluded, due to an ongoing trial specific to that population.

V. Objective response was seen in 46 patients (46%), all of which were partial responses. Duration of response was 11.1 months, progression-free survival was 8.5 months, overall survival 17.1 months, and EORTC-QLQ-LC13 cough symptom quality of life scores showed a 13-15 point reduction.

VI. Tepotinib (Tepmetko) was granted Breakthrough Therapy designation, Priority Review, and is being evaluated under FDA Real-Time Oncology Review (RTOR) pilot program – intended to be a more efficient review process to bring safe and effective treatment to patients as early as possible. The application is supported by the results of the Phase 2, ongoing VISION study that has shown potential anti-tumor activity via response rate.

VII. True medication safety and efficacy of tepotinib (Tepmetko) remain unknown given the observational nature of the trial (i.e., lack of comparator arm and open-label study design).

VIII. Safety of tepotinib (Tepmetko) has been evaluated in 152 patients, with a median exposure of 6.9 months. Eighty-nine percent of patients experienced treatment related adverse events (AE). Common AE were peripheral edema (63%), nausea (26%), diarrhea (26%), creatinine increase (18%), hypoalbuminemia (16%), amylase increase (11%), lipase increase (9%), asthenia (8%), anorexia (8%), pleural effusion (8%), and alopecia (8%).

IX. Grade 3 or 4 AE occurred in 28% of patients, mainly peripheral edema and amylase and lipase increases. Serious AE's occurred in 15%, 11% permanently discontinued due to AE's overall, and 33% of patents had a dose reduction due to AE's. Peripheral edema was the most common reason for discontinuation or dose reduction. Sixteen percent of patients had dose reduction and 18% had dose interruption based on this AE alone. Twenty-one patients had an AE leading to death while on tepotinib (Tepmetko), one of which was due to interstitial lung disease determined as related to tepotinib (Tepmetko) therapy. Currently there is unknown clinical benefit/value of tepotinib (Tepmetko), and the safety risks are outweighing until further evidence is available to support safety and efficacy of tepotinib (Tepmetko). Of note, tepotinib (Tepmetko) is in several ongoing clinical trials alone and in combination with other chemotherapeutic agents for NSCLC.

Investigational or Not Medically Necessary Uses

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

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

References

1. Paik P.K., Felip E., Veillon R., et al. Tepotinib in non-small-cell lung cancer with MET exon 14 skipping mutations. N Engl J Med. 2020; 383(10): 931-943.
2. Tepmetko [Prescribing Information]. Merck KGaA. Darmstadt, Germany. February 2021.
3. Tabrecta [Prescribing Information]. Novartis Pharmaceuticals Corporation. East Hanover, NJ. May 2020.
4. Kong-Beltran M, Seshagiri S, Zha J, et al. Somatic mutations lead to an oncogenic deletion of MET in lung cancer. Cancer Res. 2006;66(1):283-289.
5. National comprehensive Cancer Network. NCCN Guidelines: Non-small Cell Lung Cancer V8.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated September 15, 2020.
6. European Society for Medical Oncology. Metastatic non-small-cell lung cancer. ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. September 15, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP157

Description

Tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza) are reversible vesicular monoamine transporter 2 (VMAT2) inhibitors that act by regulating monoamine uptake from the cytoplasm to the synaptic vesicle. Its mechanism of action in Tardive dyskinesia or chorea-reduction is unknown.

Length of Authorization

- Initial (Tardive dyskinesia): Three months
- Initial (Chorea associated with Huntington's disease): 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tetrabenazine (Xenazine)	12.5 mg	Chorea associated with Huntington's disease	60 tablets/30 days
	25 mg		
	25 mg	Chorea associated with Huntington's disease, genotyped *extensive* and *intermediate metabolizers*	120 tablets/30 days
generic tetrabenazine	12.5 mg	Chorea associated with Huntington's disease	60 tablets/30 days
	25 mg		
	25 mg	Chorea associated with Huntington's disease, genotyped *extensive* and *intermediate metabolizers*	120 tablets/30 days
deutetrabenazine (Austedo)	6 mg	Tardive dyskinesia in adults; Chorea associated with Huntington's disease	30 tablets/30 days
	9 mg		
	12 mg		120 tablets/30 days
valbenazine (Ingrezza)	40 mg	Tardive Dyskinesia	30 capsules/30 days; 4-week Initiation Pack
	80 mg		

Initial Evaluation

I. Tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza) 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 psychiatrist; **AND**
   C. Medication will not be used in combination with another VMAT2 inhibitor [e.g. tetrabenazine (Xenazine), deutetrabenazine (Austedo) valbenazine (Ingrezza)], monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine]; **AND**
   D. A diagnosis of one of the following:
      1. **Chorea associated with Huntington's disease**; **AND**
         i. Prior treatment with at least one standard-of-care therapy for the treatment of chorea (e.g. amantadine , olanzapine, risperidone, aripiprazole, riluzole, haloperidol, fluphenazine) has been ineffective, unless all are contraindicated or not tolerated; **AND**
         ii. Member has been tested and genotyped to determine if they are poor metabolizers (PMs) or extensive metabolizers (EMs) by their ability to express the drug metabolizing enzyme, CYP2D6 (see quantity limit table based on metabolizer status); **AND**
         iii. *For deutetrabenazine (Austedo) only:* Treatment with generic tetrabenazine has been ineffective, contraindicated or not tolerated; **AND**
         iv. *For Tetrabenazine (Xenazine) only***:** Treatment with generic tetrabenazine and deutetrabenazine (Austedo) has been ineffective, contraindicated or not tolerated; **OR**
      2. [*For generic tetrabenazine, valbenazine (Ingrezza) and deutetrabenazine (Austedo) only*] **Tardive dyskinesia**; **AND**
         i. At least one of the following treatment approaches was ineffective, unless all are contraindicated, not tolerated, or put psychiatric stability at risk:
            a. Switching from a first-generation neuroleptic (e.g. fluphenazine, haloperidol, loxapine, perphenazine, trifluoperazine) to a second-generation neuroleptic (e.g. clozapine, risperidone, olanzapine, quetiapine]; **OR**
            b. Member has history of discontinuation or dose modification of the offending medication; **OR**
            c. Member has been trialed on at least one standard therapy (e.g tetrabenazine, amantadine, benztropine, benzodiazepine) for symptomatic treatment of tardive dyskinesia; **AND**
         ii. *For valbenazine (Ingrezza) only:* Treatment with generic tetrabenazine has been ineffective, contraindicated or not tolerated; **AND**
         iii. *For deutetrabenazine (Austedo) only*: Treatment with generic tetrabenazine and valbenazine (Ingrezza) has been ineffective, contraindicated or not tolerated

II. Tetrabenazine (Xenazine) and deutetrabenazine (Austedo) are considered investigational when used for all other conditions, including but not limited to:
   A. Tourette's syndrome

III. Valbenazine (Ingrezza) is considered investigational when used for all other conditions, including but not limited to:
   A. Chorea associated with Huntington's disease
   B. Tourette's 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. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

I. Safety and effectiveness in pediatric patients has not been established.
II. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) need to be prescribed by a neurologist or psychiatrist considering the serious adverse effects (depression and suicidality, cognitive decline, Parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness, and disability), complexity of the disease state and dosing of the medication.
III. Concomitant use of tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza) should not be used in combination with an MAOI.
IV. The American Academy of Neurology (AAN) recommends the use of tetrabenazine (Xenazine), amantadine, or riluzole when medication therapy for chorea is warranted. Per the Physician's Guide to the Management of Huntington's Disease 3rd edition, providers often treat chorea with neuroleptics (e.g. aripiprazole, haloperidol, fluphenazine, risperidone, olanzapine) based on clinical experience and due to safety concerns associated with VMAT2-inhibitors, namely: decreased cognition and mood, increased suicidality and depression. Studies of the anti-choreic effects of neuroleptics were excluded from the AAN guideline review due to criteria set forth; however, the AAN acknowledges neuroleptics are commonly used in clinical practice to treat chorea and recommends additional study in recognition of this use. In consideration of the Boxed Warnings and adverse effects associated with this class, a trial of therapy often considered in standards-of-care is reasonable.
V. No sufficient evidence was found to show superiority of one agent over the other.
VI. When clinically appropriate, the two main strategies of pharmacotherapy in patients who are showing signs of tardive dyskinesia include discontinuation of the offending drug and switching

from a first- to a second-generation antipsychotic drug because second generation neuroleptics have a lower risk of TD.

VII. Additional pharmacologic options [e.g. benzodiazepines, anticholinergic drugs (trihexyphenidyl, benztropine)] have been used in clinical practice for many years. AAN states use of benzodiazepines and tetrabenazine (Xenazine) as standard of care treatments is based on weak clinical evidence but it has been standard of care.

VIII. There is a lack of head-to-head trials and scientific evidence to show superiority of one medication over the other. There is history of use with tetrabenazine in tardive dyskinesia.

IX. For patients with a diagnosis of TD, additional pharmacologic interventions include the use of benzodiazepines, botulinum toxin injections, or tetrabenazine (Xenazine) to control symptoms of TD, paradoxically, resuming treatment with antipsychotic drugs in order to suppress TD.

Investigational or Not Medically Necessary Uses

I. Tourette's syndrome
   A. Tetrabenazine (Xenazine)
      A. VMAT2 inhibitors currently available in the United States include deutetrabenazine and valbenazine. Although both are being investigated in the treatment of TS, they, like tetrabenazine (Xenazine), are not yet approved by the US Food and Drug Administration (FDA).
      B. There is insufficient evidence to support the use of tetrabenazine (generic, Xenazine) for the treatment of other movement disorders, including, but not limited to dystonic tremor, or Tourette's syndrome.
   B. Deutetrabenazine (Austedo)
      i. Deutetrabenazine (Austedo) is currently being investigated for use in Tourette's syndrome in:
         a. A Pilot Study Of SD-809 (Deutetrabenazine) In Moderate To Severe Tourette Syndrome
         b. A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents
      ii. Although deutetrabenazine (Austedo) is being studied for the treatment of Tourette's syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.
   C. Valbenazine (Ingrezza)
      1. Valbenazine (Ingrezza) is currently being investigated for use in Tourette's syndrome; however, initial studies have not demonstrated efficacy for this condition.
         i. In a phase 2 trial in pediatric patients with tics associated with Tourette's syndrome, valbenazine (Ingrezza) did not meet the pre-specified primary endpoint of change from baseline between the placebo valbenazine (Ingrezza) in the Yale Global Tic Severity Scale (YGTSS) at week six in the intent-to-treat population.
         ii. Based on the above results, a second phase 2 trial will aim to evaluate a higher dose of valbenazine (Ingrezza) to suppress tics in pediatric patients.

2. Although valbenazine (Ingrezza) is being studied for the treatment of Tourette's syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.

II. Chorea associated with Huntington's disease

A. Valbenazine (Ingrezza) is currently being investigated for use in Chorea associated with Huntington's disease in a Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of valbenazine for the treatment of chorea associated with Huntington's disease.

References

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3. Ingrezza [Prescribing Information]. Neurocrine Pharmaceuticals; San Diego, CA. April 2017
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11. Efficacy, Safety, and Tolerability of Valbenazine for the Treatment of Chorea Associated With Huntington's Disease (KINECT-HD), ClinicalTrials.gov Identifier: NCT04102579, https://clinicaltrials.gov/ct2/show/NCT04102579?term=valbenazine&draw=2&rank=4
12. A Pilot Study Of SD-809 (Deutetrabenazine) In Moderate To Severe Tourette Syndrome, ClinicalTrials.gov Identifier: NCT02674321, https://clinicaltrials.gov/ct2/show/NCT02674321?term=deutetrabenazine&draw=2&rank=4
13. A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents, ClinicalTrials.gov Identifier: NCT03452943, https://clinicaltrials.gov/ct2/show/NCT03452943?term=deutetrabenazine&draw=2&rank=7
14. Safety and Efficacy of NBI-98854 (valbenazine) in Pediatric Subjects With Tourette Syndrome, ClinicalTrials.gov Identifier: NCT03530293, https://clinicaltrials.gov/ct2/show/NCT03530293?term=valbenazine&draw=2&rank=7

Policy Implementation/Update:

Date Created	December 2019
Date Effective	December 2019
Last Updated	December 2019
Last Reviewed	05/2017, 06/2017, 08/2019, 09/2017 , 12/2019

Action and Summary of Changes	Date
• Updated criteria to policy format and combined separate polices into one • Generic tetrabenazine added to tardive dyskinesia criteria • For deutetrabenazine (Austedo) only: Treatment with generic tetrabenazine and valbenazine (Ingrezza) has been ineffective, contraindicated or not tolerated • Medication will not be used in combination with another VMAT2 inhibitor , monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine], it is contraindicated	12/2019
Added Tardive Dyskinesia indication for deutetrabenazine (Austedo™)	09/2017
Updated question 5 for valbenazine (Ingrezza™) based on P&T recommendations	08/2017

tiopronin (Thiola®; Thiola EC®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP158

Description

Tiopronin (Thiola) is an active reducing agent which undergoes thiol-disulfide exchange with cystine to form tiopronin-cystine disulfide, which is more water soluble than cystine. As a result, the amount of sparingly soluble cystine in the urine is decreased and the formation of cystine calculi is reduced.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tiopronin (Thiola)	100 mg tablet	Nephrolithiasis (cystine), prevention	450 tablets/30 days
tiopronin (Thiola EC)	100 mg delayed release tablet		450 tablets/30 days
	300 mg delayed release tablet		150 tablets/30 days

Initial Evaluation

I. Tiopronin (Thiola; Thiola EC) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **OR**
      1. Younger than 18 years of age and weighing 20 kg or greater; **AND**
   B. Medication is prescribed by, or in consultation with, a nephrologist or urologist; **AND**
   C. A diagnosis of **severe homozygous cystinuria** when the following are met:
      1. Urinary cystine levels greater than 500 mg/day; **AND**
      2. Member has <u>not</u> been responsive to <u>all</u> of the following:
         i. High fluid intake
         ii. Urinary alkalinization
         iii. Diet modification (e.g. restriction of sodium and protein intake)

II. Tiopronin (Thiola; Thiola EC) is considered <u>investigational</u> 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 as indicated by a reduction in cystine stone production OR a urinary cystine concentration less than 250 mg/L.

Supporting Evidence

I. Tiopronin (Thiola; Thiola EC) is a reducing-agent that helps form tiopronin-cystine disulfide, which is more readily excreted by the body, as it is more water soluble.
II. Topronin (Thiola; Thiola EC) is FDA-approved to prevent cystine stone formation in adults and pediatric patients 20 kg and greater with severe homozygous cystinuria, who are unresponsive to high fluid intake, alkali, and diet modification.
III. The recommended initial dose in adult patients is 800 mg/day. In clinical studies, the average dose was about 1,000 mg/day.
IV. The recommended initial dose in pediatric patients 20 kg and greater is 15 mg/kg/day. Doses greater than 50 mg/kg per day should be avoided in pediatric patients. Pediatric patients receiving greater than 50 mg/kg tiopronin per day are at greater risk of proteinuria and nephrotic syndrome.
V. Tiopronin (Thiola; Thiola EC) tablets are not approved for use in pediatric patients weighing less than 20 kg as safety and efficacy has not been established in this population.
VI. Urinary cystine levels should be measured one month after initiation of tiopronin (Thiola; Thiola EC) and every three months thereafter. The dose should be adjusted to maintain a urinary cystine concentration of less than 250 mg/L.

Investigational or Not Medically Necessary Uses

I. Tiopronin (Thiola; Thiola EC) has not been sufficiently evaluated outside of severe homozygous cystinuria.

References

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2. Thiola EC [prescribing information]. San Antonio, TX: Mission Pharmacal Company; June 2019.
3. UpToDate, Inc. Cystine stones. UpToDate [database online]. Waltham, MA. Last updated March 01, 2019 Available at: http://www.uptodate.com/home/index.html.

Policy Implementation/Update:

Date Created	December 2019
Date Effective	December 2019
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date

Policy Type: PA Pharmacy Coverage Policy: UMP229

Description

Tirbanibulin (Klisyri) is a topical microtubule inhibitor.

Length of Authorization

- Initial: One-time fill
- Renewal: Not eligible/Cannot be renewed

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tirbanibulin (Klisyri)	2.5 mg/250 mg (1%) ointment in a single-dose packet	actinic keratosis (AK)	5 packets/5 days

Initial Evaluation

I. Tirbanibulin (Klisyri) 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 dermatologist; **AND**
   C. Member has <u>not</u> been treated with tirbanibulin (Klisyri) before; **AND**
   D. A diagnosis of **actinic keratosis (AK)** when the following are met:
      1. Member will treat lesions on the face or scalp; **AND**
      2. Treatment with at least **TWO** of the following have been ineffective, not tolerated, or all are contraindicated:
         i. 5-fluorouracil (5-FU) cream
         ii. Imiquimod cream
         iii. Diclofenac gel

II. Tirbanibulin (Klisyri) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Patients with recurrent AK previously treated with tirbanibulin (Klisyri)
   B. Treatment of AK on other body parts (e.g. hands, legs, neck, etc.) other than the face or scalp

Supporting Evidence

I. The safety and efficacy of tirbanibulin (Klisyri) has been studied in adult patients, with no clinical trial data to support the use in pediatric patients; however, AK is a skin condition generally seen in the older population.

II. AK is the most common precancer that forms on skin damaged by chronic exposure to ultraviolet (UV) rays from the sun or indoor tanning. Most AKs do not progress to squamous cell

carcinoma (SCC), but majority of cutaneous SCCs progress from AKs. Given AK may progress to SCC, dermatologist involvement in the patient's care is recommended.

III. Patients previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment of tirbanibulin (Klisyri). The safety and efficacy of treating with a second application (i.e., treating AK that has recurred after treatment with tirbanibulin [Klisyri]) is unknown.

IV. The safety and efficacy of tirbanibulin (Klisyri) was studied in two identically designed Phase 3, double-blind, vehicle-controlled, randomized, parallel-group, multicenter studies in 702 patients with AK of the face or scalp.

- The majority of patients were white and male, with a Fitzpatrick skin type of I (pale white skin, blue/green eyes, blond/red hair) or II (fair skin, blue eyes) and a median of six lesions.
- The primary efficacy outcome was complete response rate and the main secondary outcome was partial response.

Outcomes	Trial 1 (N=351)		Trial 2 (N=351)		Pooled data (N=702)	
	tirbanibulin (N=175)	vehicle (N=176)	tirbanibulin (N=178)	vehicle (N=173)	tirbanibulin (N=353)	vehicle (N=349)
Complete response rate*	77 (44%)	8 (5%)	97 (54%)	22 (13%)	174 (49%)	30 (9%)
Difference	40% 95% CI (32-47); p <0.001		42% 95% CI (33-51); p <0.001		41% 95% CI (35-47); p <0.001	
Partial Response rate**	119 (68%)	29 (16%)	136 (76%)	34 (20%)	255 (72%)	63 (18%)
Difference	52% 95% CI (43-60); p <0.001		57% 95% CI (48-65); p <0.001		54% 95% CI (48-60); p <0.0001	

* Proportion of subjects achieving complete clearance of all AK in the selected area
** Proportion of subjects achieving reduction of at least 75% in the number of lesions within the application area

- Tirbanibulin (Klisyri) treated patients who achieved CR (N=174) were included in a one year follow up; of those, 124 (73%) patients developed lesions within the area treated with tirbanibulin (Klisyri). Out of the 124 patents, 72 (58%) had recurrent lesions and 52 (42%) had new lesions. The sustained complete clearance is 27%.
- The most common local reactions were erythema (91% of the patients) and flaking or scaling (82%). Although generally mild, crusting, swelling, vesiculation or pustulation, erosion, and ulceration were also seen.

V. Longstanding therapies for the treatment of AK include destructive therapies [e.g., surgery, cryotherapy, dermabrasion, photodynamic therapy (PDT)], field ablation treatments (e.g., chemical peels, laser resurfacing), and topical medications (e.g., fluorouracil, imiquimod, diclofenac).

- Topical medications including fluorouracil, imiquimod and diclofenac are used as first-line therapy with a well-established long-term efficacy and safety profile.
- In a randomized controlled trial comparing the recurrence of AKs after treatment with fluorouracil 5%, imiquimod 5%, or PDT, fluorouracil had the highest cumulative probability of remaining free from treatment failure (defined as <75% reduction in AK lesions) 12 months after treatment. For fluorouracil, 75% of patients were free from treatment failure, followed by imiquimod at 54%, PDT at 38%.
- Tirbanibulin (Klisyri) is a topical ointment applied once daily for five consecutive days. Patients who were previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment cycle

of tirbanibulin (Klisyri) and had a high recurrence rate (73%) one year after treatment. There is limited data on long-term safety and efficacy.

Investigational or Not Medically Necessary Uses

I. Tirbanibulin (Klisyri) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Patients previously treated with tirbanibulin (Klisyri): Patients previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment cycle of tirbanibulin (Klisyri). The safety and efficacy of treating more than one 25cm^2 area at a time or as a second application in an area with recurrence is unknown. There is no clinical trial data to support the use in patients previously treated.
   B. Treatment of AK on other body parts (e.g. hands, legs, neck, etc.) other than the face or scalp: The safety and efficacy of tirbanibulin (Klisyri) was studied in patients with AK of the face or scalp. No patients with lesions on other body parts were included in the clinical trial. There is no clinical trial data to support the use on other parts of the body.

References

1. Blauvelt A, Kempers S, Lain E, et al. Phase 3 Trials of Tirbanibulin Ointment for Actinic Keratosis. *N Engl J Med*. 2021;384(6):512-520. doi:10.1056/NEJMoa2024040.
2. R.N. Werner, et al. Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis – International League of Dermatological Societies in cooperation with the European Dermatology Forum. EADV 2015, 29, 2069–2079 DOI: 10.1111/jdv.13180
3. Maud H.E. Jansen, M.D., et al. Randomized Trial of Four Treatment Approaches for Actinic Keratosis. N Engl J Med 2019; 380:935-946 DOI: 10.1056/NEJMoa1811850
4. Actinic keratosis: Diagnosis and treatment. Retrieved February, 2021, from https://www.aad.org/public/diseases/skin-cancer/actinic-keratosis-treatment
5. de Oliveira ECV, et al. Actinic keratosis - review for clinical practice. Int J Dermatol. 2019;58(4):400-407.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP230

Description

Tivozanib (Fotivda) is an orally administered VEGFR kinase inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tivozanib (Fotivda)	1.34 mg capsules	Relapsed or refractory advanced renal cell carcinoma, following at least two prior systemic therapies	21 capsules/28 days
	0.89 mg capsules		

Initial Evaluation

I. **Tivozanib (Fotivda)** 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. Not used in combination with any other oncology therapy (e.g., everolimus [Afinitor], temsirolimus (Torisel), ipilimumab [Yervoy], nivolumab [Opdivo]; **AND**
   D. A diagnosis of **advanced or metastatic renal cell carcinoma** when the following are met:
      1. Provider attestation the member has clear cell component histology; **AND**
      2. Member has renal cell carcinoma that is relapsed or refractory to at least **TWO** prior systemic therapies (e.g., axitinib [Inlyta], ipilimumab [Yervoy], nivolumab [Opdivo], everolimus [Afinitor]; **AND**
         i. At least **ONE** of the prior therapies is an anti-VEGFR TKI (e.g., axitinib [Inlyta], lenvatinib [Lenvima], pazopanib [Votrient], sunitinib [Sutent], cabozantinib [Cabometyx].

II. Tivozanib (Fotivda) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Renal cell carcinoma prior to third-line treatment

III. Tivozanib (Fotivda) is considered investigational when used for all other conditions, including but not limited to:
   A. Renal cell carcinoma in combination with other oncolytic therapies

B. Renal cell carcinoma prior to the relapsed refractory and/or advanced settings
C. Prostate cancer
D. Breast cancer
E. Ovarian, fallopian tube, or primary peritoneal cancer
F. Lung Cancer
G. Gastrointestinal tumors
H. Hepatocellular carcinoma
I. Cholangiocarcinoma
J. Colorectal cancer
K. Glioblastoma

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 the medication will not be used in combination with any other oncology therapy (e.g., everolimus [Afinitor], temsirolimus (Torisel), ipilimumab [Yervoy], nivolumab [Opdivo]; **AND**
IV. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

I. Tivozanib (Fotivda) is a VEGFR tyrosine kinase inhibitor (TKI) that is FDA-approved for patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more systemic therapies. Tivozanib (Fotivda)is approved for 21 days on therapy and seven days off until disease progression or unacceptable toxicity. It is the first therapy specifically FDA-approved for the third-line setting, but joins several other anti-VEGFR medications for this condition, as well as immunotherapies and mTOR inhibitors. All therapy categories are utilized in the subsequent treatment setting after members have progressive disease.
II. Other anti-VEGFR medications include: cabozantinib (Cabometyx), pazopanib (Votrient), sorafenib (Nexavar), lenvatinib (Lenvima), sunitinib (Sutent) and axitinib (Inlyta). Immunotherapy options include: ipilimumab (Yervoy), nivolumab (Opdivo), avelumab (Bavencio). The mTOR inhibitors include therapies such as everolimus (Afinitor), temsirolimus (Torisel). Often, immunotherapies will be used in combination with each other, or in combination with anti-VEGFR medications. The mTOR inhibitors are also utilized in combination with anti-VEGFR medications; however, use of two concomitant anti-VEGFR medications has not been evaluated, and given the unfavorable safety profiles of these medications, combination treatment is not advised.
III. As of March 2021, all three categories of medications are used for clear cell RCC. In the subsequent treatment setting, NCCN Cat. 1 recommended regimens include cabozantinib

(Cabometyx), nivolumab (Opdivo), axitinib (Inlyta), and lenvatinib (Lenvima) plus everolimus (Afinitor). The remainder have Cat. 2A recommendations, with the exception of sorafenib (Nexavar) which has a Cat. 2B recommendation.

IV. Treatment choice is based on stage of disease, prognosis, line of therapy, and other patient characteristics. Tolerability and safety considerations are taken into account for treatment choice as well. Given the extensive treatment options, combinations, and unfavorable safety profiles that require extensive medication monitoring, medication should be prescribed by or in consultation with a specialist.

V. In 2013 tivozanib (Fotivda) was evaluated in a Phase 3 trial vs. sorafenib (Nexavar) in 517 patients with RCC for initial targeted therapy in those that had received up to one prior systemic treatment. Patients had prior nephrectomy, clear cell RCC, and up to one prior therapy that was not an anti-VEGFR. Progression-free survival (PFS) was statistically significant favoring tivozanib (Fotivda); however, the overall survival (OS) was not statistically different. In 2013, the FDA issued a Complete Response Letter to Aveo, given an inconclusive risk benefit assessment and required another trial from the manufacturer in the advanced setting.

VI. Following the CRL, tivozanib (Fotivda) was evaluated in an open-label, randomized, Phase 3 trial vs. sorafenib (Nexavar) in 350 adults with RCC. Ninety-eight percent of patients had clear cell histology. Patients had advanced disease and were relapsed or refractory to two or three prior systemic therapies, including at least one anti-VEGFR therapy. Forty-five percent of patients had two prior anti-VEGFR therapies and 26% had prior checkpoint inhibitor therapy. About 60% of patients had intermediate, 20% had favorable, and 20% had poor prognoses. The study showed a statistical increase in PFS (5.6 months vs. 3.9 months), as well as partial responses (18% vs. 8%); however, OS was not statistically different and numerically favored sorafenib (Nexavar). To date, tivozanib (Fotivda) has not proven to have clinically meaningful outcomes such as increased survival, improvement in quality of life or symptom control. This is similar for the comparator, sorafenib (Nexavar). Thus, clinical benefit of either therapy remains unclear.

VII. To date, the safety tivozanib (Fotivda) is similar to other anti-VEGFR medications. Serious adverse events (AE) occurred in 11% of patients on tivozanib (Fotivda) and in 10% for sorafenib (Nexavar). AE more frequent with tivozanib (Fotivda): hypertension (44% vs. 31%), bleeding (17% vs. 12%), nausea (30% vs. 18%), decreased appetite (39% vs. 30%), dysphonia (27% vs. 9%), cough (22% vs. 15%), and hypothyroidism (24% vs. 11%). AE more frequent with sorafenib (Nexavar): diarrhea (54% vs. 44%), rash (52% vs. 18%), and palmar-plantar syndrome (41% vs. 16%). Stomatitis, vomiting, pain, dyspnea, and weight loss were common and occurred in similar rates between treatment arms

VIII. Dose interruption due to AE occurred in 48% of the tivozanib (Fotivda) group and 63% of the sorafenib (Nexavar) group. Dose reductions due to AE occurred in 24% for tivozanib (Fotivda) and 38% for sorafenib (Nexavar). The lower dose reduction and interruption rates for tivozanib (Fotivda) are likely attributable to the seven-day break within each cycle vs. continuous dosing with sorafenib (Nexavar). Given lack of long-term safety evaluation and lack of evaluation against placebo, true benefits and harms are unknown at this time. At this time there is insufficient safety information (given limited patient experience and duration of therapy) to definitively indicate that there is substantial safety differences between any of the anti-VEGFR therapies.

Investigational or Not Medically Necessary Uses

I. Tivozanib (Fotivda) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Renal cell carcinoma prior to third-line.
      i. Tivozanib (Fotivda) has been evaluated for first-line and second-line treatment but did not achieve FDA-approval given uncertain risks and benefits.
   B. The following indications have not been sufficiently studied for efficacy and use outside of clinical trials is not advised given the unfavorable safety profile alone or in combination with other medications:
      i. Renal cell carcinoma in combination with other oncolytic therapies
      ii. Renal cell carcinoma prior to the relapsed refractory and/or advanced settings
      iii. Prostate cancer
      iv. Breast cancer
      v. Ovarian, fallopian tube, or primary peritoneal cancer
      vi. Lung Cancer
      vii. Gastrointestinal tumors
      viii. Hepatocellular carcinoma
      ix. Cholangiocarcinoma
      x. Colorectal cancer
      xi. Glioblastoma

References

1. Fotivda [Prescribing Information]. Aveo Pharmaceuticals Inc. Boston, MA. March 2021.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP159

Description

Tobramycin (TOBI®) inhalation solution, generic tobramycin inhalation solution, tobramycin (KITABIS™) inhalation solution, tobramycin (TOBI Podhaler®) inhalation solution and tobramycin (Bethkis®) inhalation solution are aminoglycoside antibacterial drugs that act primarily by disrupting protein synthesis in the bacterial cell which eventually leads to death of the cell. Tobramycin inhalation solutions have activity against a wide range of gram-negative bacteria including *Pseudomonas aeruginosa*.

Length of Authorization

- Initial: 12 months (7 fills per year)
- Renewal: 12 months (7 fills per year)

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tobramycin (TOBI)	300 mg/5mL one single-use ampule	Cystic fibrosis with P*seudomonas aeruginosa*	56 single-dose ampules/28 days
generic tobramycin inhalation solution	300 mg/5mL one single-use ampule		56 single-dose ampules/28 days
tobramycin (KITABIS)	300 mg/5mL one single-use ampule		56 single-dose ampules/28 days
tobramycin (Bethkis)	300 mg/4 mL one single-use ampule		56 single-dose ampules/28 days
tobramycin (TOBI Podhaler)	28mg inhalation capsule		224 inhalation capsules /28 days

Initial Evaluation

I. **Generic tobramycin inhalation solution and tobramycin (KITABIS) inhalation solution** may be considered medically necessary when the following criteria below are met:
   A. Member is six 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. Member has tested positive for *Pseudomonas aeruginosa* in the lungs; **AND**
      2. Member has FEV_1 >25% or <80% ; **AND**
      3. Member is not colonized *with Burkholderia cepacia*

II. **Tobramycin (TOBI) inhalation solution and tobramycin (BETHKIS) inhalation solution** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**

B. Generic tobramycin inhalation solution and tobramycin (KITABIS) inhalation solution have been ineffective, contraindicated, or not tolerated.

III. **Tobramycin (TOBI Podhaler) inhalation solution** 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 generic tobramycin inhalation solution and tobramycin (KITABIS) inhalation solution has been ineffective, contraindicated, or not tolerated; **AND**
   C. Treatment with tobramycin (TOBI) inhalation solution and tobramycin (BETHKIS) inhalation solution has been ineffective, contraindicated, or not tolerated.

IV. Generic tobramycin inhalation solution, tobramycin (KITABIS) inhalation solution, tobramycin (TOBI) inhalation solution, tobramycin (BETHKIS) inhalation solution and tobramycin (TOBI Podhaler) inhalation solution are considered investigational when used for all other conditions, including but not limited to:
   A. Non–cystic fibrosis bronchiectasis

Renewal Evaluation

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

Supporting Evidence

I. The safety and efficacy of tobramycin inhalation solution in pediatric patients under six years of age has not been established due to the lack of clinical trial data. The use is not indicated in pediatric patients under the age of six.
II. Tobramycin inhalation solution is administered twice daily in alternating periods of 28 days. After 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle. To ensure appropriate dosing of tobramycin nebulizer or podhaler in members with cystic fibrosis, approval will allow for 7 fills within a 1 year approval period.
III. Safety and efficacy have not been demonstrated in patients with FEV1 <40% or >80% (Bethkis), FEV1 <25% or >80% (Tobi Podhaler), FEV1 <25% or >75% (Tobi and Kitabis), or patients colonized with Burkholderia cepacia.
IV. Tobramycin inhalation solution is used in treatment of cystic fibrosis and need to be prescribed by, or in consultation with, a pulmonologist because of the complexity of the disease state.
V. Guidelines developed by the Pulmonary Therapies Committee of the Cystic Fibrosis Foundation made the following recommendations for tobramycin solution for inhalation (TSI) (written prior to the approval of aztreonam lysine inhalation solution (AZLI)):
   - Moderate to severe lung disease (>6 years of age): For patients colonized with P. aeruginosa, the chronic use of TSI is strongly recommended to improve lung function and reduce exacerbations (grade A recommendation).

- Mild lung disease or asymptomatic (>6 years of age): For patients colonized with P. aeruginosa, the chronic use of TSI is recommended to reduce exacerbations (grade B recommendation).

VI. In the absence of direct comparative trails there's no evidence to conclude that one product is safer or more effective than another.

Investigational or Not Medically Necessary Uses

I. Non–cystic fibrosis bronchiectasis

A. Efficacy of adding inhaled tobramycin solution (TS) to oral ciprofloxacin was studied. In a multicenter trial, 53 patients with known P. aeruginosa infection who were having exacerbations of bronchiectasis were randomly assigned to receive ciprofloxacin plus inhaled TS or ciprofloxacin plus placebo for two weeks. The addition of inhaled TS to ciprofloxacin did not improve clinical outcomes compared to ciprofloxacin alone, although there was a marked reduction of Pseudomonas density in the sputum of patients who received inhaled TS plus ciprofloxacin. Wheezing was more common in the inhaled TS plus ciprofloxacin group. Based on current data, inhaled aerosols of antibiotics, such as TS, cannot be recommended alone or in combination with ciprofloxacin for acute exacerbations in bronchiectasis.

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Policy Implementation/Update:

Date Created	May 2013
Date Effective	March 2017
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date
• Updated criteria to policy format • Tobramycin (TOBI Podhaler) inhalation solution is considered medically necessary if treatment with tobramycin (KITABIS) inhalation solution and tobramycin (TOBI) inhalation solution has been ineffective, contraindicated, or not tolerated • Tobramycin (TOBI) inhalation solution and tobramycin (BETHKIS) inhalation solution are considered medically necessary if treatment with tobramycin (KITABIS) and generic tobramycin has been ineffective, contraindicated or not tolerated • Added tobramycin (KITABIS) to policy	12/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP068

Description

Tolvaptan (Jynarque) is a selective vasopressin V(2)-receptor antagonist.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tolvaptan (Jynarque)	15 mg tablets	Autosomal dominant polycystic kidney disease	28 tablets/28 days
	30 mg tablets		60 tablets/30 days
	15 & 15 mg tablet therapy pack		56 tablets/28 days (1 box/28 day)
	30 & 15 mg tablet therapy pack		56 tablets/28 days (1 box/28 day)
	45 & 15 mg tablet therapy pack		56 tablets/28 days (1 box/28 day)
	60 & 30 mg tablet therapy pack		56 tablets/28 days (1 box/28 day)
	90 & 30 mg tablet therapy pack		56 tablets/28 days (1 box/28 day)

Initial Evaluation

I. Tolvaptan (Jynarque) may be considered medically necessary when the following are met:
   A. Prescribed by prescribed by, or, in consultation with a nephrologist; **AND**
   B. A diagnosis of **autosomal dominant polycystic kidney disease (ADPDK)** when the following are met:
      1. Diagnosis is confirmed by imaging (e.g., ultrasound, CT, MRI) or genetic test; **AND**
      2. Member has rapidly-progressing ADPKD (e.g., reduced or declining renal function, high or increasing total kidney volume [height adjusted]); **AND**
      3. Member does not have Stage 5 chronic kidney disease (CKD) defined as a glomerular filtration rate {GFR} < 15 mL/min/1.73 m2, or receiving dialysis

II. Tolvaptan (Jynarque) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Hyponatremia

Renewal Evaluation

I. Member experienced disease stability, or improvement (e.g., reduction in number and/or rate of cyst production, change in renal function, reduction in rate of total kidney volume growth, slowed rate of kidney function decline); **AND**
II. Documented lack of unacceptable toxicity

Supporting Evidence

I. Polycystic kidney disease (PKD) includes inherited diseases that cause irreversible decline in kidney function. PKD may be inherited as an autosomal dominant or recessive trait. The autosomal dominant form (autosomal dominant PKD [ADPKD]) is the most common genetic cause of chronic kidney disease (CKD). The majority of individuals with PKD eventually require renal replacement therapy.
II. The diagnosis of ADPKD is most commonly made via screening using ultrasound, CT scan or MRI. Genetic testing is available for definitive diagnosis, but is rarely performed. Confirmed diagnosis of ADPKD via one of these tests is required prior to coverage of Jynarque.
III. Tolvaptan (Jynarque) was shown to slow the rate of decline in renal function in adults at risk of rapidly-progressing ADPKD in two phase 3 randomized controlled trials, TEMPO and REPRISE.
    - TEMPO: Included 1445 adult patients with estimated creatinine clearance >60 mL/min and total kidney volume (TKV) >750 mL. The trial met the pre-specified primary endpoint of 3-year change in TKV ($p<0.0001$). The annual decline in eGFR was slower among patients who received tolvaptan compared to placebo (-2.72 versus -3.70 mL/min/1.73 m2 per year). Tolvaptan also reduced the rate of decline in kidney function at three years (hazard ratio [HR] 0.39, 95% CI 0.26-0.57), and the incidence of clinically significant kidney pain (HR 0.64, 95% CI 0.47-0.89).
    - REPRISE: Examined the effect of tolvaptan in patients with ADPKD who had reduced eGFR; such patients were generally not included in the TEMPO trial. At 12 months, the change from baseline eGFR was lower among those assigned tolvaptan as compared with placebo (-2.34 versus -3.61 mL/min/1.73 m^2); the group difference was 1.27 mL/min/1.73 m^2 (95% CI 0.86-1.68).
    - The analysis of the REPRISE trial, and a post-hoc analysis of the TEMPO trial, showed that tolvaptan (Jynarque) may extend the time until stage 5 CKD (ie, eGFR <15 mL/min/1.73 m2) from six to nine years among patients who start tolvaptan with an eGFR <60 mL/min/1.73 m2, and, even longer among those who start tolvaptan earlier.
    - Clinical trial criteria for rapidly progressive ADPKD
        i. Age 18-50 AND eGFR ≥60ml/min/1.73m2 AND Total Kidney Volume ≥750ml
        ii. Age 18-55 AND eGFR 25 to 65ml/min/1.73m2
        iii. Age 56-65 AND eGFR 25 to 44 ml/min/1.73m2 AND documented eFGR decline of more than 2.0 ml/min/1.73m2 per year
    - The pivotal trials for Jynarque did not involve patients with Stage 5 CKD (glomerular filtration rate [GFR] < 15 mL/min/1.73 m2 or receiving dialysis).
IV. Tolvaptan (Jynarque) is a part of a Risk Evaluation and Mitigation Strategy (REMS) program to monitor for liver injury.

V. Tolvaptan (Jynarque) should not be used off-label for other diagnoses due to lack of evidence, and risk of adverse events.

VI. In clinical trials, outcomes included the reduction in rate of total kidney volume growth, the slowed rate of kidney function decline, improvement in renal function, a change in mean arterial blood pressure, and change in renal pain. Stability of disease, or improvement in at least one of these measures, is indicative of treatment response. Additionally, fatal liver injury is a significant safety concern of Jynarque; liver function tests should be monitored periodically.

Investigational or Not Medically Necessary Uses

I. Hyponatremia
   A. Samsca, is a tolvaptan formulation that is FDA approval for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium of less than 125 mEq/L or less marks hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Jynarque has not been evaluated for treatment of hyponatremia.

References

1. Jynarque [Prescribing Information]. Tokyo, Japan: Otsuka Pharmaceutical Co. April 2018
2. Muto S. Kawano H., Higashihara E., et al. The effect of tolvaptan on autosomal dominant polycystic kidney disease patients: a subgroup analysis of the Japanese patient subset from TEMPO 3:4 trial. Clin Exp Nephrol. 2015;19(5):867-877.
3. Torres, VE, Chapman, AB, Devuyst, O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. The New England journal of medicine. 2012 Dec 20;367(25):2407-18. PMID: 23121377
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5. UpToDate, Inc. Treatment of autosomal dominant polycystic kidney disease. UpToDate [database online]. Waltham, MA. Available at http://www.uptodate.com/home/index.html. Updated April 12, 2019

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to policy format. Added the following: quantity limits for new 15 mg and 30 mg tablet, therapy to be prescribed by or in consultation with nephrologist, limited use to reflect patient population included in clinical trial (i.e. rapidly progressing ADPKD and do not have stage 5 CKD).	5/2019
Date created	05/2018

tolvaptan (Samsca®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP099

Description

Tolvaptan (Samsca) is an orally administered vasopressin V2-receptor antagonist which causes an increase in urine water excretion that results in an increase in free water clearance (aquaresis), a decrease in urine osmolality, and a resulting increase in serum sodium concentrations.

Length of Authorization

- Initial: one month
- Renewal: no renewal

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tolvaptan (Samsca)	15 mg tablet	Hypervolemic or euvolemic hyponatremia	30 tablets/30 days*
	30 mg tablet		60 tablets/30 days*

*****_Therapy should not be continued past 30 days._

Initial Evaluation

I. Tolvaptan (Samsca) 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 nephrologist; **AND**
   C. Medication was initiated in the hospital; **AND**
   D. The requested treatment course will not exceed a 30-day duration per FDA recommendation; **AND**
   E. A diagnosis of **clinically significant hypervolemic or euvolemic hyponatremia** when the following are met:
      1. Serum sodium is less than 125 mEq/L; **OR**
      2. Serum sodium is greater than 125 mEq/L **and** patient has symptomatic hyponatremia (e.g., nausea, vomiting, headache, lethargy, confusion) that has resisted correction with fluid restriction

II. Tolvaptan (Samsca) is considered investigational when used for all other conditions, including but not limited to:
   A. Autosomal Dominant Polycystic Kidney Disease (ADPKD)
   B. Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms

Supporting Evidence

I. Per the label, tolvaptan (Samsca) is indicated for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).
II. Safety and effectiveness of tolvaptan (Samsca) in pediatric patients has not been established.
III. Per the label, patients should be in a hospital for initiation and re-initiation of therapy to evaluate the therapeutic response and because too rapid correction of hyponatremia can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death.
IV. To minimize the risk of liver injury, tolvaptan (Samsca) should not be administered for more than 30 days. Based largely on the hepatic injury noted in the TEMPO trial, on April 2013 the FDA recommended that: "treatment should be stopped if the patient develops signs of liver disease. Treatment duration should be limited to 30 days or less, and use should be avoided in patients with underlying liver disease, including cirrhosis".
V. It has not been established that raising serum sodium with tolvaptan (Samsca) provides a symptomatic benefit to patients.

Investigational or Not Medically Necessary Uses

I. Autosomal Dominant Polycystic Kidney Disease (ADPKD)
   A. Jynarque (tolvaptan) is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD; however, the recommended dosing in Jynarque differs from the Samsca product. Per the tolvaptan (Samsca) label, because of the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS.
II. Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms.
   A. Tolvaptan (Samsca) has not been studied in a setting of urgent need to raise serum sodium acutely.

References

1. Samsca [prescribing information]. Rockville, MD: Otsuka Pharmaceuticals; April 2018.
2. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med. 2012;367(25):2407-18.
3. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Verbalis JG, Goldsmith SR, Greenberg A,Korzelius C, Schrier RW, Sterns RH, Thompson CJ. https://doi.org/10.1016/j.amjmed.2013.07.006Am J Med. 2013;126:0.3. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. Neprhol DialTransplant 2014; 29 Suppl 2:i1.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP100

Description

Trametinib (Mekinist) is an orally administered mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and MEK1 and MEK2 activity; while also, inhibiting BRAF V600 mutation-positive melanoma cell growth. Dabrafenib (Tafinlar) is an orally administered BRAF V600 inhibitor. When used in combination, there is greater and prolonged inhibition compared to either drug alone.

Length of Authorization

- Initial: Six months
- Renewal:
  - Six months for adjuvant treatment of melanoma that had lymph node involvement and was completely resected. One time renewal only (i.e., one total year of therapy authorized).
  - 12 months for all other indications

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
trametinib (Mekinist)	0.5 mg tablet	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy	90 tablets/30 days
	2 mg tablet	Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy	30 tablets/30 days
dabrafenib (Tafinlar)	50 mg capsule	Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy	120 capsules/30 days
	75 mg capsule	Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, monotherapy in BRAF treatment naïve patients Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy	

Initial Evaluation

I. Trametinib (Mekinist) and dabrafenib (Tafinlar) may be considered medically necessary in combination 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 prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination AND no other oncolytic medication will be used concurrently; **AND**
   D. The member has not previously progressed on any prior BRAF-inhibitor therapy (e.g., vemurafenib); **AND**
   E. A diagnosis of one of the following:
      1. **Anaplastic thyroid carcinoma**; **AND**
         i. The disease has been tested and shown to have BRAF V600E mutation; **AND**
            a. The disease is metastatic (stage IV); **OR**
            b. The disease is locally advanced (stage IVA or IVB); **AND**
               i. The member has received standard of care for the condition (e.g., surgery, radiation therapy, chemotherapy) OR there is no satisfactory locoregional treatment options; **OR**
      2. **Melanoma**; **AND**
         i. The disease has been tested and shown to have BRAF V600E or V600K mutation; **AND**
         ii. Melanoma is advanced (stage III), metastatic (stage IV), or unresectable; **OR**
            a. Melanoma has lymph node involvement and will be used as adjuvant treatment after complete resection; **OR**
      3. Non-small cell lung cancer; AND
         i. The disease has been tested and shown to have V600E mutation.

II. Trametinib (Mekinist) and dabrafenib (Tafinlar) are considered not medically necessary when criteria above are not met and/or when used for:
   A. Treatment after prior BRAF inhibitor therapy

III. Trametinib (Mekinist) and dabrafenib (Tafinlar) are considered investigational when used for all other conditions, including but not limited to:
   A. Colorectal cancer
   B. Ameloblastoma
   C. Thyroid cancer
   D. Erdheim Chester Disease
   E. Lung cancer
   F. CNS, and head and neck cancers, neurofibromas
   G. Rectal cancer
   H. Heaptocellular cancer

I. Leukemias, lymphomas
J. Prostate cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent; **AND**
II. The medication is prescribed by or in consultation with an oncologist; **AND**
III. The prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination AND no other oncolytic medication will be used concurrently; **AND**
IV. Documentation is provided indicating disease response to therapy, as defined by stabilization of disease or decrease in size of tumor or tumor spread

Supporting Evidence

I. Dabrafenib (Tafinlar) plus trametinib (Mekinist) have been evaluated in several clinical trials in adults. Safety and efficacy in pediatrics have not been established.
II. Trials:
- The METRIC study evaluated trametinib (Mekinist) as monotherapy in V600E or V600K mutation-positive, unresectable or metastatic melanoma. It was an open-label trial against chemotherapy (dacarbazine or paclitaxel). The primary outcome was progression-free survival (PFS), and statistically favored trametinib (Mekinist).
- The COMBI-d study was a double-blind, active controlled trial of dabrafenib (Tafinlar) plus trametinib (Mekinist) versus dabrafenib (Mekinist) alone. Subjects included had unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Combination therapy was statistically favorable in PFS and overall-survival (OS).
- The COMBI-AD trial evaluated dabrafenib (Tafinlar) with trametinib (Mekinist) versus placebo in those with stage III melanoma with BRAF V600E or V600K mutations. Results statistically favored dabrafenib (Tafinlar) plus trametinib (Mekinist) compared to placebo.
- A study of dabrafenib (Tafinlar) alone or administered with trametinib (Mekinist) was evaluated in an open-label, Phase 2 trial in subjects with BRAF V600E mutation-positive NSCLC. Combination therapy was statistically favored in overall response rate (ORR) and duration of response (DOR).
- A study of dabrafenib (Tafinlar) administered with trametinib (Mekinist) evaluated subjects with thyroid cancer that were BRAF V600E mutation positive. The open-label, single-arm trial included those that were locally advance, unresectable or metastatic with no locoregional treatment options. Primary outcomes were ORR and DOR.
- Trametinib (Mekinist) was evaluated for efficacy in melanoma in those that had previously received BRAF inhibitor therapy. No patients achieved partial or complete response.
- Dabrafenib (Tafinlar) was evaluated as monotherapy for BRAF V600E mutation positive unresectable or metastatic melanoma in the BREAK-3 study. The open-label trial evaluated dabrafenib (Tafinlar) versus dacarbazine, which demonstrated a statistically significant increase in PFS compared to dacarbazine.

- Dabrafenib (Tafinlar) was evaluated in the BREAK-MD study as a single-arm, Phase 2, open-label trial for mutation-positive melanoma, metastatic to the brain. The primary outcomes were ORR and DOR.
- The COMBI-d study evaluated dabrafenib (Tafinlar) to trametinib (Mekinist) plus dabrafenib (Tafinlar) in first-line therapy for unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Overall survival was statistically in favor of combination therapy.
- The COMBI-v study evaluated dabrafenib (Tafinlar) plus trametinib (Mekinist) versus vemurafenib (Zelboraf) for BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, and overall survival data was statistically in favor of dabrafenib (Tafinlar) plus trametinib (Mekinist).
- Adjuvant therapy for melanoma that had lymph node involvement and was completely resected, therapy is authorized for a total of one year maximum. Safety and efficacy beyond this time frame has not been sufficiently established.

Investigational or Not Medically Necessary Uses

I. Treatment after previous BRAF inhibitor therapy
   A. Trametinib (Mekinist) did not show to have efficacy in a trial evaluating as second-line therapy after previous therapy with BRAF inhibitors.

II. Safety and efficacy of trametinib (Mekinist) and/or dabrafenib (Tafinlar) has not been sufficiently evaluated for safety and/or efficacy in the following settings:
   A. Colorectal cancer
   B. Ameloblastoma
   C. Thyroid cancer
   D. Erdheim Chester Disease
   E. Lung cancer
   F. CNS, and head and neck cancers, neurofibromas
   G. Rectal cancer
   H. Hepatocellular cancer
   I. Leukemia, lymphoma
   J. Prostate cancer

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1. Mekinist [Prescribing Information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation. July, 2019.
2. Tafinlar [Prescribing Information]. Easy Hanover, New Jersey: Novartis Pharmaceuticals Corporation. July, 2019.
3. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367(2):107-14.
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6. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAF-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. Lancet Oncol. 2017;18(10):1307-1316.
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9. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(11):1087-95.

Policy Implementation/Update:

Date Created	November, 2013
Date Effective	November, 2013
Last Updated	October, 2019
Last Reviewed	01/2015, 06/2018

Action and Summary of Changes	Date
Criteria transitioned to policy, medications combined into one policy, addition of specialty prescriber, age edit, clarification on previous or alternative therapies to be considered for thyroid cancer. Quantity level limits updated.	11/2018
Criteria updated to include new indications of NSCLC and anaplastic thyroid cancer.	06/2018

Policy Type: PA/SP Pharmacy Coverage Policy: UMP069

Description

Trifluidine is an orally administered nucleoside analog that is incorporated into DNA to interfere with DNA synthesis and proliferation, and tipiracil increases exposure to trifluridine by inhibiting thymidine phosphorylase. Together they make the product Lonsurf.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
trifluridine/tipiracil (Lonsurf)	15 mg – 6.14 mg tablets	Stomach or esophagogastric adenocarcinoma – metastatic, previously treated Colorectal cancer – metastatic, previously treated	80 tablets/28 days	189858
	20 mg – 8.19 mg tablets		80 tablets/30 days	189857

Initial Evaluation

I. Trifluridine/tipiracil (Lonsurf) 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 or gastroenterologist; **AND**
   C. Trifluridine/tipiracil is used as monotherapy; **AND**
   D. A diagnosis of one of the following:
      1. **Colorectal cancer**; **AND**
         i. The disease is metastatic (i.e., stage IV); **AND**
         ii. The tumor has been tested and is documented to be KRAS mutant-type; **OR**
         iii. The tumor has been tested and is documented to be KRAS wild-type; **AND**
            a. The member has been previously treated with an anti-EGFR therapy (e.g., cetuximab, panitumumab); **AND**

iv. The member has been previously treated with a fluoropyrimidine (e.g., fluorouracil, capecitabine, S-1), oxaliplatin and irinotecan-based chemotherapy; **AND**
v. The member has been previously treated with an anti-VEGF biological therapy (e.g., bevacizumab); **OR**

2. **Gastric or gastroesophageal junction adenocarcinoma**; **AND**
   i. The disease is metastatic (i.e., stage IV); **AND**
   ii. The member has been tested and has documentation of HER2/neu negative status; **OR**
      a. The member has been tested and has documentation of HER2/neu positive status; **AND**
      b. Has received prior HER2/neu targeted therapy (e.g., trastuzumab); **AND**
   iii. The member has been previously treated with at least two prior lines of chemotherapy; **AND**
   iv. Previous treatments included a fluoropyrimidine (e.g., fluorouracil, capecitabine, S-1), a platinum therapy (e.g., cisplatin, carboplatin, oxaliplatin), and one of the following: a taxane (e.g., docetaxel, paclitaxel) or irinotecan

II. Trifluridine/tipiracil (Lonsurf) is considered investigational when used for all other conditions, including but not limited to:
   A. Combination therapy with other oncolytic agents.
   B. Colorectal cancer prior to the metastatic setting, and/or prior to use of a fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy regimen, and/or prior to use of an anti-VEGF biological therapy, and/or if the member is KRAS mutant-type use prior to an anti-EGFR therapy.
   C. Colorectal, gastric, or gastroesophageal cancer at a dose <20 mg/m2 orally twice daily.
   D. Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type).
   E. Gastric or gastroesophageal junction adenocarcinoma prior to at least two previous lines of chemotherapy and prior to use of all of the following: a fluoropyrimidine, a platinum therapy, and one of the following – taxane or irinotecan.
   F. Biliary track cancers.
   G. Tumors that are not colorectal, gastric or gastroesophageal in nature.

Renewal Evaluation

I. The medication is prescribed by or in consultation with an oncologist or gastroenterologist; **AND**
II. Trifluridine/tipiracil (Lonsurf) continues to be used as monotherapy; **AND**
III. Body surface area is provided in meters squared; **AND**
IV. Trifluridine/tipiracil (Lonsurf) is being used at or above a dose of 20 mg/m2; **AND**
V. The member is not experiencing unacceptable toxicity from the therapy; **AND**
VI. The patient has not experienced disease progression while on trifluridine/tipiracil (Lonsurf); **OR**

VII. Documentation of compelling clinical evidence of benefit is provided if therapy is to be continued in the setting of progression.

Supporting Evidence

I. There is lack of safety and efficacy data from clinical trials for use in pediatric patients. This medication has not been evaluated outside of the adult population.
II. Pivotal clinical trials for FDA-approved indications evaluated safety and efficacy of trifluridine/tipiracil (Lonsurf) as monotherapy in heavily pretreated patients. The therapies listed in the above criteria had been tried and failed by the majority of patients enrolled in the clinical trials.
III. There is no globally accepted standard for first-line treatment of HER2/neu negative gastric or gastroesophageal adenocarcinoma. When these indications were added to the policy, NCCN guidelines were not updated to provide recommendations for this agent. Clinical trial experience with extensive patient treatment history is the basis for addition into the policy. Overall survival data in the third line treatment setting was show to be 5.7 months for trifluridine/tipiracil (Lonsurf) vs 3.6 months for placebo.

Investigational or Not Medically Necessary Uses

All indications listed below have not been sufficiently studied for safety and efficacy, or have inconclusive evidence regarding safety and efficacy for use of trifluridine/tipiracil (Lonsurf).

I. Combination therapy with other oncolytic agents.
II. Colorectal cancer prior to the metastatic setting, and/or prior to use of a fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy regimen, and/or prior to use of an anti-VEGF biological therapy, and/or if the member is KRAS mutant-type use prior to an anti-EGFR therapy.
III. Colorectal, gastric, or gastroesophageal cancer at a dose < 20 mg/m2 orally twice daily.
IV. Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type).
V. Gastric or gastroesophageal junction adenocarcinoma prior to at least two previous lines of chemotherapy and prior to use of all of the following: a fluoropyrimidine, a platinum therapy, and one of the following – taxane or irinotecan.
VI. Biliary track cancers.
VII. Tumors that are not colorectal, gastric or gastroesophageal in nature.

References

1. Lonsurf [Prescribing Information]. Princeton, NJ. Taiho Oncology, Inc. Moda Health, Inc. February 2019.
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Policy Implementation/Update:

Date Created	May 2015
Date Effective	May 2015
Last Updated	September 2019
Last Reviewed	09/05/2019

Action and Summary of Changes	**Date**
Added new indication of stomach and esophagogastric adenocarcinoma based on clinical trial data that demonstrated overall survival in the third line treatment setting.	03/2019

triheptanoin (Dojolvi™)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP210

Description

Triheptanoin (Dojolvi) is a medium-chain triglyceride oral solution that provides a source of calories and fatty acids to bypass the long-chain enzyme deficiencies.

Length of Authorization

- Initial: Four months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
triheptanoin (Dojolvi)	8.3kcal/mL oral solution	Fatty acid oxidation disorders (LC-FAOD)	Monthly quantity to allow for a maximum of 35% of prescribed daily caloric intake

Initial Evaluation

I. Triheptanoin (Dojolvi) may be considered medically necessary when the following criteria are met:
   A. Member is diagnosed with **molecularly confirmed LC-FAOD** by a specialist in genetic metabolic disorders; **AND**
   B. Member does not have pancreatic insufficiency; **AND**
   C. Member has a history of hypoglycemia or cardiomyopathy or at least one episode of rhabdomyolysis; **AND**
   D. Member has at least TWO of the following diagnostic criteria:
      1. One or more known gene mutations in: CPT2, ACADVL, HADHA, or HADHB; **OR**
      2. Disease specific elevation of acylcarnitines on a newborn blood spot or in plasma; **OR**
      3. Low enzyme activity in cultured fibroblasts; **AND**
   E. Documentation of prescribed daily caloric intake is provided; **AND**
   F. Provider attests that the member is utilizing dietary management (e.g. low fat, high carbohydrate diet, avoidance of fasting); **AND**
   G. Provider attests that treatment with over the counter MCT oil has been ineffective, contraindicated, or not tolerated.

II. Triheptanoin (Dojolvi) is considered investigational when used for all other conditions, including but not limited to:
   A. Pancreatic insufficiency

B. Fat malabsorption
C. Impaired chylomicron transport
D. Severe hyperchylomicronemia

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 attestation that the member has exhibited stability or improvement in disease activity [e.g., exercise tolerance, increased cardiac function tests]

Supporting Evidence

I. Per National Organization for Rare Disorders (NORD), disease state management of LC-FAOD is directed toward preventing and controlling acute episodes, which include symptoms such as hypoglycemia, rhabdomyolysis, and cardiac complications. Management often involves avoidance of fasting, maintaining low-fat, high-carbohydrate diet, and using low-fat nutritional supplements and MCT oil available over the counter (OTC).
II. Clinical presentation and the age of onset of LC-FAOD is variable. Signs and symptoms can be present at birth or develop later in adulthood. Even with treatment, many patients continue to experience symptom recurrence of variable frequency and severity. Hypoglycemia and cardiomyopathy typically occur at an earlier stage in life, rhabdomyolysis is usually present in asymptomatic patients later in adulthood. In addition to these three primary clinical manifestations, other symptoms are possible and include encephalopathy, peripheral neuropathy, and pigmentary retinopathy.
III. The effectiveness of triheptanoin (Dojolvi) has been established based on one phase 2, randomized, double-blind trial comparing triheptanoin (Dojolvi) with trioctanoin in 32 adult and pediatric patients (aged 7 years and older). Patients had a confirmed diagnosis of LC-FAOD, evidence of at least one significant episode of rhabdomyolysis, and at least two of the following diagnostic criteria: disease specific elevation of acylcarnitines on a newborn blood spot or in plasma, low enzyme activity in cultured fibroblasts, or one or more known pathogenic mutations in CPT2, ACADVL, HADHA, HADHB.
IV. The primary efficacy outcomes included changes in total energy expenditure (TEE), cardiac function by echocardiogram, exercise tolerance, and phosphocreatine recovery following acute exercise. Statistically significant outcomes were positive changes in left ventricular function and maximal heart rate reduction during an exercise tolerance test in the triheptanoin (Dojolvi) arm versus the trioctanoate arm.
V. The quality of the evidence was considered low because the study had a small sample size and had incomplete blinding. Moreover, there were applicability issues as some primary endpoints (cardiac function and exercise tolerance) were not clinically significant.
VI. Triheptanoin (Dojolvi) has not been directly compared to OTC MCT oil; therefore, there is insufficient evidence to conclude that triheptanoin (Dojolvi) is safer or more effective than OTC MCT oil.

VII. The most commonly reported adverse reactions for triheptanoin (Dojolvi) include gastrointestinal upset, musculoskeletal pain, fatigue, and headache.

VIII. There are no specific contraindications to using triheptanoin (Dojolvi), however, warnings include not using triheptanoin (Dojolvi) with feeding tubes manufactured of polyvinyl chloride (PVC) and avoiding use in patients with pancreatic insufficiency.

IX. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for using triheptanoin (Dojolvi) for indications other than LC-FAOD.

Investigational or Not Medically Necessary Uses

I. Triheptanoin (Dojolvi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Pancreatic insufficiency
   B. Fat malabsorption
   C. Impaired chylomicron transport
   D. Severe hyperchylomicronemia

Appendix

The recommended target daily dosage of triheptanoin (Dojolvi) is up to 35% of the patient's total prescribed daily caloric intake (DCI) divided into at least four doses and administered with mealtimes or with snacks.

I. Table 1: Dosage initiation and titration

For patients not currently taking MCT product	• Initiate at total daily dosage of 10% DCI divided into four times per day. • Increase recommended daily dose of up to 35% DCI over a period of two to three weeks.
For patients switching from another MCT product	• Discontinue use of MCT products before starting triheptanoin (Dojolvi). • Initiate triheptanoin (Dojolvi) at the last tolerated daily dose of MCT divided into four times per day. • Increase the total daily dose by approximately 5% DCI every two to three days until target dose of up to 35% DCI is achieved.

II. The quantity limit is to be determined based on the member's prescribed daily caloric intake (DCI). Maximum total daily dose may not exceed 35% DCI. Round the total daily dosage to the nearest whole number.

$$\text{Total Daily Dose (mL)} = \frac{\text{Member's DCI (kcal)} \times \text{Target (\% dose of DCI)}}{8.3 \text{ kcal/ml}}$$

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP194

Split Fill Management*

Description

Tucatinib (Tukysa) is an orally administered tyrosine kinase inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tucatinib (Tukysa)	50 mg tablets	Metastatic breast cancer	60 tablets/30 days
	150 mg tablets		120 tablets/30 days

Initial Evaluation

I. Tucatinib (Tukysa) 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. The member has **not** previously progressed on or after treatment with another tyrosine kinase inhibitor (e.g., lapatinib [Tykerb], neratinib [Nerlynx]); **AND**
   D. A diagnosis of **advanced or metastatic breast cancer** when the following are met:
      1. Documentation is provided showing the disease is HER2-positive; **AND**
      2. Will be used in combination with trastuzumab and capecitabine; **AND**
      3. Will not be used with any other oncology therapy outside of trastuzumab and capecitabine; **AND**
      4. Member does **not** have brain metastases; **AND**
         i. Member has progressed on, has a contraindicated to, or did not tolerate treatment with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1); **OR**
      5. Member has brain metastases; **AND**
         i. Member has received ≥1 prior anti-HER2-based regimens in the metastatic setting

I. Tucatinib (Tukysa) is considered investigational when used for all other conditions, including but not limited to:
   A. Colorectal 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. Will be used in combination with trastuzumab and capecitabine; **AND**
V. Will not be used with any other oncology therapy outside of trastuzumab and capecitabine; **AND**
VI. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

I. Tucatinib (Tukysa) was studied in a phase 2, double blind, placebo controlled, randomized trial (HER2CLIMB) in 612 patients with HER2-positive metastatic breast cancer with, or without, brain metastases who had been previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1). The trial evaluated treatment with tucatinib (Tukysa) in combination with trastuzumab and capecitabine versus placebo, trastuzumab, and capecitabine. Patients in the trial had a median of 4 previous lines of therapy and 48% of patients had brain metastases. Overall survival at 2 years was 44.9% with the tucatinib (Tukysa) combination and 26.6% with trastuzumab, capecitabine, and placebo combination (hazard ratio for death, 0.66; 95% CI, 0.50-0.88; P = 0.005). Median overall survival was 21.9 months (tucatinib (Tukysa) combination) and 17.4 months (placebo, trastuzumab, and capecitabine). Secondary outcome of progression free survival at 1 year in patients with brain metastases was 24.9% with the tucatinib (Tukysa) combination and 0% with trastuzumab, capecitabine, and placebo combination (hazard ratio, 0.48; 95% CI, 0.34-0.69; P < 0.001).
II. Patients in the HER2CLIMB trial were excluded if they were previously treated with neratinib, afatinib, or any HER2 tyrosine kinase inhibitor at any time previously. Those who were treated with lapatinib more than 12 months from the start of the study were allowed to enroll in the trial; however, this accounted for only 6% of patients in the HER2CLIMB trial. At this time, there is lack of scientific evaluation for safety and efficacy of tucatinib (Tukysa) following progression on or after another tyrosine kinase inhibitor.
III. Although patients in the trial were heavily pretreated having failed trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1), FDA approval was granted in adults with or without brain metastases who have received ≥1 prior anti-HER2-based regimens in the metastatic setting. Agents such as TDM-1 and other oral tyrosine kinase inhibitors (i.e., neratinib, lapatinib) also have FDA approval and overall survival data in the previously treated metastatic setting. No head to head trials are available comparing tucatinib (Tukysa) to other tyrosine kinase inhibitors in this space.
IV. Given the population included in the HER2CLIMB trial consisted of heavily pretreated patients, criteria for coverage is set to reflect this patient population. Patients with CNS metastases, however, require only ≥1 prior anti-HER2-based regimen given limited treatment options and lack of strong data with other therapies in this population.

Investigational or Not Medically Necessary Uses

I. Tucatinib (Tukysa) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Colorectal cancer
      i. As of June 2020, a phase 2 trial (MOUNTAINEER) was still recruiting to evaluate use of tucatinib plus trastuzumab in patients with HER2 positive colorectal cancer. Estimated study completion is anticipated December 31, 2021.

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

References

1. Tukysa [Prescribing Information]. Seattle Genetics, Inc.: Bothell, WA. April 2020.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP231

Split Fill Management*

Description

Umbralisib (Ukoniq) is a multikinase inhibitor of phosphatidylinositol-3-kinase-delta (PI3Kδ) and casein kinase 1-epsilon (CK1ε).

Length of Authorization

- N/A

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
umbralisib (Ukoniq)	200 mg tablet	Relapsed or Refractory Marginal Zone Lymphoma; Relapsed or Refractory Follicular Lymphoma	28 tablets/28 days

Initial Evaluation

I. **Umbralisib (Ukoniq)** is considered investigational when used for all conditions, including but not limited to relapsed or refractory Marginal Zone Lymphoma and relapsed or refractory Follicular Lymphoma.

Renewal Evaluation

I. N/A

Supporting Evidence

I. The activation of the PI3K pathway is commonly seen with marginal zone lymphoma (MZL) and follicular lymphoma (FL) which results in lymphoma cell growth and is one of the most frequently dysregulated pathways in cancer. Umbralisib (Ukoniq) is a multikinase inhibitor of phosphatidylinositol-3-kinase-delta (PI3Kδ) and casein kinase 1-epsilon (CK1ε) FDA-approved for the treatment of relapsed or refractory MZL in patients who have received at least one prior anti-CD20-based regimen and in relapsed or refractory FL in patients who have received at least three prior lines of systemic therapy.

II. Umbralisib (Ukoniq) is the fourth PI3K inhibitor on the market approved for FL and the first PI3K inhibitor approved for MZL. This once daily oral agent joins chemotherapy, immunotherapy, radioimmunotherapy, and other oral based regimens for the treatment of MZL and FL.

III. **Relapsed or refractory marginal zone lymphoma:** As of February 2021, NCCN guidelines have included umbralisib (Ukoniq) with other recommended regimens for the treatment of MZL. Preferred second-line therapies include regimens containing bendamustine, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), rituximab, lenalidomide, ibrutinib, Other recommended regimens additionally include ibritumomab tiuxetan, and PI3K inhibitors such as copanlisib, duvelisib, and idelalisib.

IV. **Relapsed or refractory follicular lymphoma:** As of February 2021, NCCN guidelines have included umbralisib (Ukoniq) with other recommended regimens. Preferred second-line therapies include regimens containing bendamustine, CHOP, lenalidomide, and rituximab, . Other recommended regimens additionally include ibritumomab tiuxetan, PI3K inhibitors such as copanlisib, duvelisib, and idelalisib, and tazemetostat, an enhancer of zeste homolog 2 (EZH2) inhibitor.

V. Umbralisib (Ukoniq) is being studied in an ongoing, open-label, single-arm trial in 69 patients with MZL who have progressed with one or more prior lines of therapy, including a CD20-directed regimen, in 117 patients with FL, and 22 patients with small lymphocytic lymphoma (SLL) who have progressed with two or more prior lines of therapy, including a CD20-directed regimen and an alkylating agent. The clinical trial is still ongoing and will further evaluate umbralisib (Ukoniq) in combination with ublituximab for the treatment of FL, MZL, SLL, mantle cell lymphoma (MCL) and in combination with ublituximab and bendamustine for the treatment of large B-cell lymphoma (DLBCL).

VI. Efficacy outcomes studied included primary endpoint of overall response rate (ORR) and secondary endpoints of disease control rate (DCR), duration of response (DOR), progression free survival (PFS), time to response (TTR), and number of patients experiencing a change in tumor volume.

VII. The overall response rate was 49.3% (95% CI 37-62) in the MZL cohort and 45.3% (95% CI 36-55) in the FL cohort. Progression-free survival (PFS) was a median of 10.6 months (95% CI 7.2-13.7) in the FL cohort; PFS was not reached for the MZL cohort.

Primary Endpoint	MZL (N=69)	FL (N=117)	SLL (N=22)
ORR, n (%) [95% CI]	**34 (49.3) [37-62]**	**53 (45.3) [36-55]**	**11 (50.0) [28-72]**
CR	11 (16) [8-27]	6 (5) [2-11]	1 (5) [0.1-22.8]
PR	23 (33) [22-46]	47 (40) [31-50]	10 (45.5) [24-68]
Secondary Endpoint	MZL (N=69)	FL (N=117)	SLL (N=22)
DCR, n (%) [95% CI]	57 (82.6) [72-91]	93 (79.5) [71-86]	19 (86.4) [65-97]
DOR, median (95% CI), months[b]	NR (10.3-NE)[c]	11.1 (8.3-15.6)[d]	18.3 (2.4-NE)
PFS, median (95% CI), months	NR (12.1-NE)	10.6 (7.2-13.7)	20.9 (7.4-24.1)
TTR, median (95% CI), months[b]	2.8 (2.7-2.9)	4.6 (3.0-5.6)	2.7 (2.4-2.8)
Change in tumor volume, n (%)	58/64 (90.6)	95/115 (83.5)	17/19 (89.5)

NR=not reported, NE=not evaluable, [b]calculations based on Kaplan-Meier estimation, [c]DOR was reported in n=34 MZL patients, [d]DOR was reported in n=53 FL patients.

VIII. The quality of evidence is considered low at this time as this was a 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. Additionally, umbralisib (Ukoniq) was FDA-approved

under the accelerated approval pathway and continued approval for the two indications may be contingent upon verification and description of clinical benefit in confirmatory trials.

IX. Safety data was evaluated in 208 patients over a median follow up of 21.4 months. The most common adverse events were diarrhea (59%), nausea (39%), fatigue (31%), vomiting (24%), cough (21%), ALT/AST increase (20%), and neutropenia (15%).

X. Serious adverse events related to umbralisib (Ukoniq) were reported in 36 patients (17%) and included diarrhea (3%), acute kidney injury (1.4%), anemia (1.4%), dehydration (1.4%), febrile neutropenia (1.4%), pneumonia (1.4%), sepsis (1.4%), and urinary tract infection (1.4%). There were no adverse events leading to death.

XI. At the time of data cutoff, 62%, 77%, and 68% of patients had discontinued the drug in the MZL, FL, and SLL cohorts, respectively. Discontinuation rate due to adverse events in the overall population was 15.4%, with 11.5% dose reduction rate, and 59.4% and 45% dose interruption rate in MZL and FL treated patients, respectively.

XII. There are no contraindications to using umbralisib (Ukoniq); however, warnings and precautions include: infections, neutropenia, diarrhea or non-infectious colitis, hepatoxicity, severe cutaneous reactions, allergic reactions, and embryo-fetal toxicity. There are no black box warnings.

XIII. Although umbralisib (Ukoniq) is thought to have comparable efficacy and a more favorable safety profile than some of the other therapies on the market due to its pharmacological properties, confirmatory trials are needed to definitively establish benefit/value of this agent.

Investigational or Not Medically Necessary Uses

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

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

References

1. Ukoniq [Prescribing Information]. TG Therapeutics: New York, NY. February 2021.
2. NCCN Guidelines for the treatment of B-Cell Lymphomas. V.2.2021. Updated February 16, 2021.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

uridine triacetate (Xuriden®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP216

Description

Uridine triacetate (Xuriden) is a pyrimidine analog for uridine replacement indicated in adult and pediatric patients for the treatment of hereditary orotic aciduria (HOA).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
uridine triacetate (Xuriden)	2 g/packet	Hereditary orotic aciduria	240 g/30 days

Initial Evaluation

I. Uridine triacetate (Xuriden) may be considered medically necessary when the following criteria are met:
   A. Member is diagnosed with **hereditary orotic aciduria (HOA)** by a provider specializing in the patient's diagnosis or in consultation with a geneticist, hematologist or specialist in metabolic disorders; **AND**
   B. Member has at least ONE of the following diagnostic criteria:
      1. Molecular genetic test indicating variations in uridine monophosphate synthetase (UMPS) gene; **OR**
      2. Urine test indicating high levels of orotic acid and/or orotidine; **AND**
   C. Member has severe disease as defined by one or more of the following:
      1. Hematologic abnormalities (e.g. megaloblastic anemia, neutropenia, leukopenia); **OR**
      2. Renal tract obstruction (due to aggregation of orotic acid crystals); **OR**
      3. Immune dysfunction; **OR**
      4. Congenital anomalies; **OR**
      5. Physical and intellectual developmental delays; **AND**
   D. Provider attestation that member does not have ornithine transcarbamoylase (OTC) deficiency; **AND**
      1. Blood ammonia levels are within normal limits

II. Uridine triacetate (Xuriden) is considered investigational when used for all other conditions, including but not limited to:
   A. Fluoropyrimidine overdose/overexposure

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 attestation that the member has exhibited stability or improvement in disease symptoms [e.g., improvement in hematologic status, improvement in growth]

Supporting Evidence

I. HOA is an extremely rare genetic disorder affecting both men and women, with fewer than 25 cases of patients with this disorder worldwide have been reported in the medical literature. It is caused by variations in the uridine monophosphate synthase (UMPS) gene which is responsible for producing an enzyme that catalyzes the last two steps of the pyrimidine biosynthesis pathway. One of these two final steps is to convert orotic acid into another chemical substance. Because of the variation in the UMPS gene, individuals with this disorder have low levels of the enzyme needed to breakdown orotic acid and subsequently have a reduced production of uridine, a nucleotide involved in multiple essential physiological functions including biosynthesis of RNA, synthesis of glycogen and glycoprotein, phospholipid synthesis, and DNA synthesis.
II. The exact mechanism by which orotic acid buildup and uridine monophosphate synthase deficiency leads to signs and symptoms of the disease is not completely understood. Orotic acid is believed to improve the metabolism of folic acid and vitamin B12 and may play a role in gene transcription.
III. HOA is a clinically heterogenous disorder and individuals who retain some UMPS activity may be asymptomatic or only mildly affected. Features of more severe disease include megaloblastic anemia that is not responsive to treatment with vitamin B12 or folic acid, neutropenia, renal tract obstruction (due to aggregation of orotic acid crystals), immune dysfunction, congenital anomalies, and physical and intellectual developmental delays.
IV. Diagnosis of HOA is confirmed by assessment of symptoms, family history, a urine test indicating high levels of orotic acid and/or orotidine, and a molecular genetic test indicating variations in uridine monophosphate synthetase (UMPS) gene. Not all patients will present with elevated orotic acid and/or orotidine urine levels; however, this is the most common laboratory abnormality seen in 80%-99% of patients. Deferential diagnosis of HOA includes urea cycle disorders one of which may also present with high blood levels of orotic acid, this disorder is known as ornithine transcarbamoylase (OTC) deficiency. OTC can be distinguished from HOA by evaluation of blood ammonia levels. Patients with HOA will have normal blood ammonia levels, whereas, patients with OTC deficiencies tend to have elevated ammonia levels.
V. Nucleotide replacement has been the mainstay of treatment of HOA. Case reports document rapid hematologic response with administration of uridine. Some patients treated with uridine have reached adulthood and some who have been treated with uridine lifelong have fathered or given birth to normal children. Supportive therapies include blood transfusions, intravenous hydration and electrolyte replacement, and treatment for renal and infectious disease complications.

VI. FDA approval of uridine triacetate (Xuriden) was based on collective evidence from case reports, pharmacokinetic studies, safety studies, and one Phase III, open-label, single-arm, six-week clinical trial and its six-month extension phase. The efficacy was evaluated in a Phase III trial which enrolled four patients with HOA (three male, one female; age range three to 19 years). Three patients were previously treated with uridine and were switched to uridine triacetate (Xuriden). One patient was treatment naïve. The study evaluated stability or improvement in patients' hematologic parameters in the initial six-week period and the extension phase. By week six, three previously treated patients met the primary endpoint and maintained stability of their hematologic parameters, while one treatment naïve patient failed to meet the primary endpoint – improvement in hematologic parameters. The secondary endpoint was improved growth parameters (height and weight). Effect on growth was assessed in three patients and remained unchanged after 24 months of treatment.

VII. Uridine triacetate (Xuriden) is the only FDA approved therapy for HOA. The National Organization for Rare Disease Disorders and other expert opinions recommend treatment with uridine triacetate (Xuriden).

VIII. Uridine triacetate (Xuriden) should not be used for the treatment of fluoropyrimidine overdose/overexposure. A different formulation of uridine triacetate (Vistogard) has been approved by the FDA for the treatment of this condition.

Investigational or Not Medically Necessary Uses

I. Uridine triacetate (Xuriden) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Fluoropyrimidine overdose/overexposure

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	01/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP223

Split Fill Management*

Description

Vandetanib (Caprelsa) is an orally administered kinase inhibitor, with activity at VEGF, EGFR, and RET kinases.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vandetanib (Caprelsa)	100 mg tablets	Locally advanced or metastatic medullary thyroid cancer	60 tablets/30 days
	300 mg tablets		30 tablets/30 days

Initial Evaluation

I. Vandetanib (Caprelsa) 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 endocrinologist; **AND**
   C. A diagnosis of **unresectable locally advanced or metastatic (stage III or IV) medullary thyroid cancer** when the following is met:
      1. Medication is not used in combination with any other oncology therapy.

II. Vandetanib (Caprelsa) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Anaplastic Thyroid Carcinoma
   B. Biliary tract cancer
   C. Breast cancer
   D. Follicular Thyroid Carcinoma
   E. Glioblastoma
   F. Ovarian cancer
   G. Renal cell carcinoma
   H. Urothelial cancer
   I. Non-small cell lung cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication is prescribed by, or in consultation with, an oncologist or endocrinologist; **AND**
IV. Will not be used with any other oncology therapy; **AND**
V. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

I. Vandetanib (Caprelsa) is a kinase inhibitor with activity at multiple kinases. *In vitro* studies show that vandetanib (Caprelsa) inhibits the activity of epidermal growth factor receptor (EGFR) family, vascular endothelial growth factor (VEGF) receptors, rearranged during transfection (RET), protein tyrosine kinase 6, TIE2, members of the EPH receptors kinase family, and members of the Src family of tyrosine kinases. In mouse models, vandetanib (Caprelsa) reduced tumor cell growth and metastasis.
II. Vandetanib (Caprelsa) was studied in a Phase 3, double blind, placebo controlled, randomized trial (ZETA) in 331 patients with symptomatic or progressive unresectable locally advanced or metastatic medullary thyroid cancer. There is currently no evidence that it is safe and effective in treating other types of cancer.
III. The ZETA trial evaluated treatment with vandetanib (Caprelsa) as monotherapy versus placebo. Patients in the trial had either hereditary, sporadic, or unknown, or metastatic disease type. Fifty nine percent of patients had a RET positive mutation while 40% had unknown RET mutation. Patients were excluded from treatment if they had significant cardiac, hematopoietic, hepatic, or renal dysfunction, were treated with chemotherapy and/or radiation therapy within four weeks of treatment with vandetanib (Caprelsa) or were taking any concomitant medications that may have affected QTc or induced CYP3A4 function.
IV. The primary endpoint evaluated in the ZETA trial was progression free survival (PFS). There was a statistically significant improvement in PFS for patients randomized to vandetanib (Caprelsa). The number of events in vandetanib (Caprelsa) arm was 59 (26%) and 41 (41%) in the placebo arm with a Hazard Ratio (HR) = 0.35; 95% Confidence Interval (CI) = 0.24-0.53; $p<0.001$. The median survival in months for the placebo arm was 16.4 while for the vandetanib (Caprelsa) arm the median survival was not reached at the time of analysis;, however, the predicted median survival was 30.5 months. The mature data for overall survival (OS) was studied as a secondary endpoint and was similar between both treatment arms at 81.6 months for vandetanib (Caprelsa) and 80.4 months for placebo arm. However, OS survival data was not powered and was confounded by patients from the placebo arm that were eligible to start treatment with vandetanib (Caprelsa) after conclusion of the study. Other secondary endpoints evaluated included objective response rate (ORR) and disease control rate, both of which reached

statistical significance when compared to placebo. Quality of life and pain reduction outcomes were not reported or could not be evaluated.

V. Fifty-five percent (55%) of the patients on the vandetanib (Caprelsa) arm experienced grade 3 or 4 adverse events. Adverse reactions resulting in death occurred in five patients treated with vandetanib (Caprelsa) due to respiratory failure, respiratory arrest, aspiration pneumonia, cardiac failure with arrhythmia, and sepsis. Causes of discontinuation in vandetanib (Caprelsa)-treated patients in >1 patient included asthenia, fatigue, rash, arthralgia, diarrhea, hypertension, prolonged QT interval, increase in creatinine, and pyrexia. Serious adverse events in vandetanib (Caprelsa) treated patients in >2% of patients included diarrhea, pneumonia, and hypertension. Patients receiving vandetanib (Caprelsa) experienced a mean prolongation of their QT interval of 35ms, and sudden death and torsades des pointes have been observed with vandetanib (Caprelsa). A Risk Evaluation and Mitigation Strategy (REMS) is used to decrease the risk of these adverse events.

VI. Vandetanib (Caprelsa) has a Category 1 recommendation by the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of recurrent or persistent medullary thyroid carcinoma and joins cabozantinib (Cabometyx) and selpercatinib (Retevmo) in the list of preferred systemic regimens. It is also recommended as the first line treatment option by the American Thyroid Association Guidelines. Vandetanib (Caprelsa) should be prescribed in consultation with, or by, an oncologist or endocrinologist for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib (Caprelsa) in patients with indolent, asymptomatic, or slowly progressive disease should only be considered after examining the treatment related risks of this agent.

Investigational or Not Medically Necessary Uses

I. Vandetanib (Caprelsa) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Anaplastic Thyroid Carcinoma
   B. Biliary tract cancer
   C. Breast cancer
   D. Follicular Thyroid Carcinoma
   E. Glioblastoma
   F. Ovarian cancer
   G. Renal cell carcinoma
   H. Urothelial cancer
   I. Non-small cell lung 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

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy was updated and transitioned from an old criteria to a new format Removal of criteria requirements that are managed by provider (drug-drug interactions, REMS program, monitoring of CrCl, QT prolongation, hepatic impairments, hypertension, and other aspects from labeled warnings and precautions)	02/2021
Criteria created	02/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP071

Description

Venetoclax (Venclexta) is an orally administered B-cell lymphoma-2 (BCL-2) inhibitor.

Length of Authorization

- Initial:
  - i. Previously untreated CLL/SLL: 12 months
  - ii. All other indications: Six months
- Renewal:
  - i. Previously untreated CLL/SLL: Cannot be renewed
  - ii. All other indications: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
venetoclax (Venclexta)	Starter Pack	Chronic lymphocytic leukemia (CLL); Small lymphocytic lymphoma (SLL)	1 pack/28 days
	10 mg tablets		28 tablets/28 days
	50 mg tablets		28 tablets/28 days
	100 mg tablets		120 tablets/30 days
	100 mg tablets	Acute myeloid leukemia	180 tablets/30 days

Initial Evaluation

I. Venetoclax (Venclexta) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   B. A diagnosis of:
      1. **Relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)**; **AND**
         - i. Received at least one prior therapy [e.g., Imbruvica (ibrutinib) or chemotherapy-containing regimen]; **AND**
         - ii. Will be used as monotherapy or in combination with rituximab (Rituxan); **OR**
      2. **Previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); AND**
         - i. Will be used in combination with obinutuzumab (Gazyva);**OR**
      3. **Newly-diagnosed acute myeloid leukemia (AML)**; **AND**
         - i. Age 75 years and older; **OR**
         - ii. Have comorbidities that preclude use of intensive induction chemotherapy such as:

a. Baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3
b. Severe cardiac or pulmonary comorbidity
c. Moderate hepatic impairment
d. CrCL ≥30 to <45 mL/min; **AND**

iii. Used in combination with azacitidine or decitabine or low-dose cytarabine

II. Venetoclax (Venclexta) is considered investigational for all other conditions, including but not limited to:
   A. Acute Myeloid Leukemia – Previously treated
   B. Multiple Myeloma (MM)
   C. Previously untreated CLL/SLL – Treatment for more than 12 months

Renewal Evaluation

I. Member has a diagnosis of relapsed/refractory CLL/SLL or newly diagnosed AML; **AND**
II. Clinical documentation of response to treatment, such as stabilization or improvement of disease; **AND**
III. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. Venetoclax (Venclexta) is FDA-approved for the treatment of CLL/SLL, in adult patients with or without 17p deletion.
II. Patients included in venetoclax (Venclexta) monotherapy studies in CLL/SLL were relapsed/refractory to fludarabine-based regimens (e.g. Rituximab+Fludarabine+Cyclophosphamide, Fludarabine+Rituximab, Fludarabine+Cyclophosphamide) or alkylator- based regimens (e.g. chlorambucil, bendamustine), or to ibrutinib (Imbruvica) or idelasilib (Zydelig). Patients included in the venetoclax (Venclexta) plus rituximab (Rituxan) trial (MURANO) for relapsed CLL/SLL had received one to three previous treatments (including at least one chemotherapy-containing regimen). Prior radiation therapy or stem cell transplant alone is not considered a prior therapy as this treatment strategy alone was not considered an inclusion in pivotal trials.
III. Venetoclax (Venclexta) approval in untreated CLL/SLL was based on the findings from the CLL14 randomized, open label, phase 3 trial. CLL14 evaluated the safety and efficacy of fixed-duration treatment with venetoclax (Venclexta) in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb) for patients with previously untreated CLL with coexisting medical conditions. Patients received 12 months of venetoclax (Venclexta) in combination with six cycles of obinutuzumab. The trial met its primary outcome of progression-free survival (PFS) in patients treated with Venclexta plus obinutuzumab compared to patients who received chlorambucil plus obinutuzumab, a commonly used standard of care. After a median follow-up of 28 months, Venclexta plus obinutuzumab reduced the risk of progression or death by 67% compared with chlorambucil plus obinutuzumab (hazard ratio: 0.33, 95%

confidence interval [CI]: 0.22, 0.51; p<0.0001). The majority of patients receiving Venclexta in the trial remained progression-free at two years.

IV. FDA granted accelerated approval to venetoclax (Venclexta) for use in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of adult patients with newly-diagnosed acute myeloid leukemia (AML) who are aged 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. Initial FDA-approval was based on two phase Ib/II trials in this setting. The findings from these trials were consolidated by phase III confirmatory studies (VIALE-A and VIALE-C).

V. Venetoclax (Venclexta) was studied in a confirmatory phase III randomized (2:1) double-blind, placebo-controlled trial (VIALE-A), which assessed the efficacy and safety of venetoclax (Venclexta) in combination with azacitidine (IV or SQ administration) versus placebo+ azacitidine (n= 431). Participants in this trial had median age of 76 years, intermediate or poor/ high risk AML and at least one comorbidity precluding intensive therapies. At median duration of follow-up (20.5 months, <0.1- 30.7), median overall survival for venetoclax- azacitidine treatment arm was 14.7 months (95% CI; 11.9, 18.7) as compared to that of 9.6 months (95% CI; 7.4, 12.7) for placebo-azacitidine arm (HR 0.66; 95% CI; 0.52-0.85; *p* <0.0001). Additionally, treatment arm (venetoclax- azacitidine) also reported complete remission in 66.4% (95% CI; 60.6, 71.9) versus 28.3% (95% CI; 21.1, 36.3) in placebo-azacitidine arm (*p*<0.001) with 43.4% participants achieving composite complete remission before cycle 2.

VI. In VIALE-C clinical trial, efficacy and safety of venetoclax (Venclexta) in combination with low-dose cytarabine (LDAC) was compared with placebo plus LDAC in an ongoing double-blind, randomized (2:1) phase 3 study. From a pool of 211 randomized study participants (n=143 in treatment arm versus n= 68 in placebo arm), median follow-up of 17.5 months (95% CI; 0.1, 23.5) was reported at data cut-off. Median overall survival (OS) was 8.4 months in the treatment (venetoclax-cytarabine) arm versus 4.1 months in placebo-cytarabine arm (HR 0.70; 95% CI 0.50–0.99; P = 0.04). This OS data was not statistically significant. Additionally, a median event-free survival (EFS) was reported at 4.9 months vs 2.1 months for treatment and placebo arms, respectively (HR 0.61; 95% CI; 0.44, 0.84; *P* = 0.003).

Investigational or Not Medically Necessary Uses

I. Acute Myeloid Leukemia – Previously treated
   A. Pivotal trials leading to FDA approval were specifically in the previously <u>untreated</u> setting. Use in the relapsed/refractory setting is not supported by clinical trials nor cited within NCCN AML guidelines.

II. Multiple Myeloma (MM)
   A. Venetoclax (Venclexta) is currently being evaluated for use in MM and is the subject of ongoing clinical trials. As of March 2019, "FDA reviewed data from the BELLINI clinical trial (NCT02755597, Study M14-031) evaluating the use of Venetoclax (Venclexta) combined with bortezomib and dexamethasone in patients with multiple myeloma. The interim trial results demonstrated an increased risk of death for patients receiving Venetoclax (Venclexta) as compared to the control group. On March 6, 2019, the FDA required no new patients be enrolled on the Bellini trial. The FDA suspended enrollment in other ongoing multiple myeloma clinical trials of Venclexta."

III. Previously untreated CLL/SLL – Treatment for more than 12 months

A. Venetoclax (Venclexta) approval in untreated CLL/SLL was based on the findings from the CLL14 randomized, open label, phase 3 trial. CLL14 evaluated the safety and efficacy of fixed-duration treatment with venetoclax (Venclexta) in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb). Patients received 12 months of venetoclax (Venclexta) in combination with six cycles of obinutuzumab. Treatment beyond 12 months has not been evaluated.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated supporting evidence for venetoclax phase III confirmatory clinical trials for newly diagnosed acute myeloid leukemia (AML)	12/2020
Added new FDA approval in untreated CLL/SLL in combination with obinutuzumab (Gazyva)	06/2019
Added new FDA approval in Acute Myeloid Leukemia.	12/2018
Included new FDA expanded indication in CLL/SLL without 19p deletion and expanded initial approval to 6 months.	08/2018

Policy Type: PA Pharmacy Coverage Policy: UMP224

Description

Vericiguat (Verquvo) is an orally administered guanylate cyclase stimulator.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vericiguat (Verquvo)	2.5 mg tablets	Reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient IV diuretics in adults with symptomatic chronic HF and ejection fraction less than 45%	30 tablets/30 days
	5 mg tablets		
	10 mg tablets		

Initial Evaluation

I. Vericiguat (Verquvo) 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 **chronic heart failure with reduced ejection fraction (HFrEF)** when the following are met:
      1. Member has HFrEF defined as New York Heart Association functional class II, III, or IV; **AND**
      2. Member has a documented reduced left ventricular ejection fraction of less than 45%; **AND**
      3. Provider attestation that member has recent evidence of worsening heart failure as defined by ONE of the following:
         i. Hospitalization for heart failure within the last six months; **OR**
         ii. Receiving intravenous (IV) diuretic therapy, within the last three months; **AND**
      4. Member is being treated with one agent from each of the following groups unless ineffective, contraindicated or not tolerated:
         i. Group 1: Beta-blocker (e.g., metoprolol succinate, carvedilol, bisoprolol)

ii. Group 2: ACE-I/ARB (e.g., lisinopril, losartan, valsartan, ramipril) OR ARNI (i.e. sacubitril/valsartan)
iii. Group 3: Mineralocorticoid antagonist (e.g., spironolactone)

II. Vericiguat (Verquvo) is considered investigational when used for all other conditions, including but not limited to:
   A. Heart failure with preserved ejection fraction (HFpEF)

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; **OR**
IV. In the absence of improvement or stability of disease symptoms, the provider attests continuation of therapy is medically necessary AND clinical rationale of medical necessity has been provided and reviewed by a Moda Health clinician.

Supporting Evidence

I. Vericiguat (Verquvo) was studied in one randomized, double-blind, placebo-controlled Phase 3 (VICTORIA) trial in 5,050 patients with chronic heart failure (NYHA functional class II, III or IV) with a reduced ejection fraction (<45%), evidence of recent decompensation or worsening heart failure, defined as recent hospitalization for heart failure in the last three months, hospitalization in the last three to six months, or receiving intravenous (IV) diuretic therapy, without hospitalization, within the last six months.
II. The primary efficacy outcome was a composite endpoint of death from cardiovascular causes or first hospitalization for heart failure. The primary endpoint was achieved by 897 patients (35.5%) in the vericiguat group and 972 patients (38.5%) in the placebo group (hazard ratio, 0.90; 95% CI 0.82 to 0.98; P=0.02).
III. Adverse events occurred in 80.5% of patients receiving vericiguat (Verquvo) with serious adverse events occurring in 32.8% of those patients. Notable side effects observed during the clinical trial include symptomatic hypotension (9.1% patients in vericiguat group vs. 7.9% in placebo group) and syncope (4.0% patients in vericiguat group vs. 3.5% in placebo group). Anemia developed in 7.6% patients in the vericiguat group compared to 5.7% patients in the placebo group. Of those developing anemia, 1.6% cases in the vericiguat group and 0.9% in the placebo group were considered serious adverse events.
IV. The 2017 AHA/ACC/HFSA guidelines recommend first-line therapy with an ACE-I or ARB and a guideline directed beta blocker (bisoprolol, carvedilol or metoprolol succinate) with use of diuretics as needed for symptom management. Spironolactone, sacubitril/valsartan, isosorbide

dinitrate, hydralazine, and ivabradine can be used as adjunct therapy to first-line agents based on patients NYHA functional class and other specified patient characteristics. In the VICTORIA trial, 60% of patients received triple therapy with a beta blocker, ACE-I/ARB/ARNI, and mineralocorticoid antagonist in addition to the study drug.

V. Vericiguat (Verquvo) was studied in adult patients age 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients.

Investigational or Not Medically Necessary Uses

I. Vericiguat (Verquvo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Heart failure with preserved ejection fraction (HFpEF)
      i. Vericiguat (Verquvo) was studied in two phase 2b trials, SOCRATES-PRESERVED and VITALITY-HFpEF, in the setting of chronic heart failure with preserved ejection fraction. The primary efficacy endpoints of change in baseline in log-transformed N-terminal pro-B-type natriuretic peptide (NT-ProBNP) and left atrial volume (LAV) and change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) PLS quality index, respectively, were not met for either study and phase III studies were not pursued.

References

1. Armstrong P, et al. Vericiguat in patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med. 2020; 382:1883-93. DOI: 10.1056/NEJMoa1915928
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4. Armstrong P, et al. Effect of Vericiguat vs Placebo on Quality of Life in Patients with Heart Failure and Preserved Ejection Fraction: The VITALITY-HFpEF Randomized Clinical Trial. JAMA. 2020;324(15):1512-1521. DOI: 10.1001/JAMA.2020.15922.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2021

Policy Type: PA/SP Pharmacy Coverage Policy: UMP072

Description

Vigabatrin's (Sabril, Vigadrone) full mechanism of action is unknown at this time; however, it is an orally administered agent that has irreversible inhibition of gamma-aminobutyric acid transaminase (GABA-T).

Length of Authorization

- Initial: Three months for complex partial epileptic seizure, and one month for West Syndrome
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
vigabatrin (Sabril)	500mg tablets	Refractory complex partial epileptic seizure, adjunct therapy	180 tablets/30 days
vigabatrin (Sabril, Vigadrone)	500mg/packet powder for oral suspension		180 packets/30 days
		West Syndrome (infantile spasms)	120 packets/30 days

Initial Evaluation

I. Vigabatrin (Sabril, Vigadrone) 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. The member has had an ophthalmologic examination prior to initiating vigabatrin (Sabril) or will be examined no later than four weeks after initiation of therapy; **AND**
      1. The member will have an ophthalmologic examination at least every three months during treatment; **OR**
   C. The member is blind prior to initiation of therapy; **AND**
   D. Generic vigabatrin OR vigabatrin (Vigadrone) is prescribed, or documentation is provided regarding clinical rationale as to why generic vigabatrin or vigabatrin (Vigadrone) is not appropriate or is contraindicated; **AND**
   E. A diagnosis of one of the following:
      1. **Complex partial epileptic seizure (focal onset impaired awareness seizure)**; **AND**
         i. Vigabatrin (Sabril, Vigadrone) will be used in combination with at least one other anti-epileptic medication (i.e., used as adjunct therapy) such as

carbamazepine, phenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, divalproex sodium, zonisamide, tiagabine; **AND**

ii. A trial and failure of at least two anti-epileptic medications listed above; **AND**

iii. Member is two years of age or older; **OR**

2. **West Syndrome (Infantile Spasms)**; **AND**

i. Member is between one month and two years of age; **AND**

ii. The prescribed dose does not exceed 150 mg/kg/day

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

A. Seizures that are not considered complex partial epileptic or focal onset impaired awareness seizures

B. Tourette's disorder

C. Substance abuse (e.g., cocaine, methamphetamine, alcohol dependence)

D. Autoimmune encephalitis

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 ophthalmologic examination has been completed every three months since initiation of therapy; **AND**

IV. Generic vigabatrin OR vigabatrin (Vigadrone) is prescribed, or documentation is provided, regarding clinical rationale as to why generic vigabatrin or vigabatrin (Vigadrone) is not appropriate or is contraindicated **AND**

V. A reduction in the severity or frequency of seizures or spasms; **AND**

A. **Complex partial epileptic seizure (focal onset impaired awareness seizure)**; **AND**

1. The medication continues to be used in combination with at least one other anti-epileptic medication (i.e., used as adjunct therapy) such as carbamazepine, phenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, divalproex sodium, zonisamide, tiagabine; **OR**

B. **West Syndrome (Infantile Spasms)**; **AND**

1. Clinical benefit has been assessed and documented within the first two to four weeks of treatment (please note: extensions will not be given if assessment has not taken place within four weeks of treatment initiation); **AND**

2. The prescribed dose does not exceed 150 mg/kg/day

Supporting Evidence

I. Vigabatrin (Sabril, Vigadrone) has a black box warning for permanent vision loss, and those who take the medication are at risk for vision loss with any amount of medication. The risk increases with greater doses and duration of vigabatrin (Sabril, Vigadrone) administration. This medication is available through a Risk Evaluation Mitigation Strategy (REMS) Program, and a specialist will need to be involved in prescribing to ascertain if the benefits of vigabatrin (Sabril, Vigadrone) outweigh the risk of vision loss.

II. Recommended ophthalmologic monitoring should start at baseline or within four weeks of initiating therapy, every three months during therapy, and through three to six months post discontinuation.

III. Vigabatrin (Sabril, Vigadrone) is FDA-approved for complex partial epileptic seizures (focal onset impaired awareness seizure) for ages two years and older and West Syndrome (infantile spasms) for ages one month to two years. In complex partial epileptic seizure, the medication is FDA-approved in the refractory setting after failure of other therapies and should be used in addition to at least one other anti-epileptic (i.e., vigabatrin [Sabril, Vigadrone] is an adjunct therapy).

IV. Vigabatrin (Vigadrone) is an AA-rated authorized generic of Sabril and is fully substitutable for both Sabril and generic vigabatrin 500mg/packet for oral solution.

V. The max dose of vigabatrin (Sabril, Vigadrone) is 3000 mg/day for complex partial epileptic seizure and a maximum of 150 mg/kg/day for West Syndrome.

VI. For West Syndrome, significant clinical benefit should be realized within four weeks of therapy initiation, and the medication should be discontinued if not. Due to the risks associated with the medication, continuation of therapy will not be grated in absence of clinical benefit.

Investigational or Not Medically Necessary Uses

All indications listed below have not been sufficiently studied for safety and efficacy or have inconclusive evidence for use of vigabatrin (Sabril, Vigadrone).

I. Seizures that are not considered complex partial epileptic or focal onset impaired awareness seizures
II. Tourette's disorder
III. Substance abuse (e.g., cocaine, methamphetamine, alcohol dependence)
IV. Autoimmune encephalitis

References

1. Sabril [Prescribing Information]. Deerfield, IL: Lundbeck. January 2020.
2. Vigadrone [Prescribing Information]. Maple Grove, MN: Upsher-Smith Laboratories, LLC. February 2020.
3. Approved Risk Evaluation and Mitigation Strategies (REMS). Food and Drug Administration. October, 2017. https://www.accessdata.fda.gov/Scripts/Cder/Rems/index.cfm?event=RemsDetails.page&REMS=364. Accessed March 4, 2019.
4. Vigabatrin Risk Evaluation and Mitigation Strategy (REMS) Program. Vigabatrin REMS for Healthcare Professionals. https://www.vigabatrinrems.com/#Main. Accessed March 4, 2019.
5. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512-521.
6. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018;91(24):1117.

7. Dean C, Mosier M, Penry K. Dose-Response Study of Vigabatrin as add-on therapy in patients with uncontrolled complex partial seizures. *Epilepsia*. 1999;40(1):74-82.
8. Köhler U, Forberg J. [Results of treatment of 718 endometrial cancers with reference to clinical and morphologic prognostic factors]. *Zentralbl Gynakol*. 1989;111(15):1033-41.

Policy Implementation/Update:

Action and Summary of Changes	Date
• Updated minimum age for use as adjunct therapy for refractory complex seizures to age two and older to align with FDA-label age-expansion • Added Vigadrone packets to policy	03/2021
Date created	03/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP198

Split Fill Management*

Description

Vismodegib (Erivedge) is an orally administered hedgehog pathway inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vismodegib (Erivedge)	150 mg capsules	Basal cell carcinoma; metastatic or locally advanced	28 capsules/28 days

Initial Evaluation

I. Vismodegib (Erivedge) 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 dermatologist; **AND**
   C. Vismodegib (Erivedge) will NOT be used in combination with any other oncologic medication; **AND**
   D. Member has not progressed on any other oncologic medication (e.g. has not progressed on sonidegib [Odomzo]); **AND**
   E. A diagnosis of **basal cell carcinoma (BCC)** when the following are met:
      1. Member has metastatic (Stage IV) basal cell carcinoma; **OR**
      2. Member has locally advanced basal cell carcinoma; **AND**
         i. Basal cell carcinoma has recurred or progressed after radiation or surgery; **OR**
         ii. Member is not a candidate for either

II. Vismodegib (Erivedge) is considered investigational when used for all other conditions, including but not limited to:
   A. Ovarian Cancer
   B. Nevoid basal cell carcinoma syndrome
   C. Prostate Cancer

D. Acute leukemia
E. Lymphoma
F. Breast Cancer
G. Medulloblastoma
H. Multiple myeloma
I. Myelofibrosis
J. Graft versus host disease
K. Pancreatic cancer
L. Lung cancer
M. Hepatocellular carcinoma

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. Vismodegib (Erivedge) is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
IV. Member has a diagnosis of **metastatic or locally advanced basal cell carcinoma; AND**
V. Member has experienced a clinical response to therapy defined by improvement or stabilization of disease or decrease or stabilization of tumor size or spread; **AND**
VI. Provider attestation that the member, either male or female, has been counseled on the teratogenicity and embryo-fetal toxicity risks with vismodegib (Erivedge).

Supporting Evidence

I. The safety and efficacy of vismodegib (Erivedge) in basal-cell carcinoma was evaluated in the pivotal ERIVANCE trial; a multicenter, international, two-cohort, open-label, single-arm study of 104 patients with metastatic basal-cell carcinoma (BCC) and those with locally advanced BCC who had inoperable disease or who were not a candidate for surgery. Patients with locally advanced disease were required to have had prior radiation therapy, unless contraindicated or inappropriate.
II. The primary efficacy endpoint was the independently assessed objective response rate (ORR) based on RECIST guidelines for metastatic disease or a decrease of 30% or more in the externally visible or radiographic dimension or complete resolution of ulceration for locally advanced disease. The key secondary endpoint was duration of response (DOR). The study met its primary endpoint in both cohorts with an ORR of 30% (95% confidence interval [CI], 16 to 48; P=0.001) in the group with metastatic BCC and 43% (95% CI, 30 to 56; P<0.001) in the group with locally advanced BCC. The median duration of objective response was 7.6 months for metastatic BCC (rang, 2.1 to 11.1) and locally advanced BCC (range, 1.0 to 12.9).
III. During the ERIVANCE trial, all patients experienced at least one adverse event (AE), with the majority classified as grade 1 or 2 in severity, and 25% experienced at least one serious adverse

event. Of those who experienced a serious adverse event, seven patients experienced a fatal adverse event and 12% had an adverse event that led to discontinuation. Common adverse events included muscle spasms, dysgeusia, alopecia, fatigue and weight loss.

IV. Patients enrolled in the study were age 18 and older and concurrent antitumor (oncologic) therapy was not permitted. The safety and/or efficacy of use in pediatric and adolescent patients or in combination with other oncologic therapies has not been evaluated.

V. Vismodegib (Erivedge) carries a black box warning for Embryo-fetal toxicity, as this agent is known to cause embryo-fetal death or severe birth defects when administered to a pregnant woman. FDA-label advises women of reproductive potential and men to use effective contraception during therapy with vismodegib (Erivedge) and for 24 months after the final dose.

VI. Long-term safety and efficacy of vismodegib (Erivedge) was evaluated in a follow-up study of the ERIVANCE trial for 39 months after the final data cutoff date of the primary analysis. The primary end point was ORR, with key secondary endpoints including DOR and overall survival (OS). Of the 104 patients enrolled at baseline, 96 discontinued for the following reasons: disease progression (27.9%), patient decision to withdraw (26.0%), and AEs (21.9%). The ORR for the mBCC cohort was 48.5% [95% CI, 30.8-66.2] and 60.3% in the laBCC cohort [47.2-71.7]. Median DOR was 14.8 months for the mBCC cohort [7.4-16.6] with a median OS of 33.4 months; Median DOR was 26.2 months [9.0-37.6] and OS was not estimable.

VII. No new safety concerns arose during the follow-up study. Again, all patients enrolled in the study experienced one or more treatment emergent adverse events (TEAEs). The incidence of TEAEs increased between the time of the primary analysis and the final data cutoff date for the follow-up study and correlated with patients who had 12 or more months of exposure to vismodegib (Erivedge). Patients who received treatment for 12 months or more had higher rates of muscle spasms, alopecia, dysgeusia, weight decreased, fatigue, and nausea. Deaths occurring during the study were considered by the investigator to be related to vismodegib (Erivedge).

VIII. Vismodegib (Erivedge) is currently recommended by NCCN guidelines for use in recurrent or advanced disease, with the caveat to be used in the FDA-approved indication of metastatic or locally advanced disease, with a category 2A recommendation.

IX. Vismodegib (Erivedge) is FDA-approved for adults with metastatic and locally advanced basal cell carcinoma. Vismodegib (Erivedge) has an overlapping indication with sonidegib (Odomzo), and if disease progression has occurred on or after one of these therapies, there is currently insufficient evidence regarding safety and/or efficacy of the other. One published piece of literature evaluated sonidegib (Odomzo) in those that were resistant to vismodegib (Erivedge); however, this trial included only nine subjects all of which showed no response to sonidegib (Odomzo) or were not evaluable for safety and/or efficacy. Available evidence disfavors use of sequential Hedgehog pathway inhibitors.

Investigational or Not Medically Necessary Uses

I. Vismodegib (Erivedge) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Ovarian Cancer
   B. Nevoid basal cell carcinoma syndrome

C. Prostate Cancer
D. Acute leukemia
E. Lymphoma
F. Breast Cancer
G. Medulloblastoma
H. Multiple myeloma
I. Myelofibrosis
J. Graft versus host disease
K. Pancreatic cancer
L. Lung cancer
M. Hepatocellular 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

1. Vismodegib (Erivedge) [Prescribing Information]. Genentech USA, INC. South San Franicos, CA. January 2012.
2. Sekulic A, et al. Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma. *N Engl J Med.* 2012 June 07; 366(23):2171-2179. Doi:10.1056/NEJMoal1113713.
3. Sekulic A, et al. Long-term safety and efficacy of vismodegib in patients with advanced basal cell carcinoma: final update of the pivotal ERIVANCE BCC study. *BMC Cancer* (2017) 17:332. Doi:10.1186/s 12885-017-3286-5/
4. National Comprehensive Cancer Network. NCCN Guidelines: Basal Cell Skin Cancer. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf
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Policy Implementation/Update:

Action and Summary of Changes	Date
Transition to policy format, addition of supporting evidence, addition of requirement attesting agent will NOT be used in combination with any other oncologic medication, removal of teratogenicity counseling attestation.	10/2020
Previous review	01/2013 12/2012
Criteria created	07/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP232

Split Fill Management*

Description

Voclosporin (Lupkynis) is an orally administered calcineurin-inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
voclosporin (Lupkynis)	7.9 mg capsules	Lupus Nephritis	180 capsules/30 days

Initial Evaluation

I. **Voclosporin (Lupkynis)** 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 biologic(s) [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)]; **AND**
   D. A confirmed positive autoantibody test [antinuclear (ANA) and/or anti-double-stranded DNA (anti-ds-DNA)]; **AND**
   E. A diagnosis of **Lupus Nephritis (LN); AND**
      1. Biopsy indicating class III (focal), IV (diffuse), or V (membranous) LN; **AND**
      2. Biopsy shows active lesions; **OR**
         i. Biopsy shows active AND chronic lesions; **AND**
      3. Provider attestation indicating medication will be given in combination with mycophenolate (CellCept) for induction and maintenance; **AND**
      4. Provider attestation the member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated; **AND**
      5. Treatment with belimumab (Benlysta) has been ineffective, contraindicated, or not tolerated.

II. Voclosporin (Lupkynis) is considered investigational when used for all other conditions, including but not limited to:
   A. Systemic Lupus Erythematosus (SLE) with absence of lupus nephritis
   B. Severe active central nervous system lupus
   C. Renal transplantation

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 **Lupus Nephritis (LN)**; **AND**
IV. 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) [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)]; **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. LN is a kidney disease that develops in about 40% of patients with SLE. Approximately 10% of patients develop end stage renal disease (ESRD). Kidney failure, dialysis, and kidney transplants are common in this patient population. Patients with SLE with any sign of kidney involvement (glomerular hematuria and/or cellular casts, proteinuria >0.5 g/24 hours [or spot urine protein-to-creatine ratio (UPCR) >500 mg/g], unexplained decrease in glomerular filtration rate (GFR)) are candidates for kidney biopsy to confirm diagnosis/class of LN, which then guides treatment.
   - Class I (minimal mesangial) and Class II (mesangial proliferative): Usually does not need specific immunosuppressive therapy but may be prone to histological transformation to more aggressive disease on repeat biopsy.
   - Class III (focal) and Class IV (diffuse): active, chronic classifications at high risk of developing ESRD, thus are targeted populations for immunosuppressive therapies.
   - Class V (membranous): presents similar to nephrotic syndrome with subendothelial deposits. Patients with Class III or IV disease may have these deposits and can be classified as Class III or IV in combination with Class V, can also present as pure Class V. Immunosuppressive therapy is indicated.
   - Class VI (advanced sclerosing): patients with sclerosing lesions; generally, do not respond to immunosuppressive therapy; treatment requires dialysis and/or kidney transplant.
II. 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. Alternatively, calcineurin inhibitors (tacrolimus or cyclosporine) can be used as monotherapy or in combination with MMF as induction/maintenance therapy particularly in refractory cases.

III. Guidelines recommend patients with LN be treated with hydroxychloroquine or an equivalent antimalarial, unless contraindicated, and adjunctive therapies be added to manage LN and attenuate complications of the disease.

IV. The safety and efficacy of voclosporin (Lupkynis) in pediatric patients has not been established.

V. The safety and efficacy of voclosporin (Lupkynis) in combination with biologic therapies [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)] has not been evaluated.

VI. Per the package insert, use of voclosporin (Lupkynis) is not recommend in patients with a baseline eGFR less than or equal to 45 mL/min/1.73m^2 unless the benefit exceeds the risk, as these patients may be at increased risk for acute and/or chronic nephrotoxicity.

VII. Policy is specific to list MMF as the induction/maintenance therapy due to potential safety concerns of additive toxic effects that may occur when co-administering voclosporin (Lupkynis) and cyclophosphamide. Per the package insert, use of voclosporin (Lupkynis) in combination with cyclophosphamide has not been established and is not recommended. The FDA review of voclosporin (Lupkynis) further adds “given the adverse reaction profile of cyclophosphamide and the lack of efficacy data for voclosporin in combination with cyclophosphamide, the review team concluded that there is reasonable concern about the benefit-risk profile in this situation, thus necessitating this limitation of use”.

VIII. Voclosporin (Lupkynis) was evaluated as an adjunct to standard therapy in a Phase 3, randomized, double-blind, placebo-controlled, 52-week trial in adults (n=357) with biopsy proven LN. The primary efficacy outcome was complete renal response at week 52, defined as a UPCR < 0.5, eGFR ≥ 60 ml/min per 1.73 m2 or a decline in no more than 20% from baseline, no rescue therapy, and a sustained dose ≤than 10 mg of prednisone. The primary endpoint was met with 73 patients (40.8%) in the voclosporin (Lupkynis) arm achieving renal response compared to 40 patients (22.5%) in the placebo arm (odds ratio 2.7; 95% CI: 1.6-4.3; P<0.001).

- All patients included in the trial were on background therapy with mycophenolate mofetil plus corticosteroids. Patients were 18 years of age and older with antibody positive SLE, ratio of urinary protein to creatinine (UPCR) of 2 or more (average patient had a baseline UPCR of 4), 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.

IX. As of date there are no head to head trials comparing voclosporin (Lupkynis) to belimumab (Benlysta). Additionally, guidelines do not have recommendations around preferring either agent in the setting of LN. However, given the potential for chronic calcineurin inhibitor-related nephrotoxicity, especially relevant to this patient population with underlying renal disease, and

the insufficient long-term controlled safety data beyond one year, the plan requires trial of or contraindication to belimumab (Benlysta) prior to use of voclosporin (Lupkynis).

Investigational or Not Medically Necessary Uses

I. Voclosporin (Lupkynis) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Systemic Lupus Erythematosus (SLE) in absence of lupus nephritis (LN)
   B. Severe active central nervous system lupus
   C. Renal Transplantation

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

References

1. Lupkynis [Prescribing Information]. Aurinia Pharma U.S., Inc.: Rockville, MD. January 2021.
2. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12(5):825-835.
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5. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney inter., Suppl.2012;2: 139–27.
6. Fanouriakis A, Kostopoulou M, Cheema K, et al. 2019 update of the joint European league against rheumatism and European renal association-European dialysis and transplant association (Eular/era-edta) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020;79(6):713-723.
7. FDA Center for Drug Evaluation and Research. Application number: 213716Orig1s000. Multi-Discipline review. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213716Orig1s000MultidisciplineR.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Von Willebrand factor (Vonvendi®)

UMP POLICY

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Policy Type: PA/SP Pharmacy Coverage Policy: UMP073

Description

Vonvendi is a recombinant von Willebrand factor indicated for use in adults (age 18 and older) diagnosed with von Willebrand disease for on-demand treatment and control of bleeding episodes, and perioperative management.

Length of Authorization

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

Quantity limits

Product Name	Dosage Form	Indication/ FDA Labeled Dosing	Quantity Limit
Vonvendi, von Willebrand factor (recombinant)	650, 1300 IU	**On-demand treatment and control of bleeding episodes:** • *Minor:* Up to 50 IU/kg for the initial dose, subsequent doses of up to 50 IU/kg every eight to 24 hours as clinically required • *Major:* Up to 80 IU/kg for the initial dose, subsequent doses of up to 60 IU/kg every eight to 24 hours for approximately two to three days, as clinically required **Perioperative management of bleeding:** A dose may be given 12 to 24 hours prior to surgery to allow the endogenous factor VIII levels to increase to at least 30 IU/dL (minor surgery) or 60 IU/dL (major surgery)	**On-demand treatment and control of bleeding episodes:** Up to the number of doses requested every 28 days **Perioperative management of bleeding:** Up to the number of doses requested every 28 days

Initial Evaluation

I. Vonvendi may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologists; **AND**
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
   C. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding 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 is known or suspected to be ineffective or contraindicated; **OR**

2. Perioperative management of bleeding

II. Vonvendi is 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

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.

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 Vonvendi was established based on a series of 22 patients with vWD over the age of 18 years of age who experienced 192 bleeding episodes (mostly mucosal, seven major). Results showed the Vonvendi was highly effective in restoring hemostasis. Most episodes were treated with a single infusion.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of Vonvendi in any other condition.

References

1. Vonvendi® [Prescribing Information]. Westlake Village, CA: Baxalta US Inc; February 2019
2. National Hemophilia Foundation. MASAC Recommendations Concerning products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Available from: https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations. Accessed July 5, 2019.
3. UpToDate, Inc. Treatment of von Willebrand disease. UpToDate [database online]. Last updated July 19, 2019.

Policy Implementation/Update:

Date Created	August 2019
Date Effective	August 2019
Last Updated	August 2019
Last Reviewed	08/2019

Action and Summary of Changes	Date
New policy created for von Willebrand factor (Vonvendi)	08/2019

Policy Type: PA/SP Pharmacy Coverage Policy: UMP217

Split Fill Management*

Description

Vorinostat (Zolinza) is an orally administered inhibitor of histone deacetylase (HDAC) enzymes (HDAC1, HDAC2, HDAC3 and HDAC6).

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Vorinostat (Zolinza)	100 mg capsules	Cutaneous T-Cell Lymphoma	120 capsules/30 days

Initial Evaluation

I. Vorinostat (Zolinza) 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 a dermatologist; **AND**
   C. Medication will not be used in combination with any other oncolytic agent; **AND**
   D. Medication will not be used in combination with skin-directed therapies (e.g. Total Skin Electron Beam Therapy [TSEBT], phototherapy); **AND**
   E. Member has not progressed on, or after, prior treatment with HDAC inhibitor (e.g. romidepsin [Istodax]); **AND**
   F. A diagnosis of **cutaneous T-cell lymphoma (CTCL) [i.e. Sezary syndrome, mycosis fungoides]** when the following are met:
      1. Member has progressive (stage II or higher) or recurrent disease; **AND**
      2. Treatment with <u>two</u> or more of the following <u>systemic</u> regimens have been ineffective or not tolerated:
         i. Systemic retinoid (e.g. bexarotene [Targretin])
         ii. Methotrexate (oral or injectable)
         iii. Systemic chemotherapy (e.g. chlorambucil, cyclophosphamide, etoposide)
         iv. Targeted immunotherapy (e.g. mogamulizumab, brentuximab)
         v. Interferons (e.g. peginterferon-alfa 2b [PegIntron], interferon gamma [Actimmune])

II. Vorinostat (Zolinza) is considered investigational when used for all other conditions, including but not limited to:
   A. Malignant pleural mesothelioma
   B. Cutaneous B-cell lymphoma
   C. Multiple myeloma
   D. Hodgkin's lymphoma

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Medication is prescribed by, or in consultation with, an oncologist or a dermatologist; **AND**
III. Member has experienced response to treatment (e.g. complete or partial remission, decrease from baseline in SWAT skin assessment scores, or PGA scores)

Supporting Evidence

I. Vorinostat (Zolinza) is FDA-approved for the treatment of cutaneous manifestations in adult patients with cutaneous T-cell lymphoma (CTCL), who have progressive, persistent, or recurrent disease on, or following, 2 systemic therapies. Its approval was based on results from 2 single-arm, open-label trials. Efficacy and safety of vorinostat has not been studied in pediatric population.
II. Sézary syndrome (SS) and mycosis fungoides (MF) are the most common subtypes of advanced cutaneous T cell lymphoma (CTCL). MF is a mature T cell non-Hodgkin lymphoma with presentation in the skin, but lymph nodes, blood, and viscera may also be involved. Skin lesions include erythroderma, patches, plaques, or tumors that may be localized or widespread. SS is a distinctive erythrodermic CTCL with leukemic involvement of malignant T cells that typically match the clone in the skin; less frequently, distinct clones may be detected in skin and blood.
III. Advanced stage MF and SS are most often chronic with a persistent or relapsing course. The choice of therapy at different time points in the disease is largely dependent on the goals of therapy, which include long-term disease control and prompt symptom relief. Therefore, management of advanced and recurrent CTCL is often orchestrated by a multidisciplinary team comprised of dermatologists, medical oncologists, and radiation oncologists.
IV. Patients with early stage CTCL are treated with skin-directed therapies. A randomized trial demonstrated that early aggressive therapy with combination chemotherapy plus total skin electron beam radiation therapy (TSEBT) does not appear to improve survival when compared with the use of sequential topical regimens. Skin directed therapies include topical corticosteroids, topical chemotherapy (nitrogen mustard or carmustine), retinoids, imiquimod, and phototherapy (UVB or PUVA). There is no standard initial therapy, and experts differ in their preferred approach. Alternatively, for patients with generalized tumors (e.g., >10 percent body surface area), equally acceptable treatment options are the use of total skin electron beam therapy (TSEBT) and systemic therapies. TSEBT often provides a complete response (CR), albeit temporary in most cases, while systemic agents generally provide partial responses but can be given in a maintenance fashion. A choice among these treatments is made based on patient preference and clinician experience. Despite decades of experience in the treatment of SS and

MF, well-designed, prospective, controlled clinical studies comparing the efficacy of various therapies are lacking.

V. NCCN guideline for the treatment of recurrent or advanced CTCL (MF and SS) includes vorinostat (Zolinza) as one of the preferred regimens (category 2A recommendation). Systemic therapies in this space generally involve use of single agents. Multiagent chemotherapy regimens are reserved for patients, who have progressed after multiple agents in the preferred regiments (e.g. bexarotene, brentuximab, interferons, methotrexate, mogamulizumab, romidepsin). Participants in the clinical trials for vorinostat (Zolinza) did not have a history of prior treatment with an HDAC inhibitor. Efficacy and safety of vorinostat (Zolinza) after progression on another HDAC inhibitor (e.g. romidepsin) has not been studied. Additionally, Safety of combining TSEBT and phototherapy with vorinostat (Zolinza) is unknown. NCCN guideline for primary T-Cell lymphoma recommend against such combination regimen.

VI. In an open-label, single-arm, multicenter, nonrandomized clinical trial (N= 74), patients (median age 61 years) with advanced refractory CTCL were treated with vorinostat (400 mg daily). An objective clinical response of 30% was reported with median duration of response 4 weeks. The majority of patients (82.4%) had stage IIB and higher CTCL and had previously failed a median of 3 prior systemic therapies (range, 1 to 12). The primary efficacy endpoint was measured as either a complete clinical response or partial response (i.e. ≥ 50% decrease in a modified severity weighted assessment tool (SWAT) score from baseline) ORR was 29.7% (n= 22) (95% CI; 19.7, 41.5) The median times to response for the overall population and individuals with stage IIB and higher CTCL was 55 days and 56 days (range, 28 to 171 days), respectively. The median time to tumor progression (50% increase in the SWAT score from the nadir) was 202 days. Response to previous systemic therapy was not a response predictor to vorinostat.

VII. In a phase 2, open-label, single-center, nonrandomized trial (n=33, median age 67 years), vorinostat exhibited treatment response among previously-treated patients with relapsed or refractory CTCL. The majority (85%) patients had stage IIB and higher CTCL, and were refractory to, or intolerant to, prior systemic therapies (median, 5; range, 1 to 15). Patients were assigned to one of the 3 groups: group 1: vorinostat 400 mg daily (n=13); group 2: vorinostat 300 mg twice daily for 3 days with 4 days rest (n=11) and group 3: vorinostat 300 mg twice daily for 14 days with 7 days rest, followed by 200 mg twice daily (n=9). Oral retinoids, vitamin A or alternative medicines were not allowed. Physician's global assessment (PGA) scores were used for assessing improvement/ partial response. Based on the intent-to-treat analysis, the ORR were 31%, 9%, and 33% in groups 1, 2, and 3, respectively. The ORR was 24.2% (n= 8) in the overall population, 25% (n= 7) in individuals with stage IIB or higher disease, and 36.4% (n= 4) in patients with Sezary syndrome.

VIII. During clinical trials, participants receiving vorinostat (Zolinza) reported significant adverse reactions and drug toxicity events. Fatigue (73%), thrombocytopenia (54%), diarrhea (49%), nausea (49%), and dysgeusia (46%) were the most common adverse drug reactions leading to dose reductions. Overall, 19% participants discontinued treatment due to adverse reactions. Vorinostat has been included in the Institute for Safe Medication Practices (ISMP) list of drug classes, which have a heightened risk of causing significant patient harm when used in error.

Investigational or Not Medically Necessary Uses

I. There is insufficient evidence to support the use of vorinostat (Zolinza) for conditions other than cutaneous T-cell lymphoma.
   A. Malignant pleural mesothelioma: Vorinostat (Zolinza) showed some evidence of efficacy in an initial phase I study. However, extensive evaluation did not confirm a clinically meaningful benefit from this approach. In a phase III trial, 661 previously treated patients were randomly assigned to either vorinostat or placebo. Progression free survival (PFS) was prolonged with vorinostat (median, 6.3 weeks versus 6.1 weeks; hazard ratio [HR] 0.75, 95% CI 0.63-0.88). However, this increase was not clinically significant. Also, the difference in overall survival was not significant (median, 30.7 weeks versus 27.1 weeks; HR 0.98, 95% CI 0.83-1.17).

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

References

1. Vorinostat (Zolinza)prescribing information. Whitehouse Station, NJ: Merck & Co, Inc; December 2018.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Primary cutaneous lymphomas. 1.2021. October 12, 2020; National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf
3. Duvic M, Talpur R, Ni X, et al: Phase II trial of oral vorinostat (suberoylanilide hydroxamic acid, SAHA) for refractory cutaneous T-cell lymphoma (CTCL). Blood 2007; 109(1):31-39.
4. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, Frankel SR, Chen C, Ricker JL, Arduino JM, Duvic M. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. J Clin Oncol. 2007 Jul 20;25(21):3109-15.
5. Krug LM, Kindler HL, Calvert H, et al. Vorinostat in patients with advanced malignant pleural mesothelioma who have progressed on previous chemotherapy (VANTAGE-014): a phase 3, double-blind, randomised, placebo-controlled trial. Lancet Oncol. 2015 Apr;16(4):447-56.

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria transitioned to policy format. Added criteria noting combination of Zolinza with other oncolytic drugs and skin-directed therapies not allowed; Added requirement of member not having progressed on HDAC inhibitors; updated detailed requirements for failure of two systemic regimens with drug classes (based on NCCN guideline and clinical data); Added investigational uses and supporting evidence section to support the intent of this PA policy	01/2021
Criteria reviews and updates	09/2012; 12/2012; 01/2013
Criteria created	03/2012

Policy Type: PA/SP Pharmacy Coverage Policy: UMP171

Split Fill Management*

Description

Voxelotor (Oxbryta) is an orally administered hemoglobin S (HbS) polymerization inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
voxelotor (Oxbryta)	500 mg tablets	Sickle Cell Disease	90 tablets/30 days

Initial Evaluation

I. Voxelotor (Oxbryta) 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 hematologist; **AND**
   C. Medication will **not** be used in combination with crizanlizumab-tmca (Adakveo); **AND**
   D. A diagnosis of **sickle cell disease (SCD)** when the following are met:
      1. Documentation of at least **one** vaso-occlusive crisis (VOC) within the previous six months requiring hospitalization, blood transfusion, or other medical intervention; **AND**
      2. Treatment with **BOTH** the following have been ineffective, contraindicated, or both are not tolerated:
         i. Hydroxyurea (generic, Siklos, Droxia) for a minimum duration of six months; **AND**
         ii. L-glutamine (available over-the-counter).

II. Voxelotor (Oxbryta) is considered investigational when used for all other conditions, AND when used in combination with crizanlizumab-tmca (Adakveo).

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 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. Use of voxelotor (Oxbryta) is **not** in combination with crizanlizumab-tmca (Adakveo); **AND**
IV. Member has exhibited improvement or stability of disease symptoms with documentation of reduced vaso-occlusive crises (VOCs) compared to baseline.

Supporting Evidence

I. Subjects of the pivotal HOPE trial (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization) were between 12 to 65 years of age with confirmed sickle cell disease with documentation of one to 10 vaso-occlusive events within the past 12 months. Hemoglobin levels among subjects prior to therapy were between 5.5 and 10.5 g/dL. Approximately two-thirds of subjects included in the HOPE trial were established on hydroxyurea at baseline.
II. The HOPE trial reported a decrease in indirect bilirubin level of 29.1% and a relative change in percent reticulocytes of 20% less in the 1500 mg voxelotor (Oxbryta) group.
III. Efficacy outcomes to support use of voxelotor (Oxbryta) in sickle cell disease include increase in hemoglobin by 24 weeks. There no data to support an increase in hemoglobin level results in a reduction in vaso-occlusive events, or other complications related to sickle cell disease. Hemoglobin represents one of many factors contributing to VOCs.
IV. Acute complications and symptoms occur intermittently in sickle cell disease and throughout its course. These complications include vaso-occlusive pain crises (VOCs), acute chest syndrome, aplastic crisis, hemolytic crisis, and the pooling of blood within bodily organs.
V. Vaso-occlusive crises (VOCs) include stroke, severe pain, kidney and other organ and/or tissue damage for which there is no other explanation than vaso-occlusive crisis.
VI. Transfusion protocol is considered the most effective therapy for secondary stroke prophylaxis. If this contraindicated or ineffective, hydroxyurea is introduced.
VII. Hydroxyurea
    - Generic hydroxyurea is considered first-line in the treatment of sickle cell disease.
    - Typically offered to patients with three or greater sickle cell-associated moderate-to-severe crises within the last 12 months.
    - Has been shown to be disease modifying at reducing the rate of pain episodes, stroke, transfusion requirement, and mortality.
    - Has been shown to reduce the number of vaso-occlusive crises (VOCs) and hospitalizations.
    - Approximately two-thirds of subjects included in the HOPE trial (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization) were established on hydroxyurea at baseline.
VIII. L-glutamine
    - Typically considered in patients who have at least two vaso-occlusive crises (VOCs) per year, despite maximally tolerated hydroxyurea dose, and considered against cost.
    - Was approved to reduce acute complications of sickle cell disease (VOCs).

- Monotherapy is considered in patients who do not tolerate hydroxyurea. Over-the-counter products are available as well as in a prescription product L-glutamine (Endari)

IX. Both hydroxyurea and L-glutamine have evidence to support disease-modifying activity and the reduction of VOC or complications related to disease.

Investigational or Not Medically Necessary Uses

X. There is currently limited to no data to support the safety and efficacy of concomitant use of voxelotor (Oxbryta) with crizanlizumab-tmca (Adakveo).

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References

1. Oxbryta [Package Insert]. Global Blood Therapeutics. San Francisco, CA. November, 2019
2. Vichinsky E, Hoppe CC, Ataga KI et al. A phase 3 randomize trial of voxelotor in sickle cell disease. N Engl J Med. 2019; 381: 509-19.
3. Buchanan GR, Yawn BP, Afenyi-Annan AN et al. Evidence-based management of sickle cell disease: expert panel report. National Heart, Lung, and Blood Institute. 2014.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2020

Policy Type: PA/SP Pharmacy Coverage Policy: UMP171

Split Fill Management*

Description

Zanubrutinib (Brukinsa) is an orally administered Bruton's Tyrosine Kinase (BTK) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
zanubrutinib (Brukinsa)	80 mg tablets	Treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy	120 tablets/30 days

Initial Evaluation

I. Zanubrutinib (Brukinsa) 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 **Mantle Cell Lymphoma (MCL)** when the following are met:
      1. Member has received one prior therapy [e.g. chemotherapy, rituximab (Rituxan), or lenalidomide (Revlimid)]; **AND**
      2. Member has not previously progressed on a BTK inhibitor [e.g. ibrutinib (Imbruvica), acalabrutinib (Calquence)]

II. Zanubrutinib (Brukinsa) is considered <u>investigational</u> when used for all other conditions, including but <u>not limited to</u>:
   A. Chronic Lymphocytic Leukemia (CLL)
   B. Diffuse Large B-cell Lymphoma (DLBCL)
   C. Follicular Lymphoma (FL)
   D. Hairy Cell Leukemia (HCL)
   E. Graft-versus Host Disease (GvHD)
   F. Marginal Zone Lymphoma (MZL)
   G. Indolent Non-Hodgkin Lymphoma (iNHL)
   H. Small Lymphocytic Lymphoma (SLL)
   I. Waldenstrom Macgroglobulinemia (WM)

J. MCL first-line therapy
K. MCL combination therapy

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The member has exhibited improvement or stability of disease symptoms (e.g. no signs of disease progression)

Supporting Evidence

I. Zanubrutinib (Brukinsa) was studied in one open-label, single-arm, Phase 2 trial, and one Phase 1/2 safety and pharmacokinetic trial in 118 patients with MCL who had progressed on prior systemic therapy. The primary efficacy outcome was the overall response rate (ORR) which was 84% in both trials. Secondary efficacy outcomes were complete response (CR), partial response (PR), and duration of response (DoR). The percentage of patients with a CR was 59% and 22% for the Phase 2 trial and Phase 1/2 trial, respectively. The percentage of patients with a PR was 24% and 62% for the Phase 2 trial and Phase 1/2 trial, respectively. Median DoR in months was 19.5 and 18.5 for the Phase 2 trial and Phase 1/2 trial, respectively. Progression-free survival was evaluated in the Phase 2 trial, and found 74.6% of patients at 12 months were progression-free.
II. Zanubrutinib (Brukinsa) was FDA-approved under the accelerated approval pathway based on ORR. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Finalized data has not been published on these trials at this time.
III. The safety profile of zanubrutinib (Brukinsa) is similar to that of other BTK inhibitors [e.g. ibrutinib (Imbruvica), acalabrutinib (Calquence)]. The most common side effects are: upper respiratory tract infection, diarrhea, rash, pneumonia, and musculoskeletal pain. There are no specific contraindications to using zanubrutinib (Brukinsa); however, warnings and precautions include: serious cytopenias (e.g. neutropenia, thrombocytopenia, anemia), infections, cardiac arrhythmias, second primary malignancies (most commonly skin cancer), hemorrhage, and embryo-fetal toxicity. Zanubrutinib (Brukinsa) showed a 23% dose interruption rate, a 1% dose reduction rate, and a 7% discontinuation rate due to intolerable adverse events in clinical trials.
IV. Zanubrutinib (Brukinsa) was studied in a head-to-head trial against ibrutinib (Imbruvica) in patients with Waldenstrom's Macroglobulinemia. Zanubrutinib (Brukinsa) had lower rates of atrial fibrillation (2% vs 15%), minor bleeding (48.5% vs 59.2%), major hemorrhage (5.9% vs 9.2%), and diarrhea (20.8% vs 31.6%) compared to ibrutinib (Imbruvica), respectively. The rate of neutropenia was 29.7% and 13.3% for zanubrutinib (Brukinsa) and ibrutinib (Imbruvica), respectively.
V. For the treatment of MCL the National Comprehensive Cancer Network guidelines recommend initial induction therapy with chemotherapy. Those that respond well to initial treatment are

candidates for an autologous stem cell transplant followed by rituximab for three years. Recommended second-line therapies are BTK inhibitors [e.g. acalabrutinib (Calquence), ibrutinib (Imbruvica), zanubrutinib (Brukinsa)], lenalidomide (Revlimid), and venetoclax (Venclaxta).

Investigational or Not Medically Necessary Uses

I. The following indications do not have sufficient evidence to support the use of zanubrutinib (Brukinsa) at this time:
   A. Chronic Lymphocytic Leukemia (CLL)
   B. Diffuse Large B-cell Lymphoma (DLBCL)
   C. Follicular Lymphoma (FL)
   D. Hairy Cell Leukemia (HCL)
   E. Graft-versus Host Disease (GvHD)
   F. Marginal Zone Lymphoma (MZL)
   G. Indolent Non-Hodgkin Lymphoma (iNHL)
   H. Small Lymphocytic Lymphoma (SLL)
   I. Waldenstrom Macgroglobulinemia (WM)
   J. MCL first-line therapy
   K. MCL combination therapy

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References

I. Brukinsa [Prescribing Information]. Beigene USA, Inc.: San Mateo, CA. November 2019.
II. Brukinsa [Manufacturer e-dossier]. Beigene USA, Inc.: San Mateo, CA. November 2019.
III. Nasdaq Investors. BeiGene Announces Results of Phase 3 ASPEN Trial of Zanubrutinib Compared to Ibrutinib for the Treatment of Patients with Waldenstrom's Macroglobulinemia. http://ir.beigene.com/news-releases/news-release-details/beigene-announces-results-phase-3-aspen-trial-zanubrutinib?loc=US. Written December 16, 2019. Accessed December 19, 2019.
IV. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology. B-cell lymphomas. Version 6.2019. November 26, 2019.

Policy Implementation/Update:

Last Reviewed: 02/2020	
Action and Summary of Changes	**Date**
Policy created	02/2020

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Uniform Medical Plan

POLICY NAME: **UMP031 ENFUVIRTIDE**

Affected Medications: FUZEON® (ENFUVIRTIDE, SUBCUTANE.)

Effective Date *(date PA/Step UM edit effective)*: 3/1/2012

Last Review Date:

Uses Considered Medically Necessary	DIAGNOSIS OF HIV-1 INFECTION.	
Required Medical Documentation	DOCUMENTED HIV VIREMIA (TWO CONSECUTIVE RNA MEASURES GREATER THAN 200 COPIES PER ML) DESPITE EITHER: AT LEAST THREE MONTHS THERAPY WITH A NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NRTI), NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI), AND A PROTEASE INHIBITOR (PI); OR VIREMIA AND DOCUMENTED RESISTANCE TO OR INTOLERANCE TO AT LEAST ONE MEMBER IN EACH OF THE NRTI, NNRTI AND PI CLASSES. FUZEON PRESCRIBED IN COMBINATION WITH AN OPTIMIZED ANTIVIRAL REGIMEN (DETERMINED BY VIRAL RESISTANCE TESTING; GENOTYPIC OR PHEOTYPIC) INCLUDING AT LEAST THREE HIV DRUGS.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	MUST BE SIX YEARS OF AGE OR OLDER.
	Provider restriction	PRESCRIBED OR SUPERVISED BY A SPECIALIST IN THE TREATMENT OF HIV INFECTION.
Coverage Duration	SIX MONTHS.	
Quantity Limits	ONE KIT PER 30 DAYS.	
Additional Information		

Washington State Rx Services
P.O. Box 40168
Portland, OR 97240-0168

Uniform Medical Plan

POLICY NAME: **UMP038 DRUGS TO TREAT GAUCHER'S DISEASE**

Affected Medications: CEREZYME® (IMIGLUCERASE, INTRAVEN.); VPRIV® (VELAGLUCERASE ALFA, INTRAVEN.)

Effective Date *(date PA/Step UM edit effective)*: 5/19/2013

Last Review Date: 5/14/13

Uses Considered Medically Necessary	DIAGNOSIS OF NON-NEUROPATHIC GAUCHER'S DISEASE, CHRONIC (MILD TO MODERATE).	
Required Medical Documentation		
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	IMIGLUCERASE: PATIENT AGE 2 YEARS OR OVER; MIGLUSTAT: PATIENT AGE 18 YEARS OR OLDER; VELAGLUCERASE ALFA: PATIENT AGE 4 YEARS OR OLDER.
	Provider restriction	
Coverage Duration	ONE YEAR.	
Quantity Limits		
Additional Information	PATIENTS TAKING MIGLUSTAT MUST NOT BE A CANDIDATE FOR ENZYME REPLACEMENT THERAPY. PATIENTS TAKING IMIGLUCERASE AND VELAGLUCERASE ALFA MUST BE MONITORED FOR HYPERSENSITIVITY REACTIONS.	

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Uniform Medical Plan

POLICY NAME: **UMP042 RIBAVIRIN ORAL**

Affected Medications: COPEGUS® (RIBAVIRIN, ORAL); MODERIBA® (RIBAVIRIN, ORAL); REBETOL® (RIBAVIRIN, ORAL); RIBAPAK (RIBAVIRIN, ORAL); RIBASPHERE (RIBAVIRIN, ORAL); RIBASPHERE RIBAPAK (RIBAVIRIN, ORAL); RIBATAB® (RIBAVIRIN, ORAL); RIBAVIRIN, ORAL.

Effective Date *(date PA/Step UM edit effective)*: 1/1/2011

Last Review Date:

Uses Considered Medically Necessary	TREATMENT OF HEPATITIS C WITH COMPENSATED LIVER DISEASE.	
Required Medical Documentation	PATIENT OF CHILD BEARING POTENTIAL HAS BEEN COUNSELED ON THE TERATOGENIC EFFECTS OF THERAPY AND WILLING TO PRACTICE CONTRACEPTION DURING AND FOR SIX MONTHS AFTER COMPLETION OF THERAPY; FEMALES OF CHILD BEARING POTENTIAL ALSO HAD A RECENT NEGATIVE PREGNANCY TEST. RIBAVIRIN USED IN COMBINATION WITH PEG-INTRON, PEGASYS, ROFERON-A, INFERGEN OR INTRON-A. RENEWAL THERAPY RESERVED FOR PATIENTS THAT HAVE ACHIEVED A GREATER THAN 2 LOG REDUCTION IN HCV RNA FROM BASELINE VALUE.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	PRESCRIBED OR SUPERVISED BY A GASTROENTEROLOGIST, HEPATOLOGIST, OR INFECTIOUS DISEASE SPECIALIST.
Coverage Duration	INITIATION THERAPY: FOUR MONTHS. RENEWAL THERAPY FOR GENOTYPE 1 OR 4: 8 MONTHS; FOR GENOTYPE 2 OR 3: 2 MONTHS.	
Quantity Limits	TABLETS/CAPSULES: 180/30; ORAL SOLUTION: 900ML/30.	
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP044 ADEFOVIR**

Affected Medications: ADEFOVIR DIPIVOXIL, ORAL (HEPSERA®)

Effective Date *(date PA/Step UM edit effective)*: 1/1/2011

Last Review Date:

Uses Considered Medically Necessary	INDICATION OF CHRONIC TYPE B VIRAL HEPATITIS	
Required Medical Documentation	PATIENTS PREGNANT OR OF CHILDBEARING POTENTIAL COUNSEELED OF PREGNANCY RISK. FAILURE OF OR CONTRAINDICATION TO THE USE OF EPIVIR-HBV. HIV POSITIVE PATIENTS TAKING CONCOMITANT HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART); OR HEPATITIS B CARRIERS REQUESTING ANTIVIRAL PROPHYLAXIS WHILE RECEIVING IMMUNOSUPPRESSIVE OR CYTOTOXIC THERAPY; OR PATIENT HAS DECOMPENSATED CIRRHOSIS; OR HBEAG POSITIVE PATIENTS WITH PERSISTENCE FOR SIX MONTHS OR GREATER AND 20,000 COPIES/ML OR MORE WITH EITHER PERSISTENTLY ELEVATED ALT (GREATHER THAN 30 IU/L FOR MEN OR 19 IU/L FOR WOMEN) OR MODERATE-SEVERE HEPATITIS EVIDENCED BY RECENT BIOPSY; OR HBEAG NEGATIVE PATIENTS WITH PERSISTENCE OF SIX MONTHS OR MORE WITH HBV DNA OF 2000 COPIES/ML OR MORE WITH EITHER PERSISTENTLY ELEVATED ALT (GREATHER THAN 30 IU/L FOR MEN OR 19 IU/L FOR WOMEN) OR MODERATE-SEVERE HEPATITIS EVIDENCED BY RECENT BIOPSY. CONTINUATION OF THERAPY FOR HBEAG POSITIVE PATIENTS THAT HAVE NOT BEEN TREATED FOR TWELVE MONTHS BEYOND SEROCONVERSION OR HBEAG NEGATIVE PATIENTS.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	18 YEARS OF AGE OR OLDER.
	Provider restriction	PRESCRIBED BY A GASTROENTEROLOGIST, INFECTIOUS DISEASE SPECIALIST OR SPECIALIST IN THE TREATMENT OF HEPATITIS B VIRUS.
Coverage Duration	ONE YEAR.	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP064 VITAMIN D ANALOGUES**

Affected Medications: CALCIJEX® (CALCITRIOL, INTRAVEN.); CALCITRIOL, INTRAVEN.; DOXERCALCIFEROL, ORAL; HECTOROL® (DOXERCALCIFEROL, ORAL); PARICALCITOL, ORAL; ROCALTROL® (CALCITRIOL, ORAL); ZEMPLAR® (PARICALCITOL, ORAL)

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date:

Uses Considered Medically Necessary	DIAGNOSIS OF HYPOCALCEMIA DUE TO MODERATE-TO-SEVERE CHRONIC KIDNEY DISEASE, HYPOCALCEMIA DUE TO CHRONIC RENAL DIALYSIS, HYPOCALCEMIA DUE TO HYPOPARATHYROIDISM/PSEUDOHYPOPARATHYROIDISM OR SECONDARY HYPOPARATHYROIDISM ASSOCIATED WITH MODERATE-TO-SEVERE CHRONIC KIDNEY DISEASE	
Required Medical Documentation		
Exclusion and Restrictions	**Exclusion**	FOR END-STAGE RENAL DISEASE (ESRD) FOR CALCITRIOL, HECTOROL, ZEMPLAR REJECTING FOR "BILL MEDICARE PART B": IF THE DRUG IS BEING USED FOR AN ESRD-RELATED CONDITION AND THE PATIENT IS ON DIALYSIS, THE MEDICATION IS NOT COVERED UNDER THE MEMBER'S PHARMACY BENEFIT
	Patient restriction	
	Provider restriction	
Coverage Duration	1 YEAR	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP067 UMP EXTENDED DURATION MULTIPLE COPAY SPECIALTY DRUGS**

Affected Medications: ILARIS® (CANAKINUMAB, SUBCUTANE.); LILETTA® (LEVONORGESTREL, VAGINAL); MIRENA® (LEVONORGESTREL, VAGINAL); NEXPLANON® (ETONOGESTREL, SUBCUTANE.); PARAGARD T 380-A® (COPPER, VAGINAL); SKYLA® (LEVONORGESTREL, VAGINAL); SUPPRELIN LA® (HISTRELIN AC, IMPLANT); VANTAS® (HISTRELIN AC, IMPLANT); MACUGEN® (PEGAPTANIB SODIUM, INTRAOCULAR); TRELSTAR® (TRIPTORELIN PAMOATE, INTRAMUSCULAR); TRELSTAR MIXJET® (TRIPTORELIN PAMOATE, INTRAMUSCULAR); ZOLADEX® (GOSERELIN ACETATE, SUBCUTANEOUS)

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date: 8/18/16

Uses Considered Medically Necessary	DIAGNOSIS OF FDA APPROVED INDICATION PER PACKAGE LABELING; FOR TRELSTAR AND TRELSTAR MIXJET: TRANSGENDER/GENDER REASSIGNMENT/GENDER DYSPHORIA ALSO COVERED	
Required Medical Documentation	DOCUMENTATION OF TREATMENT DOSE, FOLLOW UP MONITORING PLAN, PRIOR THERPAY FOR THE SUBMITTED DIAGNOSIS, PLANNED TREATMENT DURATION AND SUBMISSION OF CHART NOTES FOR REVIEW	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	6 MONTHS	
Quantity Limits	FOR ILARIS: 1 INJECTION PER 56 DAY SUPPLY; FOR MACUGEN: 1 INJECTION PER 42 DAY SUPPLY; FOR MIRENA: 1 TIME FILL OF 1 IMPLANT PER 5 YEARS; FOR SUPPRELIN LA: 1 IMPANT PER 365 DAYS SUPPLY; FOR TRELSTAR AND TRELSTAR MIXJET: 3.75MG - 1 INJECTION EVERY 4 WEEKS; 11.25MG - 1 INJECTION EVERY 12 WEEKS; 22.5MG - 1 INJECTION EVERY 24 WEEKS; FOR PARAGARD: 1 EVERY 10 YEARS; FOR LILETTA, NEXPLANON AND SKYLA: 1 IMPLANT EVERY 3 YEARS	
Additional Information	WITH THE EXCEPTION OF MEDICATIONS COVERED AT ZERO COPAY UNDER THE CONTRACEPTIVE HEALTHCARE REFORM, MULTIPLE COPAYS (2 OR 3, DEPENDING ON QUANTITY LIMIT DURATION) APPLY	

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Uniform Medical Plan

POLICY NAME: **UMP088**

Affected Medications: INTERMEZZO® (ZOLPIDEM TARTRATE, SUBLINGUAL); ZOLPIDEM TARTRATE, SUBLINGUAL

Effective Date *(date PA/Step UM edit effective)*: 5/8/2012

Last Review Date:

Uses Considered Medically Necessary	INSOMNIA	
Required Medical Documentation	TRAIL AND FAILURE OF ZOLPIDEM IR AND ZALEPLON	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	ONE YEAR	
Quantity Limits	TWENTY TABLETS PER THIRTY DAYS	
Additional Information	FEMALES: 1.75MG ONLY WITH A QLL OF 20 TABLETS PER 30 DAYS; MALES: 3.5 MG WITH A QLL OF 20 TABLETS PER 30 DAYS	

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Uniform Medical Plan

POLICY NAME: **UMP093 PEG-INTERFERON 2B**

Affected Medications: PEGINTRON REDIPEN® (PEGINTERFERON ALFA-2B, SUBCUTANE.); PEGINTRON® (PEGINTERFERON ALFA-2B, SUBCUTANE.); SYLATRON 4-PACK® (PEGINTERFERON ALFA-2B, SUBCUTANE.); SYLATRON® (PEGINTERFERON ALFA-2B, SUBCUTANE.)

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date: 10/21/16

Uses Considered Medically Necessary	DIAGNOSIS OF: HEPATITIS C, CHRONIC (PEGINTRON); MELANOMA: ADJUVANT (SYLATRON).	
Required Medical Documentation	INITIAL: HEPATITIS C, CHRONIC (PEGINTRON); MELANOMA: DIAGNOSIS WITH MICROSCOPIC OR GROSS NODAL INVOLVEMENT WITHIN 84 DAYS OF DEFINITIVE SURGICAL RESECTION INCLUDING COMPLETE LYMPHADENECTOMY.	
Exclusion and Restrictions	**Exclusion**	SYLATRON: AUTOIMMUNE HEPATITIS, HEPATIC DECOMPENSATION.
	Patient restriction	
	Provider restriction	PRESCRIBED OR SUPERVISED BY A GASTROENTEROLOGIST, HEPATOLOGIST, INFECTIOUS DISEASE SPECIALIST, ONCOLOGIST OR TRANSPLANT SPECIALIST
Coverage Duration	3 MONTHS	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP173 LOMUSTINE**

Affected Medications: CEENU® (LOMUSTINE, ORAL)

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date: 8/25/16

Uses Considered Medically Necessary	DIAGNOSIS OF BRAIN TUMORS, PRIMARY AND METASTATIC, FOLLOWING APPROPRIATE SURGICAL AND/OR RADIOTHERAPEUTIC PROCEDURES; HODGKIN'S LYMPHOMA, AS A COMPONENT OF COMBINATION CHEMOTHERAPY, IN PATIENTS WHOSE DISEASE HAS PROGRESSED FOLLOWING INITIAL CHEMOTHERAPY.	
Required Medical Documentation	INITIAL: BRAIN TUMORS, FOLLOWING APPROPRIATE SURGICAL AND/OR RADIOTHERAPEUTIC PROCEDURES; HODGKIN'S LYMPHOMA, AS A COMPONENT OF COMBINATION CHEMOTHERAPY, AFTER PROGRESSION FOLLOWING INITIAL CHEMOTHERAPY.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST OR NEUROLOGIST.
Coverage Duration	INITIAL: SIX MONTHS. RENEWAL: SIX MONTHS.	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP178 MITOTANE**

Affected Medications: LYSODREN® (MITOTANE, ORAL)

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date: 8/25/16

Uses Considered Medically Necessary	DIAGNOSIS OF ADRENAL CORTICAL CARCINOMA, INOPERABLE, FUNCTIONAL OR NON-FUNCTIONAL.	
Required Medical Documentation	INITIAL: DIAGNOSIS OF INOPERABLE ADRENAL CORTICAL CARCINOMA. RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON THERAPY.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST.
Coverage Duration	INITIAL: 6 MONTHS. RENEWAL: ONE YEAR.	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP181 THIOGUANINE**

Affected Medications: TABLOID® (THIOGUANINE, ORAL)

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date: 8/25/16

Uses Considered Medically Necessary	DIAGNOSIS OF ACUTE NONLYMPHOCYTIC LEUKEMIAS, FOR REMISSION INDUCTION AND REMISSION CONSOLIDATION.	
Required Medical Documentation	RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION ON THERAPY.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST.
Coverage Duration	INITIAL: 3 MONTHS. RENEWAL: SIX MONTHS.	
Quantity Limits	40 MG TABLET, WEIGHT BASED DOSING 2-3 MG/KG/DAY.	
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP187 MERCAPTOPURINE MONOHYDRATE**

Affected Medications: PURIXAN® (MERCAPTOPURINE, ORAL)

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date: 8/25/16

Uses Considered Medically Necessary	DIAGNOSIS OF ACUTE LYMPHOCYTIC LEUKEMIA.	
Required Medical Documentation	RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON THERAPY.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST.
Coverage Duration	INITIAL: THREE MONTHS. RENEWAL: ONE YEAR.	
Quantity Limits	2000 MG/100 ML SOLUTION, WEIGHT BASED DOSING 1.5 TO 2.5 MG/KG/DAY	
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP188 LEUCOVORIN CALCIUM**

Affected Medications: CALCIUM FOLINATE (LEUCOVORIN CALCIUM, INJECTION); LEUCOVORIN CALCIUM, INJECTION

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date: 8/26/16

Uses Considered Medically Necessary	DIAGNOSIS OF RESCUE, AFTER TREATMENT WITH HIGH DOSE METHOTREXATE THERAPY IN OSTEOSARCOMA; MEGALOBLASTIC ANEMIAS, WHEN ORAL THERAPY IS NOT FEASIBLE; COLORECTAL CANCER, ADVANCED, IN COMBINATION WITH 5-FLUOROURACIL.	
Required Medical Documentation	INITIAL: POST TREATMENT WITH HIGH DOSE METHOTREXATE THERAPY IN OSTEOSARCOMA; COLORECTAL CANCER, IN COMBINATION WITH 5-FLUOROURACIL. RENEWAL: DOCUMENTATION OF TREATMENT BENEFIT FROM THERAPY.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	INITIAL: ONE YEAR. RENEWAL: ONE YEAR.	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP190 RUFINAMIDE**

Affected Medications: BANZEL® (RUFINAMIDE, ORAL)

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date: 8/16/16

Uses Considered Medically Necessary	DIAGNOSIS OF SEIZURE ASSOCIATED WITH LENNOX-GASTAUT SYNDROME	
Required Medical Documentation	DOCUMENTATION OF TREATMENT DOSE, FOLLOW UP MONITORING PLAN, PRIOR THERPAY FOR THE SUBMITTED DIAGNOSIS, PLANNED TREATMENT DURATION AND SUBMISSION OF CHART NOTES FOR REVIEW	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	1 YEAR	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP200 PREDNISONE**

Affected Medications: RAYOS® (PREDNISONE, ORAL)

Effective Date *(date PA/Step UM edit effective)*: 10/27/2016

Last Review Date: 10/27/16

Uses Considered Medically Necessary	DIAGNOSIS OF: USE AS AN ANTI-INFLAMMATORY OR IMMUNOSUPPRESSIVE AGENT, TREATMENT OF CERTAIN ENDOCRINE CONDITIONS OR PALLIATE OF CERTAIN NEOPLASTIC CONDITIONS.	
Required Medical Documentation	INITIAL: TRIAL AND FAILURE OF OR CONTRAINDICATIONS TO IMMEDIATE RELEASE PREDNISONE. RENEWAL: DOCUMENTATION INDICATING CLINICAL BENEFIT FROM TREATMENT.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	ONE YEAR	
Quantity Limits	1 MG, 2 MG, 5 MG TABLETS: 30 TABLETS PER 30 DAYS	
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP210 DIMETHYL SULFOXIDE**

Affected Medications: RIMSO-50® (DIMETHYL SULFOXIDE, INTRAVESIC)

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date: 8/16/16

Uses Considered Medically Necessary	DIAGNOSIS OF INTERSTITIAL CYSTITIS	
Required Medical Documentation	DOCUMENTATION OF TREATMENT DOSE, FOLLOW UP MONITORING PLAN, PRIOR THERPAY FOR THE SUBMITTED DIAGNOSIS, PLANNED TREATMENT DURATION AND SUBMISSION OF CHART NOTES FOR REVIEW	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	1 YEAR	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP213 DINOPROSTONE**

Affected Medications: PROSTIN E2 VAGINAL SUPPOSITORY® (DINOPROSTONE, VAGINAL)

Effective Date *(date PA/Step UM edit effective)*:

Last Review Date: 8/16/16

Uses Considered Medically Necessary	DIAGNOSIS OF ABORTION	
Required Medical Documentation	DOCUMENTATION OF TREATMENT DOSE, FOLLOW UP MONITORING PLAN, PRIOR THERPAY FOR THE SUBMITTED DIAGNOSIS, PLANNED TREATMENT DURATION AND SUBMISSION OF CHART NOTES FOR REVIEW	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	1 MONTH	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP214 DEFEROXAMINE MESYLATE**

Affected Medications: DEFEROXAMINE MESYLATE, INJECTION; DESFERAL® (DEFEROXAMINE MESYLATE, INJECTION)

Effective Date *(date PA/Step UM edit effective)*: 10/28/2016

Last Review Date: 10/28/16

Uses Considered Medically Necessary	DIAGNOSIS OF: ACUTE IRON INTOXICATION AND OF CHRONIC IRON OVERLOAD DUE TO TRANSFUSION-DEPENDENT ANEMIAS.	
Required Medical Documentation	INITIAL: ACUTE IRON INTOXICATION AND OF CHRONIC IRON OVERLOAD DUE TO TRANSFUSION-DEPENDENT ANEMIAS. RENEWAL: DOCUMENTATION INDICATING CLINICAL BENEFIT FROM THERAPY.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	THREE MONTHS	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP217 CAPSAICIN**

Affected Medications: QUTENZA® (CAPSAICIN/SKIN CLEANSER, TOPICAL)

Effective Date *(date PA/Step UM edit effective)*: 10/27/2016

Last Review Date: 10/27/16

Uses Considered Medically Necessary	DIAGNOSIS OF: NEUROPATHIC PAIN ASSOCIATED WITH POSTHERPETIC NEURALGIA	
Required Medical Documentation	INITIAL: TREATMENT OF NEUROPATHIC PAIN ASSOCIATED WITH POSTHERPETIC NEURALGIA. RENEWAL: DOCUMENTATION INDICATING CLINICA BENEFIT FROM TREATMENT.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	ONE YEAR	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP218 CYANOCOBALAMIN**

Affected Medications: NASCOBAL® (CYANOCOBALAMIN (VITAMIN B-12), NASAL)

Effective Date *(date PA/Step UM edit effective)*: 10/11/2016

Last Review Date: 10/11/2016

Uses Considered Medically Necessary	PERNICIOUS ANEMIA IN PATIENTS WHO ARE IN REMISSION FOLLOWING INTRAMUSCULAR VITAMIN B12 THERAPY AND HAVE NO NERVOUS SYSTEM INVOLVEMENT; VITAMIN B12 DEFICIENCY	
Required Medical Documentation	INABILITY TO ABSORB VITAMIN B12 ORALLY.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration		
Quantity Limits		
Additional Information	DOSING IS ONE SPRAY IN ONE NOSTRIL ONCE WEEKLY.	

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Uniform Medical Plan

POLICY NAME: **UMP221 FACTOR XIII A-SUBUNIT RECOMBINANT**

Affected Medications: TRETTEN® (FACTOR XIII A-SUBUNIT,RECOMB, INTRAVEN.)

Effective Date *(date PA/Step UM edit effective)*: 10/12/2016

Last Review Date: 10/12/16

Uses Considered Medically Necessary	USE IN ROUTINE PROPHYLAXIS FOR BLEEDING IN PATIENTS WITH CONGENITAL FACTOR XIII A-SUBUNIT DEFICIENCY	
Required Medical Documentation		
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration		
Quantity Limits		
Additional Information	THE DOSE FOR ROUTINE PROPHYLAXIS FOR BLEEDING IN PATIENTS WITH CONGENITAL FACTOR XIII (FXIII) A-SUBUNIT DEFICIENCY IS 35 INTERNATIONAL UNITS (IU) PER KILOGRAM BODY WEIGHT ONCE MONTHLY TO ACHIEVE A TARGET TROUGH LEVEL OF FXIII ACTIVITY AT OR ABOVE 10% USING A VALIDATED ASSAY. CONSIDER DOSE ADJUSTMENT IF ADEQUATE COVERAGE IS NOT ACHIEVED WITH THE RECOMMENDED 35 IU/KG DOSE.	

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Uniform Medical Plan

POLICY NAME: **UMP225 ETOPOSIDE Affected**

Medications: ETOPOSIDE, ORAL **Effective Date**

***(date PA/Step UM edit effective)*: Last Review**

Date: 8/26/16

Uses Considered Medically Necessary	DIAGNOSIS OF SMALL CELL LUNG CANCER, IN COMBINATION WITH OTHER CHEMOTHERAPEUTIC AGENTS, AS FIRST LINE TREATMENT.	
Required Medical Documentation	INITIAL: SMALL CELL LUNG CANCER IN COMBINATION WITH OTHER CHEMOTHERAPEUTIC AGENTS. RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON THERAPY.	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST.
Coverage Duration	INITIAL: THREE MONTHS. RENEWAL: ONE YEAR.	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP248 PYRIMETHAMINE**

Affected Medications: PYRIMETHAMINE (DARAPRIM®), ORAL TABLET

Effective Date *(date PA/Step UM edit effective)*: 3/1/2016

Last Review Date: 2/28/16

Uses Considered Medically Necessary	TREATMENT FOR: TOXOPLASMOSIS AND MALARIA	
Required Medical Documentation	TRIAL OF COMPOUNDED PYRIMETHAMINE	
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	3 MONTHS	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP256 VIRAZOLE**

Affected Medications: RIBAVIRIN INHALATION SOLUTION (VIRAZOLE®)

Effective Date *(date PA/Step UM edit effective)*: 01/27/17

Last Review Date: 01/27/17

Uses Considered Medically Necessary	DIAGNOSIS OF HOSPITALIZED INFANTS AND YOUNG CHILDREN WITH SEVERE LOWER RESPIRATORY TRACT INFECTIONS DUE TO RESPIRATORY SYNCTIAL VIRUS (RSV).	
Required Medical Documentation		
Exclusion and Restrictions	**Exclusion**	
	Patient restriction	
	Provider restriction	
Coverage Duration	ONE MONTH	
Quantity Limits		
Additional Information		

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Uniform Medical Plan

POLICY NAME: **UMP280 ZURAMPIC**

Affected Medications: ZURAMPIC (LESINURAD), DUZALLO (LESINURAD-ALLOPURINOL)

Effective Date *(date PA/Step UM edit effective)*: 11/01/2017

Last Review Date: 11/17/2017

Uses Considered Medically Necessary	DUZALLO: TREATMENT OF HYPERURICEMIA ASSOCIATED WITH GOUT IN PATIENTS WHO HAVE NOT ACHIEVED TARGET SERUM URIC ACID LEVELS WITH A XANTHINE OXIDASE INHIBITOR ALONE. ZURAMPIC: TREATMENT OF HYPERURICEMIA ASSOCIATED WITH GOUT IN PATIENTS WHO HAVE NOT ACHIEVED TARGET SERUM URIC ACID LEVELS WITH A XANTHINE OXIDASE INHIBITOR ALONE, IN COMBINATION WITH A XANTHINE OXIDASE INHIBITOR.	
Required Medical Documentation	TRIAL OF XANTHINE OXIDASE INHIBITOR MONOTHERAPY AND A TRIAL OF PROBENACID	
Exclusion and Restrictions	**Exclusion**	NONE
	Patient restriction	NONE
	Provider restriction	NONE
Coverage Duration	INITIAL: 12 MONTHS INITIAL RENEWAL: 12 MONTHS	
Quantity Limits	30 TABLETS PER 30 DAYS	
Additional Information		

UMP STEP POLICY

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Please see the UMP Preferred Drug list for more details on prescription drugs that have step requirements:

PEBB	https://ump.regence.com/pebb/benefits/prescriptions
SEBB	https://ump.regence.com/sebb/benefits/prescriptions

Nondiscrimination notice

We follow federal civil rights laws. We do not discriminate based on race, color, national origin, age, disability, gender identity, sex or sexual orientation.

We provide free services to people with disabilities so that they can communicate with us. These include sign language interpreters and other forms of communication.

If your first language is not English, we will give you free interpretation services and/or materials in other languages.

If you need any of the above, call Customer Service at:

1-888-361-1611 (TRS: 711)

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

If you need help filing a complaint, please call Customer Service.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services Office for Civil Rights at ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone:

U.S. Department of Health
and Human Services
200 Independence Ave. SW, Room 509F
HHH Building, Washington, DC 20201

800-368-1019, 800-537-7697 (TDD)

You can get Office for Civil Rights complaint forms at hhs.gov/ocr/office/file/index.html.

Dave Nesseler-Cass coordinates our nondiscrimination work:

Dave Nesseler-Cass,
Chief Compliance Officer
601 SW Second Ave.
Portland, OR 97204
855-232-9111
compliance@modahealth.com

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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).

CHÚ Ý: Nếu bạn nói tiếng Việt, có dịch vụ hổ trợ ngôn ngữ miễn phí cho bạn. Gọi 1-888-361-1611 (TRS: 711)

注意：如果您說中文，可得到免費語言幫助服務。請致電 1-888-361-1611（聾啞人專用 TRS：711）

주의: 한국어로 무료 언어 지원 서비스를 이용하시려면 다음 연락처로 연락해주시기 바랍니다. 전화 1-888-361-1611 (TRS: 711)

PAUNAWA: Kung nagsasalita ka ng Tagalog, ang mga serbisyong tulong sa wika, ay walang bayad, at magagamit mo. Tumawag sa numerong 1-888-361-1611 (TRS: 711)

تامدخ كانهف ،ةيرعلا تدحتت تنك اذإ :هيبنت مقرب لصتا
اناجم كل ةحاتم ةيوغل ةدعاسم.
يصنلا فتاهلا(1-888-361-1611 :TRS)

د جهتو: ودرا یا گرا (URDU) نیلسا تو لتےیو
ےیا سد ضهومعا لا ل کے یا ےعا
کر لکا پر 1-888-361-1611 (TRS: 711)

ВНИМАНИЕ! Если Вы говорите по-русски, воспользуйтесь бесплатной языковой поддержкой. Позвоните по тел. 1-888-361-1611 (текстовый телефон TRS: 711).

ATTENTION : si vous êtes locuteurs francophones, le service d'assistance linguistique gratuit est disponible. Appelez au 1-888-361-1611 (TRS: 711)

تامدخ ،دیناک یم تبحص یسراف هب هک یتروص رد :هجوت اب .تسا
دوجوم امش یارب ناگیار تروص هب همجرت
دیریگب سامت. 1-888-361-1611 (TRS: 711)

ध्यान द: यदद आप दिदी बोलत ि, तो आपको भाषाई सियायता बना कोई पैसा ददए उपलब्ध ि । 1-888-361-1611 पर कॉल कर (TRS: 711)

Achtung: Falls Sie Deutsch sprechen, stehen Ihnen kostenlos Sprachassistenzdienste zur Verfügung. Rufen sie 1-888-361-1611 (TRS: 711)

注意：日本語をご希望の方には、日本語サービスを無料で提供しております。1-888-361-1611（TRS：テレタイプライターをご利用の方は711）までお電話ください。

અગત્યનું: જો તમે (ભાષાંતર કરેલ ભાષા અહીં દરાવો) બોલો છો તો તે ભાષામાં તમારે માટે વના મૂલ્યે સહાય ઉપલબ્ધ છે.
1-888-361-1611 (TRS: 711) પર કોલ કરો

ໂປດຊາບ: ຖ້າທ່ານເວົ້າພາສາລາວ, ການຊ່ວຍ
ຫຼື ອດ້ານພາສາແມ່ນມີໃຫ້ທ່ານໂດຍບໍ່ເສ
ຍຄ່າ. ໂທ 1-888-361-1611 (TRS: 711)

УВАГА! Якщо ви говорите українською, для вас доступні безкоштовні консультації рідною мовою. Зателефонуйте 1-888-361-1611 (TRS: 711)

ATENȚIE: Dacă vorbiți limba română, vă punem la dispoziție serviciul de asistență lingvistică în mod gratuit. Sunați la 1-888-361-1611 (TRS: 711)

THOV CEEB TOOM: Yog hais tias koj hais lus Hmoob, muaj cov kev pab cuam txhais lus, pub dawb rau koj. Hu rau 1-888-361-1611 (TRS: 711)

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