Uniform Medical Plan (UMP) coverage limits for drugs covered under UMP’s prescription drug benefit
Updates effective 10/01/2020

These coverage limits apply to these UMP plans:
- UMP Classic (PEBB)
- UMP Consumer-Directed Health Plan (UMP CDHP) (PEBB)
- UMP Plus–Puget Sound High Value Network (UMP Plus–PSHVN) (PEBB)
- UMP Plus–UW Medicine Accountable Care Network (UMP Plus–UW Medicine ACN) (PEBB)
- UMP Achieve 1 (SEBB)
- UMP Achieve 2 (SEBB)
- UMP High Deductible (SEBB)
- UMP Plus–Puget Sound High Value Network (UMP Plus–PSHVN) (SEBB)
- UMP Plus–UW Medicine Accountable Care Network (UMP Plus–UW Medicine ACN) (SEBB)

As a state-sponsored health plan, UMP must follow the Washington State Pharmacy and Therapeutics (P&T) Committee’s coverage decisions. The committee consists of Washington health care professionals, including physicians and pharmacists. The UMP Preferred Drug List (PDL) includes the committee’s coverage recommendations. 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 these drugs, the Washington State Rx Services P&T Committee makes coverage recommendations for UMP’s review. UMP then determines a drug’s tier level, which tells you how much you will have to pay for a covered prescription drug.

Some drugs require preauthorization to determine whether they are medically necessary and meet UMP coverage criteria. If you do not receive 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).

Drugs covered under UMP medical benefits rather than the prescription drug benefit have different rules for preauthorization. To preauthorize a drug covered under the medical benefit, 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 hca.wa.gov/ump-coc
- Call Washington State Rx Services at 1-888-361-1611 (TRS: 711)
- Refer to the UMP Preferred Drug Lists
  - PEBB members: https://www.hca.wa.gov/ump-pebb-pdl
  - SEBB members: https://www.hca.wa.gov/ump-sebb-pdl
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP074

Description
Abemaciclib (Verzenio) is an orally administered small molecule cyclin-dependent kinase (CKD) 4/6 inhibitor.

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

Quantity limits

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>abemaciclib (Verzenio)</td>
<td>50 mg tablets</td>
<td>Breast cancer, HER2-negative, HR-positive, advanced or metastatic, for initial endocrine therapy in combination with an aromatase inhibitor</td>
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<td>199757</td>
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<td></td>
<td>100 mg tablets</td>
<td>Breast cancer, HER2-negative, HR-positive advanced or metastatic, for progression following endocrine therapy in combination with fulvestrant</td>
<td>56 tablets/28 days</td>
<td>199758</td>
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<tr>
<td></td>
<td>150 mg tablets</td>
<td>Breast cancer, HER2-negative, HR-positive advanced or metastatic, for progression following endocrine therapy in combination with fulvestrant</td>
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<td>199759</td>
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<td></td>
<td>200 mg tablets</td>
<td>Breast cancer, HER2-negative, HR-positive advanced or metastatic, for progression following endocrine therapy and chemotherapy in the metastatic setting, monotherapy</td>
<td></td>
<td>199760</td>
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</table>

Initial Evaluation

I. Abemaciclib (Verzenio) 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; AND
   C. Abemaciclib (Verzenio) will not be used in combination with any other oncolytic medication, with the exception of aromatase inhibitors (e.g., anastrozole, letrozole) or fulvestrant; AND

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
D. The member has not previously progressed on or after treatment with another CDK4/6 inhibitor (e.g., ribociclib [Kisqali], palbociclib [Ibrance]); **AND**

E. A diagnosis of **breast cancer** when the following are met:
   1. The member has hormone receptor-positive (HR+), and HER2-negative (HER2-) disease; **AND**
   2. The member is female; **AND**
   3. Disease is advanced (stage III) or metastatic (stage IV); **AND**
      i. The medication is prescribed for one of the following settings:
         a. As initial endocrine-based therapy in combination with an aromatase inhibitor (e.g., anastrozole, letrozole); **AND**
            i. The member is postmenopausal (natural or pharmacotherapy induced [e.g., GnRH therapy used concomitantly [e.g., Lupron]]; **OR**
         b. Following progression on endocrine therapy, in combination with fulvestrant; **OR**
         c. Metastatic (stage IV) disease, following endocrine and chemotherapy, which were administered in the metastatic (stage IV) setting.

II. Abemaciclib (Verzenio) is 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
   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 **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. Abemaciclib (Verzenio) will not be used in combination with any other oncolytic medication with the exception of an aromatase inhibitor (anastrozole, letrozole) or fulvestrant; **AND**
V. Documentation is provided indicating disease response to therapy, as defined by stabilization of disease, decrease in size of the tumor, or tumor spread.

Supporting Evidence

I. 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 subjects 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).

II. Clinical trials to date have not included significant numbers of subjects previously treated with other CDK4/6 inhibitors; thus, safety and efficacy of subsequent administration is unknown at this time. Additionally, CDK4/6 inhibitors have been evaluated as monotherapy, and sufficient safety and efficacy evidence in combination with therapies outside of aromatase inhibitors and fulvestrant remain unknown. National Comprehensive Cancer Network (NCCN) notes a lack of data to support use of an additional CDK4/6 inhibitor after progression on a CDK4/6 regimen.

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

Investigational or Not Medically Necessary Uses

I. Abemaciclib (Verzenio) has not been FDA-approved, or sufficiently studied for safety and efficacy, for the conditions or settings listed below:
   A. In combination with, or following progression on or after, another CDK4/6 inhibitor (e.g., ribociclib [Kisqali], abemaciclib [Verzenio])
B. Breast cancer in males – consider palbociclib (Ibrance) as an alternative  
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

References

Policy Implementation/Update:

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<th>Date Created</th>
<th>January 2018</th>
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<tr>
<td>Date Effective</td>
<td>February 2018</td>
</tr>
<tr>
<td>Last Updated</td>
<td>March 2018, October 2019</td>
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<td>Last Reviewed</td>
<td>March 2018, October 2019</td>
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<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria transitioned to policy. Addition of adult age, clarification around coverage for concomitant therapies, removal of subgroup analysis exclusions, improvement of renewal criteria to follow standard practice.</td>
<td>10/2019</td>
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<tr>
<td>New indication added, first-line treatment in combination with an aromatase inhibitor.</td>
<td>03/2018</td>
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<td>Clarified use of concomitant medication</td>
<td>09/2017</td>
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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

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

Initial Evaluation

I. Acalabrutinib (Calquence) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; AND
   C. Member has not experienced disease progression while on a BTK inhibitor [e.g. zanubrutinib (Brukinsa®), ibrutinib (Imbruvica®)]; AND
   D. A diagnosis of one of the following:
      1. **Mantle cell lymphoma (MCL); AND**
         i. Treatment with at 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 one of the following settings:
            a. Previously untreated CLL/SLL; AND
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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

b. Relapsed or refractory after at least one prior systemic therapy; AND
   i. Member has not experienced disease progression while on venetoclax (Venclexta) or a phosphoinositide-3 kinase inhibitor (e.g., duvelisib (Copiktra), idelalisib (Zydelig)); AND
   ii. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy)

II. Acalabrutinib (Calquence) is considered 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


Policy Implementation/Update:

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

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<td>Updated criteria to policy format. Addition of age requirement to ages 18 and older. Require member has not experienced disease progression while on a BTK inhibitor. Added new indication of CLL/SLL.</td>
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<td>Criteria created</td>
<td>01/2018</td>
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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

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<tr>
<td>alirocumab (Praluent)</td>
<td>75 mg/mL pen injector</td>
<td>Heterozygous familial hypercholesterolemia; Atherosclerotic cardiovascular disease</td>
<td>2 mL (2 injections)/28 days</td>
<td>189256, 189258</td>
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<td></td>
<td>150 mg/mL pen injector</td>
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<td>189257, 189259</td>
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<tr>
<td>evolocumab (Repatha)</td>
<td>140 mg/mL auto injector; prefilled syringe</td>
<td></td>
<td>2 mL (2 injections)/28 days</td>
<td>1839578, 189578</td>
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<td>420 mg/mL solution cartridge</td>
<td>Heterozygous familial hypercholesterolemia; Homozygous familial hypercholesterolemia; Atherosclerotic cardiovascular disease</td>
<td>3.5 mL (1 injection)/28 days</td>
<td>193637</td>
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</tbody>
</table>

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 rosvastatin [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 one 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 one of the following
         a. Genotyping or clinical criteria using either the Simon Broome diagnostic criteria (definite diagnosis classification) or Dutch Lipid Network criteria (score of at least 8)
         b. Physical signs of familial hypocholesteremia (e.g., arcus cornealis, tendon xanthomas, xanthelasma)
         c. Clinical documentation or a DNA mutation analysis supporting the diagnosis of heterozygous familial hypercholesterolemia; OR
   3. Homozygous familial hypercholesterolemia; AND
      i. The member is 13 years of age or older; AND
      ii. The request is for evolocumab (Repatha); AND
      iii. 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; AND
      iv. Evolocumab (Repatha) will not be used in combination with mipomersen (Kynamro) or lopitamide (Juxtapid);
II. Alirocumab (Praluent) or evolocumab (Repatha) are considered not medically necessary when used for all other conditions, including but not limited to:
   A. Hypercholesterolemia non-familial cause

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

Renewal Evaluation

I. 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) to 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. 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. 2011 National Lipid Association (NLA) familial hypercholesterolemia guidelines define therapy as ineffective as inability to achieve a LDL-C of less than 70 mg/dL with treatment in atherosclerotic cardiovascular disease.

VI. **Atherosclerotic cardiovascular disease (ASCVD):** 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).

- 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, 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 PCSK9 inhibitors suggest the absolute treatment benefit will likely be modest (e.g. < 1% change in risk).”

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

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

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.
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.

### Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia

<table>
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<tr>
<th>Criteria</th>
<th>Points</th>
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<tbody>
<tr>
<td><strong>Family history</strong></td>
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<tr>
<td>• First-degree relative with known premature (men: &lt;55 years; women: &lt;60 years) coronary or vascular disease, or</td>
<td>1</td>
</tr>
<tr>
<td>• First-degree relative with known LDL-C above the 95th percentile</td>
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<tr>
<td>• First-degree relative with tendinous xanthomata and/or arcus cornealis, or</td>
<td>2</td>
</tr>
<tr>
<td>• Children &lt;18 years of age with LDL-C above the 95th percentile</td>
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<td><strong>Clinical History</strong></td>
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</tr>
<tr>
<td>• Patient with premature (men: &lt;55 years; women: &lt;60 years) coronary artery disease</td>
<td>2</td>
</tr>
<tr>
<td>• Patient with premature (men: &lt;55 years; women: &lt;60 years) cerebral or peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td><strong>Physical examination</strong></td>
<td></td>
</tr>
<tr>
<td>• Tendinous xanthomata</td>
<td>6</td>
</tr>
<tr>
<td>• Arcus cornealis before age 45 years</td>
<td>4</td>
</tr>
<tr>
<td><strong>LDL-C levels</strong></td>
<td></td>
</tr>
<tr>
<td>• LDL-C ≥8.5 mmol/L (325 mg/dL)</td>
<td>8</td>
</tr>
<tr>
<td>• LDL-C 6.5-8.4 mmol/L (251-325 mg/dL)</td>
<td>5</td>
</tr>
<tr>
<td>• LDL-C 5.0-6.4 mmol/L (191-250 mg/dL)</td>
<td>3</td>
</tr>
<tr>
<td>• LDL-C 4.0-4.9 mmol/L (155-190 mg/dL)</td>
<td>1</td>
</tr>
<tr>
<td><strong>DNA analysis</strong></td>
<td></td>
</tr>
<tr>
<td>• Functional mutation in the LDLR, apoB, or PCSK9 gene</td>
<td>8</td>
</tr>
</tbody>
</table>

Choose only one score per group, the highest applicable diagnosis (diagnosis is based on the total number of points obtained)

- A "definite" FH diagnosis requires >8 points
- A "probable" FH diagnosis requires 6-8 points
- A "possible" FH diagnosis requires 3-5 points

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

### VIII. Homozygous familial hypercholesterolemia (HoFH)

Only evolocumab (Repatha) is FDA-approved in the setting of HoFH and includes patients ages 13 and older. In one multi-center, double-blind, randomized, placebo-controlled trial (TESLA Part B), Repatha was studied in patients greater than or equal to 13 years of age with homozygous familial hypercholesterolemia. Patients in the clinical trial had familial hypercholesterolaemia 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 hypercholesterolaemia in both parents.
Use of evolocumab (Repatha) with mipomersen (Kynamro) or lopitamide (Juxtapid) has not been studied 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.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated to policy format. Added requirement of ezetimibe trial and failure in ASCVD.</td>
<td>06/2019</td>
</tr>
<tr>
<td>Removed alternate statin dosing strategies in patients who are statin intolerant. Decreased LDL cutoff to &gt;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.</td>
<td>06/2018</td>
</tr>
<tr>
<td>Addition of Repatha 420mg/3.5mL pushtronex system to the approval language.</td>
<td>11/2018</td>
</tr>
<tr>
<td>Removed triple step therapy with an additional LDL lowering agent. Increased initial authorization to 6 months.</td>
<td>02/2016</td>
</tr>
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</table>

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

**Pharmacy Coverage Policy: UMP002**

**Split Fill Management** (applies to 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 crizotinib (Xalkori), ceritinib (Zykadia), and brigatinib (Alunbrig).
- Renewal: 12 months

**Quantity limits**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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<tbody>
<tr>
<td>crizotinib</td>
<td>200 mg capsules</td>
<td>ALK+ NSCLC, metastatic</td>
<td>60 capsules/30 days</td>
<td>168671</td>
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<tr>
<td></td>
<td>250 mg capsules</td>
<td>ROS1+ NSCLC, metastatic</td>
<td>60 capsules/30 days</td>
<td>168670</td>
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<tr>
<td>ceritinib</td>
<td>150 mg capsules</td>
<td>ALK+ NSCLC, metastatic</td>
<td>84 capsules/28 days</td>
<td>183765</td>
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<tr>
<td></td>
<td>150 mg tablets</td>
<td></td>
<td>84 tablets/28 days</td>
<td>206607</td>
</tr>
<tr>
<td>alectinib</td>
<td>150 mg capsules</td>
<td>ALK+ NSCLC, metastatic</td>
<td>240 capsules/30 days</td>
<td>191329</td>
</tr>
<tr>
<td>brigatinib</td>
<td>30 mg tablets</td>
<td>ALK+ NSCLC, metastatic</td>
<td>180 tablets/30 days</td>
<td>197898</td>
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<td>90 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
<td>201302</td>
</tr>
<tr>
<td></td>
<td>90 mg and 180 mg tablet titration pack</td>
<td></td>
<td>30 tablets/30 days</td>
<td>201306</td>
</tr>
<tr>
<td></td>
<td>180 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
<td>201304</td>
</tr>
<tr>
<td>lorlatinib</td>
<td>25 mg tablets</td>
<td></td>
<td>90 tablets/30 days</td>
<td>204668</td>
</tr>
<tr>
<td></td>
<td>100 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
<td>204669</td>
</tr>
</tbody>
</table>

**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 progress on alectinib (Alecensa); OR
            ii. The member has progressed on ceritinib (Zykadia); OR
            iii. The member has progressed on crizotinib (Xalkori) AND one other agent in this policy.
      2. **ROS1+ Non-Small Cell Lung Cancer as detected by an FDA-approved test; AND**
         i. The request is for crizotinib (Xalkori)

II. Crizotinib (Xalkori), ceritinib (Zykadia), alectinib (Alecensa), brigatinib (Alunbrig), and lorlatinib (Lorbrena) are considered **investigational** when used for all other conditions, including but not limited to:
   A. ROS1+ NSCLC for any agent in this policy except for crizotinib (Xalkori)
   B. NSCLC prior to the metastatic setting, or outside of the ROS1+ or ALK mutation (e.g., RET-rearranged NSCLC)
   C. NSCLC in combination with other therapies
   D. Thyroid cancer
   E. Melanoma
F. Gastrointestinal cancer  
G. Prostate cancer  
H. Leukemias or lymphomas  
I. Urothelial cancer  

Renewal Evaluation  
I. The medication is prescribed by, or in consultation with, an oncologist; AND  
II. The medication continues to be used as monotherapy for ALK+ or ROS1+ NSCLC; AND  
III. 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. Any open prior authorizations for other ALK-inhibitors will be closed if coverage is approved an agent in this policy. These agents have only been studied in the metastatic and adult populations 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. Alectinib (Alecensa) is the preferred agent for first-line treatment per the National Comprehensive Cancer Network (NCCN) for the treatment of ALK-positive NSCLC. 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 non-small cell lung cancer. As of July 2019, a phase III clinical trial was in the enrollment stage to determine the comparative efficacy against crizotinib (Xalkori).  
V. Crizotinib (Xalkori) is currently FDA-approved for ROS1+ NSCLC. Several other agents are being evaluated in clinical trials; however, safety and efficacy data was not available as of July 2019.  
VI. 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 clinical significant outcomes such as overall survival and quality of life parameters.  
VII. There is currently no evidence that ALK-inhibitors improve clinical outcomes (e.g., overall survival, quality of life) in patients with NSCLC. 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. ROS1+ NSCLC for any agent in this policy except for crizotinib (Xalkori)
   B. NSCLC prior to the metastatic setting, or outside of the ROS1+ or ALK mutation (e.g., RET-rearranged NSCLC)
   C. NSCLC in combination with other therapies
   D. Thyroid cancer
   E. Melanoma
   F. Gastrointestinal cancer
   G. Prostate cancer
   H. Leukemias or lymphomas
   I. Urothelial cancer

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

References


**Policy Implementation/Update:**

<table>
<thead>
<tr>
<th>Date Created</th>
<th>December 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>December 2011</td>
</tr>
<tr>
<td>Last Updated</td>
<td>July 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>12/2012, 09/2014, 12/2015, 06/2017, 01/2018, 02/2019, 07/2019</td>
</tr>
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<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria update: Transitioned prior authorization criteria to policy format and consolidated all agents into one policy. Brigatinib now allowed for first-line setting if member has CI or intolerance to preferred therapy. Quantity level limits updated to reflect currently available products and package sizes. Addition of Zyka tablets that are available in addition to the capsules.</td>
<td>07/2019</td>
</tr>
</tbody>
</table>

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. Zyka 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. Alecsa 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 |
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

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

Initial Evaluation
I. **Grastek, Odactra, Oralair, or Ragwitek** may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an allergist or ear, nose, and throat (ENT) specialist; **AND**

Washington State Rx Services is administered by Moda Health

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

October 01, 2020
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 (Singular); **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; **AND**
      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 Grastek or Oralair; **OR**
      iii. Short ragweed pollen; **AND**
         a. Member is 18 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. 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.

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

III. Safety and efficacy of Grastek and Oralair has not been established in patients younger than five years old.

IV. Safety and efficacy of Odactra and Ragwitek has not been established in patients younger than 18 years old.

V. Allergen avoidance and pharmacotherapy should be considered first when treating allergic rhinitis. Intranasal glucocorticoids are considered first line for allergic rhinitis and can be used in combination with oral antihistamine if symptoms are not controlled. Symptom management with pharmacotherapy should be considered first prior to initiating immunotherapy.

Investigational or Not Medically Necessary Uses

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

References


Policy Implementation/Update:

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<td>12/2019, 01/2020</td>
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Action and Summary of Changes

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<th>Date</th>
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<td>Updated to policy format. Combined existing criteria into one policy, added age requirements to match FDA-indications.</td>
<td>01/2020</td>
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<tr>
<td>Edit to Allergen Immunotherapy Criteria; add Odactra information and related mapping; general edits to format and criteria to accommodate Odactra.</td>
<td>02/2018</td>
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<tr>
<td>Combine existing criteria to create Allergen Immunotherapy Criteria</td>
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<tr>
<td>Effective and created date of Grastek, Oralair, and Ragwitek criteria</td>
<td>09/2014</td>
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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP003

Split Fill Management*

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

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

Quantity limits

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<th>DDID</th>
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<tr>
<td>alpelisib (Piqray)</td>
<td>150 mg tablets (2 x 150 = 300 mg daily dose pack)</td>
<td>PIK3CA mutation, HR+, HER2-, advanced or metastatic breast cancer</td>
<td>56 tablets/28 days</td>
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<td></td>
<td>200 mg tablets (200 mg daily dose pack)</td>
<td></td>
<td>28 tablets/28 days</td>
<td>206829</td>
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<td></td>
<td>200 mg and 50 mg tablets (200 + 50 = 250 mg daily dose pack)</td>
<td></td>
<td>56 tablets/28 days</td>
<td>206828</td>
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Initial Evaluation

I.  Alpelisib (Piqray) may be considered medically necessary when the following criteria are met:
   A. The member is 18 years of age or older; AND
   B. The medication is prescribed by, or in consultation with, an oncologist; AND
   C. Diagnosis of advanced or metastatic breast cancer when the following are met:
      1. The breast cancer is HR-positive, HER2-negative; AND
      2. PIK3CA mutation has been tested and confirmed; AND
      3. The provider attests the member is endocrine resistant or refractory; AND
      4. The member has not previously progressed on a CDK4/6 inhibitor (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.]; AND
      5. The medication will be used in combination with fulvestrant (Faslodex) only; AND
         i. Alpelisib (Piqray) will not be used in combination with ANY other oncolytic medication including but not limited to CDK4/6 inhibitors (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.).
II. Alpelisib (Piqray) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Breast cancer that is not PIK3CA mutated.

III. Alpelisib (Piqray) is considered investigational when used for all other conditions, including but not limited to:
   A. Breast cancer that is not HR+, HER2-, PIK3CA mutated, and/or advanced or metastatic
   B. Meningioma
   C. Oropharyngeal cancer
   D. Melanoma
   E. Renal cell cancer
   F. Pancreatic cancer
   G. Head and neck cancers
   H. Ovarian cancer

Renewal Evaluation

I. The medication is prescribed by, or in consultation with, an oncologist; AND
II. The member will be using in combination with fulvestrant (Faslodex); AND
   A. Alpelisib (Piqray) will not be used in combination with ANY other oncolytic medication including but not limited to CDK4/6 inhibitors (e.g., palbociclib [Ibrance], abemaciclib [Verzenio], ribociclib [Kisqali], etc.); AND
III. The member has experienced positive response to treatment, defined by the stabilization of disease or a decrease in tumor size or tumor spread.

Supporting Evidence

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

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

III. Of the 169 patients that received alpelisib (Piqray), 9 (5.3%) had history of use of a CDK4/6 inhibitor (e.g., Ibrance, Kisqali, Verzenio). It is unknown whether these patients had progressed on therapy, or, discontinued due to intolerance; however, at this time the evidence for safety and efficacy in the CDK4/6 inhibitor treatment refractory or relapsed population is unknown. Too few patients were included in the trial with this characterization to extrapolate the entirety of the trial results to the patients that have progressed on CDK4/6 inhibitors and it is currently unknown how this population would respond.

Washington State Rx Services is administered by Moda Health.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
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 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.
D. Melanoma  
E. Renal cell cancer  
F. Pancreatic cancer  
G. Head and neck cancers  
H. Ovarian cancer

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

References

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

Policy Implementation/Update:

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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

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<td>10 mg tablets</td>
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<td>amifampridine (Ruzurgi)</td>
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<td>LEMS</td>
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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

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
D. 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 ≥ 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.
   - Inflammatory muscle disease
   - Limb-girdle muscular dystrophy
   - Myasthenia gravis
   - Congenital myasthenic syndrome
   - Motor neuron disease (i.e. amyotrophic lateral sclerosis, multifocal motor neuropathy)

References

4. FDA. Center for Drug Evaluation and Research. Application number: 209321Orig1s000 Summary Review.


**Policy Implementation/Update:**

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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

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<td>590 mg/8.4 mL suspension</td>
<td>Mycobacterium avium complex</td>
<td>252 mL/30 day</td>
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Initial Evaluation

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

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

Renewal Evaluation

I. Received therapy with amikacin liposomal (Arikayce) as part of a multi-drug regimen; **AND**
II. Has not received or will not receive 18 months or more of therapy with amikacin liposomal (Arikayce); **AND**
III. Negative sputum culture obtained within the last 30 days; **AND**
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 MAC lung disease in adults who do not achieve negative sputum cultures after 6 months of a multidrug background regimen therapy.

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

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

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

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

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

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

Investigational or Not Medically Necessary Uses

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

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

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


Anabolic Steroids
UMP POLICY

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

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<td>oxymetholone</td>
<td>50 mg tablets</td>
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<td>Cachexia: 90 tablets/30 days</td>
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<td>oxandrolone</td>
<td>2.5 mg tablets</td>
<td>Weight gain associated with surgery, infections, trauma; Catabolism with prolonged corticosteroid use; Bone pain associated with osteoporosis; Cachexia associated with AIDS</td>
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<td>Pediatrics: ≤0.1 mg/kg/day</td>
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Initial Evaluation
I. Oxymetholone (Anadrol-50) may be considered medically necessary when the following criteria below are met:
   A. Member has a diagnosis of anemia caused by deficient red cell production associated with one of the following conditions:
      1. Acquired aplastic anemia; OR
2. Congenital aplastic anemia; OR
3. Fanconi’s anemia; OR
4. Hypoplastic anemias caused by the administration of myelotoxic drugs, or myelosuppression due to chemotherapy; OR
5. Myelofibrosis; OR

B. Member has a diagnosis of **cachexia associated with AIDS; AND**
   1. Medication is prescribed by, or in consultation with, a specialist in gastroenterology, nutritional support, or infectious disease; **AND**
      i. Member has ≥ 10% *unintentional* weight loss over a 12 month period; **OR**
      ii. Member has ≥ 7.5% *unintentional* weight loss over a 6 month period; **OR**
      iii. Member has ≥ 5% body cell mass (BCM) loss within 6 months; **OR**
      iv. For males, BCM < 35% and body mass index (BMI) < 27 kg/m²; **OR**
      v. For females, BCM < 23% and BMI < 27 kg/m²; **OR**
      vi. BMI < 18 kg/m²; **AND**
      vii. Weight loss is *not* attributable to other causes

II. **Generic oxandrolone** may be considered medically necessary when the following criteria below are met:
   A. Medication will be used as adjunctive therapy to promote weight gain; **AND**
      1. Weight loss is due to one of the following conditions:
         i. Extensive surgery; **OR**
         ii. Chronic infections; **OR**
         iii. Severe trauma; **OR**
         iv. Member fails to gain or maintain normal weight without definite pathophysiological reasons; **OR**
   B. Medication will be used to offset the protein catabolism associated with prolonged administration of corticosteroids; **OR**
   C. Medication will be used for the treatment of bone pain associated with osteoporosis; **OR**
   D. Member has a diagnosis of **cachexia associated with AIDS; AND**
      1. Medication is prescribed by, or in consultation with, a specialist in gastroenterology, nutritional support, or infectious disease; **AND**
         i. Member has ≥ 10% *unintentional* weight loss over a 12 month period; **OR**
         ii. Member has ≥ 7.5% *unintentional* weight loss over a 6 month period; **OR**
         iii. Member has ≥ 5% body cell mass (BCM) loss within 6 months; **OR**
         iv. For males, BCM < 35% and body mass index (BMI) < 27 kg/m²; **OR**
         v. For females, BCM < 23% and BMI < 27 kg/m²; **OR**
         vi. BMI < 18 kg/m²; **AND**
         vii. Weight loss is *not* attributable to other causes; **OR**
   E. Member has a diagnosis of Turner Syndrome

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

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

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

Supporting Evidence

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

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

III. Oxandrolone is FDA-approved as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite pathophysiological reasons, fail to gain or maintain normal weight. It is also indicated to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of bone pain that may accompany osteoporosis.
• Current osteoporosis guidelines do not make recommendations regarding use of oxandrolone for osteoporosis related pain.

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

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

VI. Anabolic steroids, such as oxandrolone may be used as an adjunct to growth hormone (GH) in patients with Turner Syndrome. It is well established that GH therapy is effective in increasing final adult height. For those less than nine years of age, growth-promoting therapy is generally initiated with GH alone. However, in older patients, or those with extreme short stature, consideration can be given to adding an agent such as oxandrolone.
• Therapy should be continued until a satisfactory height has been attained or until little growth potential remains (e.g. bone age ≥ 14 years and growth velocity < 2 cm/year)

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

Investigational or Not Medically Necessary Uses

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

References

1. Oxandrin prescribing information. Savient Pharma, Inc. June 2005
3. Olson, TS. Management and prognosis of Fanconi anemia. In: UpToDate, Mahoney, DH (Ed), UpToDate, Waltham, MA, 2019
4. Bruera, E. Assessment and management of anorexia and cachexia in palliative care. In: UpToDate, Smith, TJ (Ed), UpToDate, Waltham, MA, 2019
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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Washington State Rx Services is administered by moda HEALTH

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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP087

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

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

Quantity limits

<table>
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<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<td>10 mg/mL Subcutaneous</td>
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Initial Evaluation

I. Apomorphine (Apokyn) may be considered medically necessary when the following criteria below are met:
   A. Member must 18 years of age or older; **AND**
   B. Must be prescribed by or in consultation with a neurologist; **AND**
   C. Not used in combination with a 5-HT₃ receptor antagonist (e.g. ondansetron, granisetron, dolasetron, etc.); **AND**
   D. A diagnosis of **Parkinson’s disease** when the following are met:
      1. Provider must attest that the first dose will be done in office and the member will be monitored; **AND**
      2. Treatment with 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**
         iii. One of the following:
            a. Dopamine agonist (e.g. pramipexole, ropinirole, rotigotine)
            b. Monoamine oxidase-B (MAO-B) inhibitor (e.g. selegiline, rasagiline)
            c. 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:

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October 01, 2020
A. Erectile dysfunction

**Renewal Evaluation**

I. Member has demonstrated benefit through reduction of “off” episodes/hypomobility; **AND**
II. Absence of unacceptable toxicity (e.g. coronary events, QTc prolongation, serious hypotension, etc.)

**Supporting Evidence**

I. Apomorphine (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. Use of apomorphine (Apokyn) 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.

**Investigational or Not Medically Necessary Uses**

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

**References**

Policy Implementation/Update:

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

Pharmacy Coverage Policy: UMP006

Description
Asfotase alfa 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

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<th>Indication</th>
<th>Quantity Limit</th>
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<td>asfotase alfa (Strensiq)</td>
<td>18mg/0.45mL vial</td>
<td>infantile, pediatric, or juvenile onset hypophosphatasia</td>
<td>24 vials/28 days</td>
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<td>190485</td>
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<td>40mg/1 mL vial</td>
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<td>24 vials/28 days</td>
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<td>80mg/0.8 mL vial</td>
<td></td>
<td>24 vials/28 days</td>
<td>190488</td>
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</table>

*See appendix A for dose recommendations

Initial Evaluation

I. Asfotase alfa (Strensiq) may be considered medically necessary when the following criteria below are met:
   A. Diagnosis is made by or in consultation with a geneticist, metabolic specialist, endocrinologist, or bone and mineral specialist; **AND**
   B. A diagnosis of **perinatal/infantile-onset and juvenile-onset hypophosphatasia (HPP)** when the following are met:
      1. Documented tissue-non-specified alkaline phosphatase (TNSALP) gene mutation status; **OR**
      2. Documented serum alkaline phosphatase (ALP) level below the age and gender-adjusted normal range; **AND**
         i. Elevated TNSALP substrate levels as determined by age and gender specific reference range:
            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 12, as may be documented by the signs and/or symptoms, which may include, but are not limited to the following:
         i. Respiratory insufficiency, vitamin B6 responsive seizures, hypotonia, failure to thrive, delayed walking, waddling gate, dental abnormalities, low-trauma fracture; **OR**
ii. Radiographic evidence supporting the diagnosis of HPP prior to the age of
12 (e.g. craniosynostosis, infantile rickets, non-traumatic fracture); **AND**

4. One of the following
i. Baseline ophthalmologic examination and renal ultrasound; **OR**
ii. Provider attestation member will be monitored for ectopic calcification

II. A fostase alfa (Strensiq) is considered **not medically necessary** when criteria above are not met
and/or when used for:

A. Adult-onset HPP
B. Odontohypophosphatasia
C. Pseudohypophosphatasia
D. Other forms or causes of osteomalacia: X-linked hypophosphatemia, low bone mass,
inappropriate treatment with bisphosphonates, osteoporosis

**Renewal Evaluation**

II. Renewal of a fostase 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:
      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 12,
as may be documented by the signs and/or symptoms, which may include, but
are not limited to the following:
   i. Respiratory insufficiency, vitamin B6 responsive seizures, hypotonia, failure
to thrive, delayed walking, waddling gate, dental abnormalities, low-
trauma fracture; **OR**
   ii. Radiographic evidence supporting the diagnosis of HPP prior to the age of
12 (e.g. craniosynostosis, infantile rickets, non-traumatic fracture); **AND**
4. One of the following:
   i. Documentation of recent ophthalmologic examination and renal
ultrasound, in addition to baseline; **OR**
   ii. Provider attests to the continuance of monitoring for ectopic calcifications.

**AND**
C. The documentation of a positive response to therapy with asfotase alfa, which may include the improvement and/or stabilization (upon subsequent renewals) in the clinical signs and symptoms of hypophosphatasia.

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. Associated with a high mortality rate, survival rate has been 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-gate is considered a surrogate marker and is not interpreted as an improvement in clinical outcome. Radiographic analysis showed improvement in all subjects with treatment however, using change in rickets severity and assess 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 is unknown in the adult population.
- The presence of a defective TNSALP allele without sign or symptoms of dental or arthritic complications determines helps determine the patient is a carrier only.
- Ectopic calcification has been reported. Per label, monitoring for ectopic calcification by means of opthalmic examination and renal ultrasound is recommended at baseline and periodically during treatment.

Investigational or Not Medically Necessary Uses

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October 01, 2020
I. Adult-onset HPP
   A. Asfotase alfa (Strensiq) is FDA-indicated for the treatment of members with perinatal/infantile- and juvenile-onset HPP; these populations are known to have the most severe disease and the benefit of enzyme replacement therapy is supported by data.
   B. There are limited to no research studies to support the efficacy of asfotase alfa (Strensiq) in the setting of adult-onset HPP without history of infantile and/or juvenile onset HPP. Evidence is currently limited to case-reports only.
   C. Adult-onset HPP treatment is currently limited to supportive therapy.

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

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

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

Appendix A:

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

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Dose to Inject</th>
<th>Volume to Inject</th>
<th>Vial Configuration</th>
<th>Number of Vials per 28 days</th>
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</thead>
<tbody>
<tr>
<td>3</td>
<td>6 mg</td>
<td>0.15 mL</td>
<td>18mg/0.45mL</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>8 mg</td>
<td>0.2 mL</td>
<td>18mg/0.45mL</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>10 mg</td>
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<td>18mg/0.45mL</td>
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</tr>
<tr>
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<tr>
<td>10</td>
<td>20 mg</td>
<td>0.5 mL</td>
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<td>40mg/mL</td>
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Weight-Based Dosing for Administration of 1 mg/kg six times per week

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October 01, 2020
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<table>
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<tr>
<th>Body Weight (kg)</th>
<th>Dose to Inject (mg)</th>
<th>Volume to Inject (mL)</th>
<th>Vial Configuration (mg/mL)</th>
<th>Number of Vials per 28 Days</th>
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Action and Summary of Changes

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

Date: 09/2019
and 6 month renewal. As the overall benefit of Strensiq is seen over the course of pediatric development, a longer renewal period was implemented.
Avapritinib (Ayvakit™)
Policy Type: PA/SP
Pharmacy Coverage Policy: UMP181

Split Fill Management*

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

Length of Authorization
- N/A

Quantity Limits

<table>
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<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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Initial Evaluation
I. Avapritinib (Ayvakit) is considered investigational when used for all conditions, including but not limited to gastrointestinal stromal tumor (GIST).

Renewal Evaluation
I. N/A

Supporting Evidence
I. The National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology guidelines state most PDGFRα mutations respond to imatinib (Gleevec), with the exception of PDGFRα 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 PDGFRα 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 PDGFRα mutated, and 10%-15% do not express KIT or PDGFRα. PDGFRα D842V mutants make up 60% of all PDGFRα 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 PDGFRα mutations.

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October 01, 2020
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


Policy Implementation/Update:

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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
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<td>05/2020</td>
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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:
  - Avatrombopag (Doptelet), eltrombopag (Promacta) and fostamatinib (Tavalisse)
    - Chronic Immune Thrombocytopenia (ITP), refractory severe aplastic anemia, chronic thrombocytopenia due to chronic hepatitis C: six months
### Quantity Limits

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<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<tr>
<td>avatrombopag (Doptelet)</td>
<td>20 mg tablet</td>
<td>Thrombocytopenia associated with chronic liver disease, prior to planned procedure</td>
<td>15 tablets/30 days</td>
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<td>eltrombopag (Promacta)</td>
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<td>lusutrombopag (Mulpleta)</td>
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<td>Thrombocytopenia associated with chronic liver disease, prior to planned procedure</td>
<td>7 tablets/365 days</td>
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<td>fostamatinib (Tavalisse)</td>
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**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 [e.g. pegylated interferon (Pegasys®) and ribavirin]; **AND**  
         b. Request is for *eltrombopag (Promacta)* tablet formulation; **OR**  
         c. Request is for *eltrombopag (Promacta)* packets; **AND**  
            1. Member is unable to swallow tablets; **OR**  
   2. **Chronic Immune Thrombocytopenia;** **AND**  
      i. Treatment with first-line therapies (e.g corticosteroids, immunoglobulins, or splenectomy) have been ineffective, contraindicated, or not tolerated;  
         **AND**  
      ii. Documentation of platelet count that is less than 30 x 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 antithymocyte globulin (ATG) and cyclosporine A (CSA) has been ineffective, contraindicated or not tolerated; AND
   iv. Request is for eltrombopag (Promacta) tablet formulation; OR
   v. Request is for eltrombopag (Promacta) packets; AND
      a. Member is unable to swallow tablets

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

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

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

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

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

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

III. Member has exhibited improvement or stability of disease symptoms; AND
   A. Chronic thrombocytopenia due to chronic Hepatitis C; AND
      1. Member is unable to initiate or maintain interferon-based treatment [e.g. pegylated interferon (Pegasys®) and ribavirin]; OR
   B. Chronic Immune Thrombocytopenia; AND
      1. Platelet count has increased to greater than or equal to 50 x 10^9/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
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

V. 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.

   o 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 x 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 x 10^3/μL as at least a 100% increase in ANC, or an ANC increase >0.5 x 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
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.

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 37 participants.

2. Fostamatinib had limited anti-tumor activity in this first clinical trial in patients with advanced refractory solid tumors; reduction in CECs and CEPs was indicative of anti-angiogenic effects. Abnormal liver testing at baseline appeared to influence drug tolerability.

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

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

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

E. T-cell lymphoma
   i. Phase II, multicenter, open label, single assessment group, simon two-stage study of fostamatinib disodium in patients with relapsed or refractory T-cell lymphoma in 18 participants. The clinical trial was not blinded or randomized. It wasn’t powered enough to show efficacy or safety of fostamatinib (Tavalisse) in T-cell lymphoma.

F. Rheumatoid arthritis (RA)
   i. A Long-term, open label, single assignment study to assess the safety of fostamatinib in the treatment of rheumatoid arthritis in Asia was terminated.
      o Adult patients were randomized (1:1:1) to fostamatinib [100 mg bid for 24 weeks (n=105; Group A)], or 100 mg bid for 4 weeks, then 150 mg qd (n=108; Group B), or to placebo (n=110; Group C) for 24 weeks. Nonresponders at Week 12 could enter a long-term extension study. The primary endpoint was the proportion of patients achieving an American College of Rheumatology 20% (ACR20) response at Week 24.
      o Due to efficacy and safety results from the clinical trial, the companies developing fostamatinib have decided not to study it further in RA at this time.

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

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

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

References

15. Dan Xu, Nanfang Hospital of Southern Medical University. Eltrombopag Used in Thrombocytopenia after Consolidation Therapy in AML. ClinicalTrials.gov Identifier: NCT03701217


19. Zhang Lei, Institute of Hematology & Blood Diseases Hospital. Evaluate the Efficacy and Safety of Eltrombopag for Thrombocytopenia With Chronic HBV Infection. ClinicalTrials.gov Identifier: NCT03664518


24. AstraZeneca. Study to Learn if 200mg Test Drug (Fostamatinib) Helps People With Large B-Cell Lymphoma, a Type of Blood Cancer. ClinicalTrials.gov Identifier: NCT01499303

25. Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Clinical Trial of Combined Fostamatinib and Paclitaxel in Ovarian Cancer. ClinicalTrials.gov Identifier: NCT03246074


27. AstraZeneca. A Long Term Study to Assess the Safety of Fostamatinib in Patients in Asia With Rheumatoid Arthritis (OSKIRA-Asia-1X). ClinicalTrials.gov Identifier: NCT01640054


29. Imperial College London. Fostamatinib in the Treatment of Chronic Active Antibody Mediated Rejection (FOSTAMR). ClinicalTrials.gov Identifier: NCT03991780

30. Stefanie Sarantopoulos, MD, PhD. Evaluation of Fostamatinib in Patients With cGVHD After Allogeneic Stem Cell Transplant. ClinicalTrials.gov Identifier: NCT02611063

Policy Implementation/Update:

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

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

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
</thead>
<tbody>
<tr>
<td>axitinib (Inlyta)</td>
<td>1 mg tablets</td>
<td>Advance renal cell carcinoma</td>
<td>180 tablets/30 days</td>
<td>171511</td>
</tr>
<tr>
<td></td>
<td>5 mg tablets</td>
<td></td>
<td>60 tablets/30 days</td>
<td>171512</td>
</tr>
</tbody>
</table>

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:

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October 01, 2020
A. Non-metastatic Stage I-III Renal Cell Carcinoma

Renewal Evaluation

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

Supporting Evidence

I. Axitinib (Inlyta) is indicated for advance renal cell carcinoma (RCC) after failure of one prior systemic therapy; or as first-line therapy when used in combination with pembrolizumab (Keytuda); or as first-line therapy when used in combination with avelumab (Bavencio).

II. The FDA approval of axitinib (Inlyta) in the setting of advanced RCC after failure of one prior systemic therapy was based on the results of a phase 3 trial (AXIS). In the AXIS trial, the primary end point was progression free survival in the intention-to-treat population. The median PFS was 6.7 months with axitinib compared to 4.7 months with sorafenib (hazard ratio 0.665; 95% CI 0.544-0.812; one-sided p<0.0001).
   - Note: Sunitinib (Sutent) is considered the first systemic agent to use for adjuvant treatment for all stages of RCC after primary treatment (surgical).

III. The FDA approval of pembrolizumab (Keytruda) in combination with axitinib (Inlyta) was based on the results of KEYNOTE-426, an open-label, phase 3 trial. In the KEYNOTE-426 trial, the primary end points were overall survival and progression-free survival in the intention-to-treat population. Statistical significance as achieved after a median follow-up of 12.8 months, the estimated percentage of untreated advanced RCC patients who were alive at 12 months was 89.9% in the pembrolizumab-axitinib group compared to 78.3% in the sunitinib group.
   - Note: Sunitinib (Sutent) is considered the first systemic agent to use for adjuvant treatment for all stages of RCC after primary treatment (surgical).

IV. The FDA approval of avelumab (Bavencio) in combination with axitinib (Inlyta) was based on positive results from the Phase III JAVELIN Renal 101 study, involving previously untreated advanced RCC patients. In the JAVELIN Renal 101 study, the median progression-free survival was 13.8 months with avelumab plus axitinib, as compared with 7.2 months with sunitinib.
   - Note: Sunitinib (Sutent) is considered the first systemic agent to use for adjuvant treatment for all stages of RCC after primary treatment (surgical).

Investigational or Not Medically Necessary Uses

I. Non-metastatic Stage I-III Renal Cell Carcinoma
   A. Axitinib (Inlyta) has not been studied in non-metastatic, non-advanced (stage I-III) renal cell carcinoma.
*The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>July 2012</th>
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<tbody>
<tr>
<td>Date Effective</td>
<td>April 2016</td>
</tr>
<tr>
<td>Last Updated</td>
<td>June 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>03/2016, 06/2019</td>
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</table>

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>06/2019</td>
</tr>
</tbody>
</table>
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

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

* total of 7 fills in one year

Initial Evaluation
I. Aztreonam (Cayston) may be considered medically necessary when the following criteria are met:
   A. Prescribed by, or in consultation with, a pulmonologist; AND
   B. Member is 7 years of age or older; AND
   C. A diagnosis of cystic fibrosis with Pseudomonas aeruginosa when the following are met:
      1. Member has FEV₁ of 25% to 75% predicted; AND
      2. Member is not colonized with Burkholderia cepacia

Renewal Evaluation
I. Member has received a previous prior authorization approval for this agent through this health plan; AND
II. Member is not continuing therapy based on being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND
III. Member has exhibited improvement or stability of disease symptoms (e.g., reduction of cough/wheezing, reduction in sputum production, improvement in FEV₁, decrease in pulmonary exacerbations)

Supporting Evidence
I. Aztreonam (Cayston) was studied in a randomized, double-blind, placebo-controlled, multicenter trial that enrolled 164 patients who were seven years of age or older with cystic fibrosis (CF) and pseudomonas aeruginosa (P. aeruginosa) colonization for a period of 28 days.
The treatment difference at Day 28 between the patients in the aztreonam (Cayston) arm and placebo arm were 10% (95% CI: 6%, 14%), the 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria added: Member is not colonized with Burkholderia cepacia</td>
<td>06/2020</td>
</tr>
<tr>
<td>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.</td>
<td>10/2019</td>
</tr>
<tr>
<td>Criteria update: quantity limit has been updated to reflect the clinical use of Cayston.</td>
<td>2/2019</td>
</tr>
<tr>
<td>Created and effective</td>
<td>07/2011</td>
</tr>
</tbody>
</table>
Belimumab (Benlysta®)

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>belimumab</td>
<td>200 mg/mL syringe</td>
<td>Systemic Lupus Erythematosus (SLE)</td>
<td>4 syringes/28 days</td>
</tr>
</tbody>
</table>

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; AND
   C. Not used in combination with other biologic(s) or intravenous cyclophosphamide; AND
   D. A diagnosis of Systemic Lupus Erythematosus (SLE) when the following are met:
      1. A confirmed positive autoantibody test [antinuclear (ANA) and/or anti-double-stranded DNA (anti-ds-DNA)]; AND
      2. A SLE Disease Activity Index (SELENA-SLEDAI) score of ≥ 8 supported by documentation in chart notes; AND
      3. Documentation of baseline Physician’s Global Assessment (PGA) score; AND
      4. Treatment with one standard therapy agent from each category, has been ineffective, contraindicated, or ALL are not tolerated:
         i. Antimalarials (e.g., chlorquine, hydroxychloroquine)
         ii. NSAIDs (e.g., ibuprofen, naproxen)
         iii. Immunosuppressive (e.g., azathioprine, mycophenolate mofetil, methotrexate); AND
      5. Member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated.

II. Belimumab (Benlysta) is considered investigational when used for all other conditions, including but not limited to:
A. Severe active lupus nephritis
B. 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. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in SELENA-SLEDAI score or PGA score); AND
IV. Not used in combination with other biologic(s) or intravenous cyclophosphamide; AND
V. Member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated.

Supporting Evidence

I. The safety and efficacy of belimumab (Benlysta) in the setting of pediatric population was only studied with 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).
III. Per label, the use of belimumab (Benlysta) in combination with other biologics or intravenous cyclophosphamide 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.

Investigational or Not Medically Necessary Uses

I. Severe active lupus nephritis and severe active central nervous system lupus
A. Per label, the use of belimumab (Benlysta) in the setting of severe active lupus nephritis or 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 those instances.

References


Policy Implementation/Update:

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

Action and Summary of Changes

| 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 |

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Policy Type: PA

Pharmacy Coverage Policy: UMP182

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

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

Quantity Limits

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

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); 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
         i. The member has a history of statin intolerance defined as failure of TWO statin medications due to at least ONE of the following:
            a. CK exceeds 10 times the upper limit of normal

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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

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

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

Washington State Rx Services is administered by moda HEALTH

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

October 01, 2020
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 the 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy created</td>
<td>05/2020</td>
</tr>
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</table>
Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP174

Description
Benralizumab (Fasenra Pen) is a subcutaneously administered monoclonal antibody (IgG1, kappa) that antagonizes IL-5 signaling for the indication of severe eosinophilic asthma (SEA).

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

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>benralizumab (Fasenra)</td>
<td>30 mg/mL autoinjector</td>
<td>Severe eosinophilic asthma</td>
<td>Loading: 1 autoinjector/28 days for 3 doses;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 1 autoinjector/56 days</td>
</tr>
</tbody>
</table>
| Provider Administered Agents*
| benralizumab (Fasenra)| 30 mg/mL Syringe | Severe eosinophilic asthma       | Loading: 1 autoinjector/28 days for 3 doses;         |
|                       |             |                                   | Maintenance: 1 autoinjector/56 days                   |

*Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit.

Initial Evaluation
I. Benralizumab (Fasenra Pen) may be considered medically necessary when the following criteria below are met:
A. Must not be used in combination with another monoclonal antibody (e.g., mepolizumab, omalizumab, reslizumab, etc.); AND
B. A diagnosis of Severe Eosinophilic Asthma (SEA); AND
   1. Member is 12 years of age or older; AND
   2. The member has severe asthma as defined by any one of the following:
      i. Symptoms throughout the day
      ii. Nighttime awakenings, often 7 times per week
      iii. Short-acting beta agonist (SABA) 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 more frequent and intense relative to moderate asthma; **AND**

3. The member must have asthma with an eosinophilic phenotype defined as blood eosinophils ≥150 cells/μL within 6 weeks of dosing; **AND**

4. Must be used for add-on maintenance treatment in members **regularly** receiving **BOTH** of the following:
   i. Medium to high-dose inhaled corticosteroids; **AND**
   ii. An additional controller medication (e.g., long-acting beta agonist, etc.); **AND**

5. Members 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 above).

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

**Renewal Evaluation**

I. Member has received a previous prior authorization approval for this agent through this health plan; **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 in asthma symptoms or asthma exacerbations as evidenced by decrease in **one** or more of the following:
   A. Use of systemic corticosteroids  
   B. Two-fold or greater decrease in inhaled corticosteroid use for at least 3 days  
   C. Hospitalizations  
   D. Emergency department (ED) visits  
   E. Unscheduled visits to healthcare provider; **OR**

IV. Member has exhibited improvement from baseline in forced expiratory volume in 1 second (FEV₁)

**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 was evaluated in one 52-week dose ranging exacerbation trial; and three confirmatory randomized, double-blind trials, and one 12-week lung function trial.

- 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.
- 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 (Fascenra) 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).
- The third confirmatory trial was 28 weeks in duration and evaluated the effects of benralizumab (Fascenra) 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 (Fascenra) arm was 75% compared to 25% in placebo (95% CI: 60, 88).
- The 12-week lung function trial measured lung function by the change from baseline FEV₁ at week 12. The benralizumab (Fascenra) arm showed an increase of 0.057 liters compared to -0.016 liters in placebo (p=0.040)

Investigational or Not Medically Necessary Uses

I. Benralizumab (Fasenra) would be considered investigational when used for any of the following indications due to lack of studies:
   A. Non-severe, non-eosinophilic phenotype asthma
   B. Atopic dermatitis
   C. Eosinophilic gastritis
   D. Exercise-induced asthma
   E. Hypereosinophilic syndrome

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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>New policy</td>
<td>02/2020</td>
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</table>
betaine anhydrous (Cystadane®)

UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP113

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

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

Quantity limits

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

Initial Evaluation

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

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

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

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

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

III. Member has exhibited improvement or stability of disease symptoms

Supporting Evidence

I. Betaine anhydrous (Cystadane) is indicated in pediatric and adult patients for the treatment of homocystinuria, and is used to decrease elevated homocysteine blood concentrations. Homocystinuria results from deficiencies or defects in cystathionine beta-synthase (CBS), 5,10-methylenetetrahydrofolate reductase (MTHFR), and/or cobalamin cofactor metabolism (CBL).

II. Homocystinuria is a rare autosomal recessive disorder characterized by severe elevations in plasma and urine homocysteine concentrations. It may result from a deficiency of several enzymes involved in the conversion of methionine to cysteine or, less commonly, it is due to impaired conversion of the compound homocysteine to methionine. There are multiple forms of homocystinuria, which are distinguished by their signs, symptoms, and genetic cause. Clinical manifestations of homocystinuria includes developmental delay, Marfanoid appearance, osteoporosis, ocular abnormalities, thromboembolic disease, and severe premature atherosclerosis. The signs and symptoms of homocystinuria usually develop within the first year of life; although, the mildly-affected may not develop features until later in childhood or adulthood.

III. Guidelines for CBS deficiency state:
   - Betaine should be considered as adjunct treatment in patients who cannot achieve target levels of homocysteine by other means. Betaine treatment alone seldom achieves target homocysteine levels in those with a pyridoxine-unresponsive CBS deficiency. It is best used as adjunct treatment in patients who are partially responsive to pyridoxine, or, who are on dietary treatment but cannot achieve adequate control.
   - Patient response to betaine can vary, and, optimal doses require individualization. Standard initial dosing for children is 50 mg/kg twice daily; meanwhile, adults start at three grams two times a day. The dose and frequency are adjusted to the response of treatment with an added note that exceeding a dose of 150-200 mg/kg/day is unlikely to result in any additional benefit.

IV. Guidelines for MTHFR deficiency state:
   - Early identification and treatment with betaine for MTHFR deficiency is strongly recommended. Pre-symptomatic betaine treatment prevents severe neurological impairment with a high quality of evidence.
Investigational or Not Medically Necessary Uses

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

References


Policy Implementation/Update:

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

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

Policy Type: PA

Pharmacy Coverage Policy: UMP114

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

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

Quantity Limits

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

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

Renewal Evaluation

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

Supporting Evidence

I. Betrixaban (Bevyxxa) is FDA-approved only for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
II. There is currently no evidence to demonstrate the use of betrixaban (Bevyxxa) beyond 42 days. Total duration of use listed by the provider should be evaluated to ensure this limit is not exceeded. However, if a member is re-hospitalized, clinician should review as a new course of therapy.
III. The recommended duration of treatment is 35 to 42 days.
IV. Though extended duration (42 days) of betrixaban (Bevyxxa) is associated with significantly less VTEs compared to standard duration (14 days) enoxaparin, it has higher non-major bleeding risk in comparison to enoxaparin for VTE prophylaxis. Therefore, if betrixaban (Bevyxxa) was not initiated in the hospital, it may be more beneficial to utilize enoxaparin over betrixaban (Bevyxxa) unless patient has a very low bleeding potential.
V. Patients who are actively bleeding or are at risk for bleeding should not start betrixaban (Bevyxxa); there is currently no reversal (antidote) for betrixaban (Bevyxxa).

Investigational or Not Medically Necessary Uses

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

References

Policy Implementation/Update:

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

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

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

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

Initial Evaluation

I. Bexarotene (Targretin) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an oncologist; **AND**
   C. Bexarotene (Targretin) will **not** be used in combination with mechlorethamine (Valchlor); **AND**
   D. If the member is a woman of child-bearing potential, the prescriber attests the member has had a negative pregnancy test prior to starting therapy; **AND**
   E. A diagnosis of **primary cutaneous T-cell lymphoma** (e.g., mycosis fungoides, Sezary Syndrome) when the following are met:
      1. For the request of **bexarotene capsules or liquid capsules**;
         i. The member is relapsed and/or refractory to one prior systemic therapy (e.g., oral retinoids, interferon, methotrexate, cyclophosphamide, chemotherapy); **AND**
         ii. The request is for **generic** bexarotene capsules or liquid capsules, unless generic bexarotene has been ineffective or contraindicated; **AND**
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 seen after eight weeks of therapy. Tumor response was assessed by observation using Composite Assessment of Index Lesion Disease Severity. The endpoint was based on a summation of the grades, erythema, scaling, plaque elevation, hypo or hyperpigmentation and area of involvement. Presence or absence of cutaneous tumors and extra cutaneous manifestations was considered in the response assessment. Tumor responses required confirmation over at least two assessments separated by at least four weeks and partial response was defined as improvement of at least 50% in the index lesions without worsening or development of new cutaneous tumors or non-cutaneous manifestations. At the initial dose of 300 mg/m²/day, one subject had complete clinical tumor response, and 30% (19/62) had partial response. Median duration of tumor response had not been reached by the end of the study. Responses may be seen as early as four weeks. Due to the single-arm, open-label trial design, results should be interpreted with caution.

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

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

V. The cost of one 60-gram tube of topical bexarotene (Targretin) is approximately $30,500; therefore, a quantity limit of one tube per 30-day supply is in place to ensure appropriate use without waste. Should a quantity exception be requested, clinical consideration will be taken to the amount of body surface area the medication is being applied, rate of application, and amount utilized with administration.
Investigational or Not Medically Necessary Uses

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

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

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
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<td>October 2008</td>
</tr>
<tr>
<td>Last Updated</td>
<td>November 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>07/2012, 09/2012, 12/2012, 11/2019</td>
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</tr>
</thead>
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<tr>
<td>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.</td>
<td>11/2019</td>
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Washington State Rx Services is administered by Moda Health

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

October 01, 2020
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP116

Split Fill Management*

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

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

Quantity Limits

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

Initial Evaluation

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

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

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

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

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

III. The medication is prescribed by, or in consultation with, an oncologist; AND

IV. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); AND

V. Documentation of response to treatment, defined by the stabilization of disease or a decrease in tumor size or tumor spread.

Supporting Evidence

I. Bosutinib (Bosulif) is indicated for the treatment of adult patients with chronic, accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy OR newly diagnosed chronic phase Ph+ CML.

II. Prior therapy may include, but is not limited to, one of the following: imatinib (Gleevec), dasatinib (Sprycel), and/or nilotinib (Tasigna).

III. All TKIs are all highly effective with no differences in overall survival between imatinib and the second generation TKI therapies bosutinib, dasatinib, or imatinib.

IV. Members with primary treatment resistance to imatinib can be treated with any second generation TKI therapy (bosutinib, dasatinib, or nilotinib), while giving consideration to BCR-ABL1 mutation status. The second-generation TKI therapies are active against many mutations resistant to imatinib.

V. Members with primary treatment resistance to bosutinib, dasatinib, or nilotinib may be treated with any alternate TKI other than imatinib and giving consideration for BCR-ABL Mutation status.

VI. Treatment recommendations from NCCN Guidelines - Version 02.2020 CML

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

VII. Intolerance is defined as progression while taking a TKI, and/or the inability to tolerate the current minimum recommended dose, or inability to dose-increase due to toxicity. Resistance and intolerance to both dasatinib (Sprycel) and nilotinib (Tasigna) are manifested similarly to that of imatinib (Gleevec).

VIII. Disease progression is defined as transformation to accelerated or blast phase, or loss of previously attained response. Treatment was continued until disease progression (transformation to accelerated or blast phase, or loss of previously attained response), unacceptable toxicity, or withdrawal of consent. Patients were removed from the study if they were unable to tolerate a bosutinib (Bosulif) dose of ≥ 300 mg/d.
Investigational or Not Medically Necessary Uses

I. There is limited to no evidence to support the use of bosutinib (Bosulif) in any other condition.

II. Glioblastoma
   
   A. Bosutinib (Bosulif) was evaluated in small phase 2 study in adults with recurrent glioblastoma, however the study met pre-specified criteria for early closure due to progression. Bosutinib (Bosulif) monotherapy does not appear to be effective in recurrent glioblastoma.

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

References


Policy Implementation/Update:

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<tr>
<td>Date Effective</td>
<td>February 2013</td>
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<tr>
<td>Last Updated</td>
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<td>Last Reviewed</td>
<td>01/2018, 12/2018</td>
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<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior authorization criteria transitioned to policy format. Updated requirement of prior therapy to state prior tyrosine kinase inhibitor rather than stating imatinib. Extended renewal duration from four months to 12 months. Required agent be used as monotherapy and not in combination with other oncologic medications.</td>
<td>12/2019</td>
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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP009

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

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

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEIBA, anti-inhibitor coagulant complex</td>
<td>500, 1000, 2500 units</td>
<td>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</td>
<td>Control and prevention of bleeding – Hemophilia A or B with inhibitors: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Routine prophylaxis – Hemophilia A or B with inhibitors: Up to 85 units/kg every other day</td>
<td>Routine prophylaxis – Hemophilia A or B with inhibitors: Up to 1,190 units/kg every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>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</td>
<td>Perioperative management – Hemophilia A or B with inhibitors: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td>NovoSeven RT, coagulation factor VIIa (recombinant)</td>
<td>1 mg/vial (1000 mcg/vial)</td>
<td>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</td>
<td>Control and prevention of bleeding – Hemophilia A or B with inhibitors: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td></td>
<td>2 mg/vial (2000 mcg/vial)</td>
<td>Control and prevention of bleeding episodes – Acquired hemophilia: Up to 90 mcg/kg every two to three hours until hemostasis is achieved</td>
<td>Control and prevention of bleeding episodes – Acquired hemophilia: Up to the number of doses requested every 28 days</td>
</tr>
</tbody>
</table>

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

October 01, 2020
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td></td>
<td>5 mg/vial (5000 mcg/vial)</td>
<td>Control and prevention of bleeding episodes – Factor VII deficiency: Up to 30 mcg/kg every four to six hours until hemostasis is achieved</td>
<td>Control and prevention of bleeding episodes – Factor VII deficiency: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td></td>
<td>8 mg/vial (8000 mcg/vial)</td>
<td>Control and prevention of bleeding episodes – Glanzmann’s Thrombasthenia: Up to 90 mcg/kg every two to six hours until hemostasis is achieved</td>
<td>Control and prevention of bleeding episodes – Glanzmann’s Thrombasthenia: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Routine prophylaxis – hemophilia A or B with inhibitors: 90 mcg/kg once daily</td>
<td>Routine prophylaxis – Hemophilia A or B with inhibitors: 2,520 mcg/kg per 28 days</td>
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<tr>
<td></td>
<td></td>
<td>Perioperative management – hemophilia A or B with inhibitors: Up to 90 mcg/kg immediately before surgery, repeat every two hours during surgery, then up to 90 mcg/kg every two hours after surgery for five days, then every four hours or by continuous infusion, via pump, at 50 mcg/kg/hr until healing occurs</td>
<td>Perioperative management – hemophilia A or B with inhibitors: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perioperative management – acquired hemophilia: Up to 90 mcg/kg immediately before surgery and every two to three hours for the duration of surgery and until hemostasis is achieved</td>
<td>Perioperative management – acquired hemophilia: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perioperative management – factor VII deficiency: Up to 30 mcg/kg immediately before surgery and every four to six hours for the duration of surgery and until hemostasis is achieved</td>
<td>Perioperative management – factor VII deficiency: Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perioperative management – Glanzmann’s Thrombasthenia: Up to 90 mcg/kg immediately before surgery and repeat every two hours for the duration of the procedure,</td>
<td>Perioperative management – Glanzmann’s Thrombasthenia: Up to the number of doses requested for 28 days</td>
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<tr>
<td>Product Name</td>
<td>Dosage Form</td>
<td>Indication/ FDA Labeled Dosing</td>
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<tr>
<td>Sevenfact, coagulation factor VIIa (recombinant) [eptacog beta]</td>
<td>1 mg/vial (1000 mcg/vial)</td>
<td>Treatment and control of bleeding – Hemophilia A or B with inhibitors: 75 mcg/kg repeated every 3 hours until hemostasis is achieved Or Initial dose of 225 mcg/kg. If hemostasis is not achieved within 9 hours, additional 75 mcg/kg doses may be administered every 3 hours as needed to achieve hemostasis</td>
<td>Treatment and control of bleeding – Hemophilia A or B with inhibitors: Up to the number of doses requested every 28 days</td>
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<td>5 mg/vial (5000 mcg/vial)</td>
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**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 emizumab-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)**

*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.*

October 01, 2020
I. **FEIBA** or **NovoSeven RT** may be considered medically necessary when the following criteria below are met:
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   B. A diagnosis of hemophilia B has been confirmed by blood coagulation testing; **AND**
   C. Clinical documentation confirming that the member has inhibitors to factor IX [i.e. high anti-IX titer (≥ 5 Bethesda units)]; **AND**
   D. Use is planned for one of the following indications:
      1. On-demand treatment and control of bleeding episodes; **OR**
      2. Perioperative management of bleeding; **OR**
      3. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
         i. Member has had more than one documented episode of spontaneous bleeding; **OR**
         ii. Member has had an inadequate response to Immune Tolerance Induction (ITI)

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

**Acquired Hemophilia**

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

**Congenital Factor VII Deficiency**

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

**Glanzmann’s Thrombasthenia**

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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.*

October 01, 2020
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


Policy Implementation/Update:

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

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

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

### 3. Hepatocellular (Liver) carcinoma

1. Disease is progressive and advanced stage or greater (stage III or IV); AND
2. Member has been previously treated with sorafenib (Nexavar); AND
3. Member has not received more than two previous systemic treatment for advanced or metastatic disease; AND
4. 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

1. Medication is used as monotherapy; AND
2. Medication is prescribed by or in consultation with an oncologist; AND
3. 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

1. 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;
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

References


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<td>Removed step therapy in RCC; Updated renewal language to assess response to therapy</td>
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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

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

Initial Evaluation

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

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

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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.

October 01, 2020
Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**

II. Member has received a previous prior authorization approval for this agent; **AND**

III. Medication is prescribed by, or in consultation with a nephrologist or endocrinologist; **AND**

IV. Member has a diagnosis of stage 3 (GFR 30-59 mL/min) or stage 4 (GFR 15-29 mL/min) chronic kidney disease (CKD); **AND**

V. Member has a diagnosis of secondary hyperparathyroidism (enlarged parathyroid glands due to excessive secretion of parathyroid hormone); **AND**

VI. Member is not on dialysis; **AND**

VII. Member has exhibited improvement or stability of disease symptoms defined by the following:
   A. Intact parathyroid hormone (PTH) remains above the treatment goal; **AND**
   B. Total 25-hydroxyvitamin D serum level is between < 100 ng/mL; **AND**
   C. Serum calcium < 9.8 mg/dL; **AND**
   D. Serum phosphorous < 5.5 mg/dL

Supporting Evidence

I. Calcifediol (Rayaldee) was studied in two identical multicenter, randomized, placebo-controlled, double-blind trials in 429 patients with secondary hyperparathyroidism with stage 3 or 4 CKD and serum concentration of 25-hydroxyvitamin D levels between 10 and 30 ng/mL.

II. The primary efficacy outcome was the reduction in plasma PTH from baseline when comparing calcifediol (Rayaldee) to placebo which were 33% versus 8% in trial one and 34% versus 7% in trial two by 26 weeks.

III. There is currently insufficient evidence to suggest that there is a difference between calcifediol ER (Rayaldee) from other vitamin D analogs.

IV. The treatment goal for intact PTH is patient dependent, and will be defined by the provider. In clinical trials the patient’s Rayaldee dose was increased to 60 mcg per day when the intact PTH level was greater than 70 pg/mL, the serum 25-hydroxyvitamin D level was less than 65 ng/mL, and the serum calcium level was less than 9.8 mg/dL.

V. Stages of CKD

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

Stage 1 or Stage 2 are not considered CKD in the absence of kidney damage.
Investigational or Not Medically Necessary Uses

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

References


Policy Implementation/Update:

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<tr>
<td>Criteria was transitioned into policy format with the addition of renewal criteria, investigational section, and supporting evidence.</td>
<td>10/2019</td>
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Policy Type: PA  Pharmacy Coverage Policy: UMP011

Description
Cannabidiol (Epidiolex) is an orally administered FDA approve cannabinoid formulation for the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) or Dravet Syndrome in patients 2 years of age and older.

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

Quantity limits

<table>
<thead>
<tr>
<th>cannabidiol (Epidiolex)</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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<tr>
<td>100 mg/mL solution</td>
<td>Lennox-Gastaut Syndrome</td>
<td>420mL/30days</td>
<td>203391</td>
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<tr>
<td></td>
<td>Dravet Syndrome</td>
<td></td>
<td></td>
</tr>
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</table>

Initial Evaluation
I. Cannabidiol (Epidiolex) 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:
      1. Lennox-Gastaut Syndrome; **OR**
      2. Dravet Syndrome
   C. Refractory to two or more anticonvulsant medications

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

Renewal Evaluation
I. Documentation of treatment benefit with use of cannabidiol (Epidiolex) such as reduction in drop or convulsion seizures.

Supporting Evidence
I. Cannabidiol (Epidiolex) was studied in 3 phase III, double blind, randomized placebo-controlled clinical trial in patients with baseline characteristics of history of use of two or more anticonvulsant drugs.

Investigational or Not Medically Necessary Uses

I. Tuberous Sclerosis Complex
   A. Ongoing clinical trials in this setting

II. Infantile Spasms
    A. Ongoing clinical trials in this setting

III. Other non-FDA approve seizure disorder
     A. Ongoing clinical trials in this setting

IV. Substance use disorder
    A. Ongoing clinical trials in this setting

V. Prader-Willi Syndrome
   A. Ongoing clinical trials in this setting

VI. Gastrointestinal disorders
    A. Ongoing clinical trials in this setting

VII. Parkinsons Disease/Essential tremors
     A. Ongoing clinical trials in this setting

References


Policy Implementation/Update:

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

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

Pharmacy Coverage Policy: 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

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<tr>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>11mg vial</td>
<td>aTTP</td>
<td>30 vials/30 days</td>
<td>205773</td>
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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

   Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
c. High serum troponin levels

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

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

Renewal Evaluation

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

Supporting Evidence

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

   - Scoring
     i. Low risk category
        1. Score of 0-4
        2. 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

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

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Policy 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

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<tr>
<td>capmatinib (Tabrecta)</td>
<td>200 mg tablets</td>
<td>Metastatic Non-Small Cell Lung Cancer with a mutation that leads to MET exon 14 skipping</td>
<td>112 tablets/28 days</td>
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<td>150 mg tablets</td>
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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


Policy Implementation/Update:

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

Pharmacy Coverage Policy: UMP013

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

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

Quantity limits

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<th>Cenegermin-bkbi (Oxervate)</th>
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<th>DDID</th>
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<td>0.002% (20 mcg/mL) vial</td>
<td>Neurotrophic keratitis</td>
<td>56mL per lifetime</td>
<td>204913</td>
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Initial Evaluation

I. Cenegermin-bkbi (Oxervate) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by or in consultation with an ophthalmologist; AND
   B. A diagnosis of Neurotropic Keratitis; AND
   C. Documentation of cause not due to infective or autoimmune keratitis; AND
   D. Lack of active ocular infection (bacterial, viral, fungal, or protozoal); AND
   E. Lack of current severe blepharitis and/or severe meibomian gland disease; AND
   F. Stage 2 (persistent epithelial defect) or Stage 3 (corneal ulceration) disease; AND
   G. History of use of all of the following:
      1. Antibiotic drops in combination with preservative-free artificial tears; AND
      2. Topical collagenase inhibitor (e.g. N-acetylcysteine, tetracycline, medroxyprogesterone); AND
      3. Therapeutic contact lens

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

Renewal Evaluation

I. Treatment beyond the initial eight week duration is considered experimental and investigational.

Supporting Evidence

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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.

October 01, 2020
I. Clinical trials was studied in two 8-week, phase II multi-center, randomized, double blind, placebo controlled clinical trials with specific inclusion and exclusion protocol to which policy aligns.

II. Standard of care therapies include history of use of antibiotic eye drops in combination with artificial tears, topical collagenase inhibitors and therapeutic contact lens.

III. Lack of studies to demonstrating efficacy beyond a single 8 weeks course of treatment.

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 demonstrating efficacy beyond a single eight weeks course of treatment.

References


Policy Implementation/Update:

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<th>January 2019</th>
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Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP089

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

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

Quantity limits

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

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

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

   **October 01, 2020**
e. Sterol 27-hydroxylase (CYP27A1) deficiency
f. Smith-Lemli-Opitz; AND

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

2. Peroxisomal Disorders (PD); AND
   i. Member has ONE of the following peroxisomal disorders:
      a. Neonatal Adrenoleukodystrophy
      b. Generalized Peroxisomal Disorder
      c. Refsum Disease
      d. Zellweger Syndrome
      e. Peroxisomal Disorder, Type Unknown; AND
   ii. Member exhibits manifestation of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption; AND
   iii. Member will be using cholic acid (Cholbam) as adjunctive treatment

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

Renewal Evaluation

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

Supporting Evidence

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

II. For the indication of preoxisomal disorders (PDs) cholic acid (Cholbam) was studied in two clinical trials. Trial 1 was an open-label, single-arm trial in 29 patients followed over an 18 year period; while trial 2 was an extension trial with 12 patients enrolled. Response to cholic acid (Cholbam) treatment was assessed with the following end points: ALT or AST values reduced to less than 50 U/L or baseline levels reduced by 80%, total bilirubin values reduced to less than or equal to 1 mg/dL, no evidence of cholestasis on liver biopsy, body weight increased by 10% or...
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 has not yet been evaluated.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>April 2015</th>
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<tbody>
<tr>
<td>Date Effective</td>
<td>April 2015</td>
</tr>
<tr>
<td>Last Updated</td>
<td></td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>10/2019</td>
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</table>

Action and Summary of Changes

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.

<table>
<thead>
<tr>
<th>Date</th>
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<tr>
<td>10/2019</td>
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</table>
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP014

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

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

Medications Included in this Policy

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

**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 anti-rheumatic 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:

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) or tocilizumab (Actemra)** may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A)-I(C) above are met; **AND**
   B. Treatment with adalimumab (Humira) 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.

References


Systemic Juvenile Idiopathic Arthritis (SJIA)

Initial Evaluation

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

   A. Member is 2 years of age or older; **AND**

   B. Member is being managed by or in consultation with a rheumatologist; **AND**

   C. A diagnosis of **active SJIA** when the following are met:

      1. Treatment with at least one NSAID (e.g. ibuprofen, naproxen, indomethacin, meloxicam, celecoxib, etc.) or glucocorticoid (i.e. prednisone, hydrocortisone,
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

I. 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 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 in the tocilizumab trial 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. Based off expert opinion, however, 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 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 and tocilizumab sequentially, abatacept 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 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


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:


**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 patient 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:

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:

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 based on safety and efficacy data from randomized-controlled trials.
II. The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) published a joint guideline in 2019 on the use of biologic agents in plaque psoriasis. The
guidelines state that a majority of patients with mild-to-moderate disease (<10% BSA) are capable of controlling the disease solely with topical medications or phototherapy. The guideline provides a strong recommendation for use of TNF inhibitor monotherapy in patients with moderate to severe plaque psoriasis.

III. Non-TNF inhibitor biologics are also recommended as monotherapy in patients with moderate to severe plaque psoriasis according to the AAD/NPF guidelines. While specific recommendations for choice of treatment are not made, head-to-head studies have suggested IL-17 inhibitors may be more effective for some patients. For instance, the CLEAR study which compared secukinumab (Cosentyx) to ustekinumab (Stelara) found that at week 16 secukinumab (Cosentyx) patients were more likely to have achieved a Psoriasis Area and Severity Index (PASI) 90 response. Similar results have been demonstrated when compared to TNF inhibitors. For instance, in the FIXTURE study, secukinumab (Cosentyx) patients had a statistically significant superior 77.1% PASI 75 response rate compared to 44% with etanercept (Enbrel).

IV. At this time, the AAD/NPF states that there is insufficient data to make specific recommendations regarding switching from one biologic treatment to another. A number of studies have demonstrated response after switching from one TNF inhibitor to another. For instance, in the BELIEVE study, 61.7% of the 448 patients who had received prior TNF inhibitor treatment for plaque psoriasis demonstrated a PASI 75 response by week 16 after switching to adalimumab.

V. Risankizumab (Skyrizi) was evaluated in four Phase 3, randomized-controlled trials. The SELECT-clinical trials program. Various patient populations were evaluated, from treatment naïve to several (3+) biologic failures. Risankizumab (Skyrizi) showed superiority to methotrexate, other oral DMARDS, adalimumab (Humira), and ustekinumab (Stelara) in PASI 90, PASI 100, sPGA scores, and patient reported outcomes in all trials. The evidence was considered high quality due to the multiple RCTs, placebo and active controlled trials, statistically and clinically meaningful outcomes, and large magnitudes of effect.

VI. Ustekinumab (Stelara) was evaluated in pediatric populations 6 years or older, in a phase III, open-label, single arm trial as part of the CADMUS clinical trial program. The CADMUS JR clinical trial (N=44) evaluated efficacy and safety of weight-based dosing of ustekinumab (Stelara) in patients 6 to 12 years old with moderate to severe plaque psoriasis. Primary endpoint was proportion of patients achieving sPGA 0/1 at week 12. Significant secondary outcomes included improvement in PASI responses (PASI 75, PASI90), pharmacokinetics (PK), and biomarker analysis. At week 12, 77% subjects achieved a sPGA 0/1, with 84% and 64% reporting PASI75 and PASI90, respectively. Although this trial consisted of small population size and an open-label design, PK parameters and biomarker analysis (IL-17 and IL-22 serum levels) helped correlate the observed efficacy with the physiological effects of Stelara. Overall quality of evidence is considered low to moderate.

VII. In a phase III double-blind RCT (IXORA-PEDS), ixekizumab (Taltz) was compared with placebo for efficacy and safety in pediatric populations (N=171, age 6 to < 18 years). Primary endpoints were PASI response (PASI75) and sPGA 0/1 at week 12. Ixekizumab (Taltz) showed superiority to placebo at week 12 with PASI75 response in 89% and 25% of the patients in treatment arm and the placebo arm, respectively. At week 12, 81% (N= 93) patients on Taltz achieved a sPGA of 0 or 1 as compared to 9.8% to those in placebo arm. Due to a small sample size (N=2, 1.16%), clinical applicability of ixekizumab (Taltz) in patients with body weight < 25 kg is uncertain and the quality of evidence in this patient subset is considered low. Additionally, patients weighing <50 kg require administration of ixekizumab (Taltz) by a healthcare professional. Therefore,
coverage of Taltz for patients < 50 kg body weight should be considered under the members medical benefits.

References:


Crohn’s Disease

Initial Evaluation

1. **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:


Ulcerative Colitis

Initial Evaluation

I. **Adalimumab (Humira) or ustekinumab (Stelara)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Member is being managed by or in consultation with a gastroenterologist; **AND**
   C. A diagnosis of moderate to severe ulcerative colitis when the following are met:
      1. Previous treatment with at least one systemic corticosteroid (e.g. prednisone, hydrocortisone, methylprednisolone, etc.) has been ineffective to induce remission, contraindicated, or not tolerated; **AND**
      2. Previous treatment with at least one thiopurine (azathioprine or 6-mercaptopurine) over an eight week period to maintain remission has been ineffective, contraindicated, or not tolerated

II. **Golimumab (Simponi) and tofacitinib (Xeljanz/Xeljanz XR)** 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 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 ulcerative colitis based on safety and efficacy data from randomized-controlled trials.
II. The ACG published guidelines on the management of ulcerative colitis in adults recently in 2019. In patients with moderately to severely active disease to any extent, a strong recommendation is made for the use of oral systemic corticosteroids to induce disease remission. TNF inhibitors, vedolizumab, and tofacitinib also carry similar strong recommendations for induction of remission. For patients achieving remission, a conditional recommendation is made to use thiopurine therapy (and to avoid methotrexate therapy) to maintain remission. The guidelines note that a systematic review of 1,632 patients with UC that encompassed 30 studies demonstrated that azathioprine and mercaptopurine had a 76% mean efficacy in maintaining remission. For those patients initially using a biologic of tofacitinib to induce remission, guidelines support continuing with the same agent to maintain remission.
III. In two phase 3 double-blind RCTs (ULTRA-1 and ULTRA-2) comparing adalimumab to placebo in patients with moderately to severely active ulcerative colitis, patients were included if they were on a stable dose of systemic corticosteroids prior to baseline and/or underwent at least a 90 day course of thiopurine therapy prior to baseline. Based off this inclusion criteria, adalimumab is FDA approved in patients who had an inadequate response to corticosteroids and/or thiopurines.

References:

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

II. 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:


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:

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:


**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:

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:

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

IV. Graft Versus Host Disease (GVHD)
   A. A number of observational trials have examined etanercept in acute GVHD. Treatment regimens vary significantly between these observational studies. Data from a pilot and phase II trial pooled against observational data of standard of care patients receiving standard of care with steroids observed a higher complete response rate in those treated with etanercept. The results are significantly limited, however, by the observational, nonrandomized nature and thus prospective, randomized trials are needed to fully establish possible benefit in GVHD. The use of tocilizumab has also been studied in a small population (n = 8) with refractory GVHD. While response was observed in four of the six tocilizumab treated patients, the limited sample size is insufficient to confirm efficacy at this time.

V. Grave’s Ophthalmopathy
   A. A small, phase III RCT (n = 32) analyzed tocilizumab use compared to placebo in this disease state. A statistically significant reduction was observed in the clinical activity score from baseline by week 16, but given the small sample size, the American Academy of Ophthalmology has recommended that larger studies be completed to fully establish safety and efficacy for this indication.

VI. Guttate Psoriasis
   A. In this form of psoriasis, case reports suggest that the use of TNF inhibitors may induce flares when used. Typical treatment involves phototherapy and topical
corticosteroids/vitamin D analogs, with tonsillectomy or antibiotics used for more refractory disease. There is no established efficacy data for the use of biologics or targeted DMARDs in this setting at this time.

VII. Interstitial Cystitis
   A. TNF inhibitors such as adalimumab and certolizumab pegol have been studied in small, phase III RCTs. In the study of certolizumab pegol, no difference was observed in interstitial cystitis compared to placebo at week 2. Secondary outcomes indicate benefit may occur in this population by week 10-18 of therapy. A similar study was completed with adalimumab, with no statistical difference observed in the primary outcome at week 12 compared to placebo. Further studies are needed to analyze efficacy in this population.

VIII. Lupus Nephritis and Systemic Lupus Erythematosus (SLE)
   A. Abatacept was analyzed in a large phase III RCT (n = 695) in patients with lupus nephritis and in combination with mycophenolate and steroids. No difference was observed in the primary outcome of complete renal response at one year compared to placebo. Studies utilizing baricitinib and ustekinumab are currently recruiting in patients with SLE.

IX. Osteoarthritis
   A. Infliximab and adalimumab have been examined for use in patients with erosive, hand osteoarthritis. Mixed results have been seen so far. Open-label, observational studies of infliximab have shown potential benefit, while studies with adalimumab have been inconclusive. For instance, in a RCT of 60 patients, the difference in proportion of active disease in the adalimumab versus placebo group was not statistically significant. Further studies are needed to establish safety and efficacy.

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

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

XII. Polymyositis and Dermatomyositis
   A. One phase III trial is currently recruiting to analyze abatacept in patients with polymyositis and dermatomyositis. Anakinra has also been examined in a single group study (n = 15). Decrease in certain inflammatory markers was observed, however, the clinical and patient-centered outcomes of anakinra use in this population requires further analysis. Another single-group, non-randomized trial (n = 13) looked at infliximab use in this population.
population. None of the included patients had improvement in muscle strength by manual, and only two patients saw any improvement in disease activity scores.

XIII. Pulmonary Sarcoidosis
   A. The TNF inhibitors infliximab, adalimumab, and etanercept have been studied to some extent in pulmonary sarcoidosis. A phase II study (n = 138) saw a statistically significant increase in functional vital capacity at week 24 compared to placebo, however, the effect size was small with a mean increase of just 2.5% from baseline. A small, open-label phase II study with etanercept was terminated early due to an excessive number of treatment failures. Case reports of adalimumab exist, and one study which examined 18 patients who switched after infliximab use saw improvement in just over one-third of patients, however, further prospective, randomized trials would be needed to fully establish safety and efficacy.

XIV. Pyoderma gangrenosum
   A. Case reports of the use of TNF inhibitors are available in this patient population. Most reports have involved patients with another indication for a TNF inhibitor, such as IBD or RA. A Phase III trial for this disease state is currently recruiting in Japan.

XV. Sciatica
   A. One small RCT has examined adalimumab in patients with acute/severe radicular leg pain and imagine-confirmed lumbar 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 disectomies was also seen,

XVI. Systemic sclerosis (scleroderma)
   A. A phase III RCT (n = 212) comparing tocilizumab to placebo in patients with systemic sclerosis did not observe a statistically significant difference in change from baseline to week 48 in the primary outcome in the Modified Rodnan Skin Score (mRSS).

XVII. Sjogren’s Syndrome
   A. Studies with TNF inhibitors etanercept and infliximab have not demonstrated benefit in Sjogren’s syndrome. A RCT (n = 103) found no difference in disease activity between infliximab and placebo by week 22. Likewise, a smaller RCT (n = 28) found no statistical difference with etanercept versus placebo at 12 weeks after treatment initiation. Small, open-label studies have also been done with abatacept, though sample size has been small and data has been mixed, with one trial demonstrating improvement in salivary gland biopsy and extraglandular manifestations, and one showing no change in tear flow or improvement in other symptoms.

XVIII. Wegener’s Granulomatosis
   A. One phase III RCT (n = 181) exists for the use of etanercept in patients with Wegener’s Granulomatosis. Compared to standard of care (steroids plus cyclophosphamide or methotrexate), patient on etanercept demonstrated an initial sustained remission for at least six months that was not statistically different from standard of care. Likewise, a large proportion of patients lost response over the 27 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.
References:


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated PA policy to include FDA approvals for Stelara and Taltz for plaque psoriasis in pediatric population. Updated supporting information section for plaque psoriasis to include clinical trial data supporting use of Stelara and Taltz in pediatric patients</td>
<td>09/2020</td>
</tr>
<tr>
<td>Updated the products for psoriatic arthritis to include guselkumab (Tremfya). Updated the supporting evidence section for psoriatic arthritis to reflect no changes in the guidelines with regard to guselkumab (Tremfya). Updated non-radiographic axial spondyloarthritis (nr-axSpA) criteria to include secukinumab (Cosentyx) and ixekizumab (Taltz). Updated nr-axSpA supporting evidence section to include trial information regarding new addition of secukinumab (Cosentyx) and ixekizumab (Taltz), as well as updated ACR guidelines.</td>
<td>08/2020</td>
</tr>
<tr>
<td>Removed Behcet syndrome from the E/I section</td>
<td>02/2020</td>
</tr>
<tr>
<td>Updated preferred products to also include Cosentyx, Stelara, and Otezla within their FDA label designation.</td>
<td>01/2020</td>
</tr>
<tr>
<td>Updated policy to add new indications for Stelara and Taltz. Included Familial Mediterranean Fever to experimental/investigational section.</td>
<td>11/2019</td>
</tr>
<tr>
<td>Criteria updated to new policy format. Specific changes include: Rheumatoid Arthritis • Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement • Removed requirements for diagnosis due to varying methods to diagnose and limited value of this question from health plan standpoint • Clarified use of oral DMARD requirement may be bypassed if all of them are contraindicated • Added newly approved upadacitinib (Rinvoq) as a non-preferred alternative Polyarticular Juvenile Idiopathic Arthritis (PJIA)</td>
<td>08/2019</td>
</tr>
</tbody>
</table>
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

**Systemic Juvenile Idiopathic Arthritis (SJIA)**
- 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

**Psoriatic Arthritis**
- Added requirement of the presence of active severe disease and provided specific indicators of severe disease
- Added clinical note: “If a patient has a diagnosis of both plaque psoriasis and psoriatic arthritis, approval of the requested medication can be made as long as the patient fulfills the criteria for at least one of the disease states and associated medication criteria.”

**Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthitis**
- Removal of the requirement of DMARDs per the 2015 ACR guideline and 2016 ASAS/EULAR guideline
- Added requirement of a trial of two or more NSAIDS for an adequate trial of at least 4 weeks, also based on the above guidelines

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

**Crohn’s Disease**
- Added age requirement of six years of age or older
- Incorporated definition of moderate to severe Crohn’s disease to help confirm disease severity
- Addition of breakdown to separate severe/fulminant Crohn’s disease with definition to help confirm disease severity
  - Addition of IV corticosteroids as appropriate for this level of severity
  - Addition of breakdown to Crohn’s disease with surgical resection completed or planned
    - With further addition requiring presence of one additional factor demonstrating medical necessity of biologic treatment

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

**Behcet’s Disease**
- New indication added following approval of Otezla in this setting
- Literature supports TNF therapy in oral and ophthalmic manifestations for Bechet’s. A path to approval was added to the criteria
- Otezla was added as a potential option after TNF have been found inefficacious or are contraindicated

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

**Uveitis/Panuveitis**
• Added age of 2 years or older
• Improved trial/fail wording to state “ineffective, contraindicated, or not tolerated”
  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

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

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

*Please note – acetaminophen products are limited to 4000 mg per day
‡Includes Extended release (ER) formulations as well as short acting or immediate release (IR) formulation use beyond 6 weeks.

Initial Evaluation

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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added APAP limit wording to QL box</td>
<td>03/2020</td>
</tr>
<tr>
<td>Creation of policy</td>
<td>02/2020</td>
</tr>
</tbody>
</table>
Coagulation Factor X, human (Coagadex®)

UMP POLICY

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP090

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

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

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation Factor X, human (Coagadex)</td>
<td>250 IU/vial, 500 IU/vial</td>
<td>Factor X deficiency: On-demand treatment &lt;12 years: 30 IU/kg/dose &gt;12 years: 25 IU/kg/dose Repeat every 24 hours until bleeding stops. Max of 60 IU/kg/day</td>
<td>On-demand Treatment: Amount requested OR a max of 60 IU/kg/day (whichever value is lower) and no more than 5 on-demand doses on hand</td>
</tr>
</tbody>
</table>

|          |               | 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 | Routine Prophylaxis: 480 IU/kg every 28 days |
|          |               | Perioperative management Max of 60 IU/kg/day | Perioperative Management: Amount requested OR a max of 60 IU/kg/day (whichever value is lower) Up to the number of doses requested for 28 days |

Initial Evaluation

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

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

October 01, 2020
3. Used for perioperative management of surgical bleeding in patients with mild (Factor X level 6-10%) and moderate (Factor X level 1-5%) deficiency

II. Coagulation Factor X, human (Coagadex) is considered investigational when used for all other conditions.

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent; AND
II. Any increases in dose must be supported by an acceptable clinical rationale (i.e. weight gain, half-life study results, increase in breakthrough bleeding when patient is fully adherent to therapy, etc.) as verified by a Moda Health pharmacist; AND
III. Used for on-demand treatment and control of bleeding episodes; AND
   • Member does NOT have more than five on-demand doses on hand; OR
IV. Used for routine prophylaxis to reduce the frequency of bleeding episodes; AND
   • Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline

Supporting Evidence

I. Perioperative management of bleeding in major surgery in patients with severe hereditary Factor X deficiency has not been studied.
II. Dose and duration of the treatment depend on the severity of the Factor X deficiency, location and extent of the bleeding, the patient’s age (<12 years or >12 years) and on the patient’s clinical condition.
III. The dose and frequency is based on the individual clinical response. With a max dose of 60 IU/kg daily.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of coagulation Factor X, human (Coagadex) in any other condition.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>January 2016</th>
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</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>January 2016</td>
</tr>
<tr>
<td>Last Updated</td>
<td>November 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>11/2019</td>
</tr>
<tr>
<td>Action and Summary of Changes</td>
<td>Date</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Removed age requirement as now also approved in patients less than 12 years of age. Addition of agent to be prescribed by hematologist, limited to only allow 5 doses on hand in on demand treatment setting, added requirement of severe factor X deficiency or at least two spontaneous bleeds into joints for prophylaxis use, limited perioperative use to mild or moderate deficiency as per label. Updated initial approval duration from one month to now six months. Addition of renewal criteria.</td>
<td>11/2019</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>corticotropin (Acthar)</td>
<td>400 Units/5mL</td>
<td>Infantile Spasms</td>
<td>4 vials/28 days</td>
</tr>
</tbody>
</table>

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 not medically necessary 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 investigational when used for all other conditions, including but not limited to:
A. Uveitis
B. Prophylaxis of MS exacerbation
C. Adrenal insufficiency diagnosis
D. Rheumatoid Arthritis
E. Sarcoidosis

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 hypersrrhythmia 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 hypersrrhythmia 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. Sarcoidosis

Washington State Rx Services is administered by moda HEALTH

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

October 01, 2020
References

3. Multiple Sclerosis Association of America. Treating Multiple Sclerosis Relapse. October 2017. Available at: https://mymsaa.org/ms-information/treatments/relapses/

Policy Implementation/Update:

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Policy Type: PA

Pharmacy Coverage Policy: UMP015

Description
Cyproheptadine is an orally administered antihistamine.

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

Quantity limits

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>cyproheptadine</td>
<td>4 mg tablets</td>
<td>Appetite stimulation; Migraine prophylaxis</td>
<td>120 tablets/30 days</td>
<td>005604</td>
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<tr>
<td>cyproheptadine</td>
<td>2 mg/5mL</td>
<td></td>
<td>1,200 mL/30 days</td>
<td>005603</td>
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</table>

Initial Evaluation

I. Cyproheptadine may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      1. Loss of appetite; AND
         i. Member is less than 18 years of age
      2. Headache or migraine prophylaxis; AND
         i. Member is less than 18 years of age; OR
         ii. Member is 18 years of age or older; AND
            a. Documentation of history of trial and failure of prophylactic therapy with at least one agent listed in each of the following groups (of note, if a group of agents is contraindicated, a trial and failure of at least three agents listed in the remaining groups is required):
               i. Group 1: propranolol, metoprolol, atenolol, timolol, nadolol
               ii. Group 2: amitriptyline, venlafaxine
               iii. Group 3: topiramate, sodium valproate, divalproex sodium; AND
            b. Documentation of use of each of the prophylactic therapies at therapeutic doses for at least 3 months
II. Cyproheptadine is considered **not medically necessary** when criteria above are not met and/or when used for:
   A. Use for other indications as there are over the counter alternatives for antihistamine products.

III. Cyproheptadine is considered **investigational** when used for all other conditions, including but **not limited to**:
   A. Functional abdominal pain
   B. Weight loss with cancer
   C. Combination therapy or monotherapy for ADHD
   D. Fatigue post stroke

Renewal Evaluation

I. Confirmed diagnosis of:
   A. Appetite stimulation; **AND**
      1. Documentation of treatment benefit as indicated by weight stability or gain.
   B. Migraine prophylaxis; **AND**
      1. Documentation of treatment benefit as indicated by a decrease in the number or severity of migraines.

Supporting Evidence

I. Plan covers use for appetite stimulation in pediatric population.

II. Guidelines recommend select beta blockers, antidepressants, anticonvulsants, and onabotulinumtoxinA, as efficacious or probably efficacious (Level A and B, respectively) for the prophylactic treatment of migraine in adults. If onabotulinumtoxinA has been stated, this may be used as one qualifier of the three required agents to meet payment consideration for a quantity exception. Agents not listed here have lower level, or conflicting evidence. This includes, but is not limited to SSRIs, cyproheptadine, clonidine, guanfacine, nebivolol, pindolol, carbamazepine, lisinopril, candesartan, duloxetine, calcium channel blockers, gabapentin, pregabalin, lamotrigine, oxcarbazepine, clonipramine, telmisartan, and benzodiazepines. There is limited evidence for efficacy for any class of agents for pediatric patients. Coupled with safety concerns of many of the convention migraine agents in pediatric patients, trial and failure of other conventional agents prior to coverage of cyproheptadine is not indicated at this time.

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

IV. Antihistamines are not covered in adults due to over-the-counter products.
Investigational or Not Medically Necessary Uses

I. Clinical trials are ongoing for the following indications:
   A. Indication of functional abdominal pain
   B. Indication of weight loss with cancer
   C. Indication of combination therapy for ADHD
   D. Indication of fatigue post stroke.

References


Policy Implementation/Update:

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</tr>
<tr>
<td>Last Updated</td>
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<tr>
<td>Last Reviewed</td>
<td>05/2018, 06/2019</td>
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<tr>
<td>Converted to policy</td>
<td>06/06/2019</td>
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<tr>
<td>Criteria update: Added indication of migraine prophylaxis in pediatric patients, updated document to standard format, and updated questions to yes/no format for systematic implementation into criteria builder for Cover My Meds programming.</td>
<td>05/30/2018</td>
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<tr>
<td>Criteria update: Excluded samples and updated renewal language to general improvement.</td>
<td>1/11/2016</td>
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Washington State Rx Services is administered by Moda Health.

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP118

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

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

Quantity limits

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>cysteamine (Cystagon)</td>
<td>50 mg capsule</td>
<td></td>
<td>60 capsules/30 days</td>
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<tr>
<td></td>
<td>150 mg capsule</td>
<td></td>
<td>1.95 g/m²/day</td>
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<tr>
<td>cysteamine (Procysbi)</td>
<td>25 mg DR capsule</td>
<td>Nephropathic cystinosis</td>
<td>60 capsules/30 days</td>
</tr>
<tr>
<td></td>
<td>75 mg DR capsule</td>
<td></td>
<td>1.95 g/m²/day</td>
</tr>
<tr>
<td></td>
<td>75 mg DR granule packet</td>
<td></td>
<td>1.95 g/m²/day</td>
</tr>
<tr>
<td></td>
<td>300 mg DR granule packet</td>
<td></td>
<td>1.95 g/m²/day</td>
</tr>
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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 **ONE** of the following:
         i. Presence of corneal cystine accumulation; **OR**
         ii. CTNS gene analysis; **OR**
         iii. Elevated intracellular cystine levels (>1 nmol cystine/mg protein); **AND**
      2. **If Procysbi is requested**, documentation member has an intolerance, or contraindication to, Cystagon; **OR**
         i. Documentation of unavoidable non-adherence to cysteamine IR (Cystagon) that prevents the achievement of optimal white blood cell (WBC) cystine levels (<1 nmol ½ cystine per mg protein); **AND**
      3. Dose does not exceed 1.95 g per m² per day

II. Cysteamine bitartrate (Cystagon, Procysbi) is considered **investigational** when used for all other conditions.
Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; AND
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; AND
III. Member has exhibited improvement or stability of disease symptoms; AND
IV. Member is responding positively to therapy as evidenced by improvement in the leukocyte cystine concentration within the past 3 months; AND
V. If request is for a dose increase, new dose does not exceed 1.95 g per m² per day

Supporting Evidence

I. Cystinosis is a rare, multisystem genetic disorder caused by mutations within the CTNS gene on chromosome 17p13, which is characterized by the accumulation of cystine in different organs and tissues, increasing the potential for severe organ dysfunction. It is further classified into three forms known as nephropathic cystinosis, intermediate cystinosis and non-nephropathic (or ocular) cystinosis. Corneal cystine crystal accumulation may present in all three types of cystinosis. Therapy of cystinosis is comprised of the amelioration of symptoms, the administration of cysteamine, and renal transplantation for those who progress to end-stage renal disease (ESRD). Topical cysteamine is prescribed to prevent corneal deposits, because the oral formulation does not reach the cornea due to absent corneal vascularization.

II. Diagnosis of cystinosis is confirmed by elevated intraleukocyte cystine content, (i.e. measuring cystine levels in polymorphonuclear leukocytes), detection of CNTS gene mutation, or demonstration of cystine corneal crystals by the slit lamp examination.

III. The immediate-release preparation of cysteamine bitartrate is the most commonly used formulation. The dose should be progressively increased from 10 to 50 mg/kg per day (maximum dose of 1.95 gm/m² per day), given in divided doses every six hours. Cystine levels are measured in white blood cells once a maintenance dose is reached; this is then followed by monitoring monthly for three months, quarterly for one year, and then twice a year. Blood sampling should be obtained six hours after taking a dose of cysteamine.

IV. The goal of cysteamine therapy is to lower WBC cystine levels to an optimal target level of less than 1 nmol half-cystine/mg protein.

V. Cysteamine bitartrate (Procysbi) is a delayed-release formulation of cysteamine bitartrate (Cystagon). The delayed-release (Procysbi) formulation is dosed twice daily, while the immediate release (Cystagon) is dosed four times daily. Currently, there is insufficient evidence to support an additional adherence benefit from taking cysteamine DR (Procysbi) when considered together with the extensive increase in cost (estimated 90x increase). Additionally, in the pivotal trial for cysteamine DR (Procysbi), there was a higher incidence of adverse reactions in patients taking the delayed release product compared to patients taking immediate-release cysteamine (Cystagon).
References


Policy Implementation/Update:

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Policy Type: PA/SP 

Pharmacy Coverage Policy: UMP119

Description
Cysteamine (Cystaran™) 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

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<tbody>
<tr>
<td>cysteamine (Cystaran)</td>
<td>0.44% ophthalmic solution</td>
<td>Corneal cystine crystals</td>
<td>4 bottles (60 mL)/28 days</td>
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Initial Evaluation
I. Cysteamine (Cystaran) 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) 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.

Investigational or Not Medically Necessary Uses

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

References

2. UpToDate, Inc. Cystinosis. UpToDate [database online]. Waltham, MA. Last updated February 27, 2019 Available at: http://www.uptodate.com/home/index.html.
3. National Organization for Rare Disorders. Cystinosis. Available at: https://rarediseases.org/rare-diseases/cystinosis/

Policy Implementation/Update:

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**Cystic Fibrosis, CFTR Modulators**

**UMP POLICY**

**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**

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<td>ivacaftor (Kalydeco)</td>
<td>150 mg tablet</td>
<td>Cystic fibrosis, one mutation in the CFTR gene that is responsive to ivacaftor</td>
<td>56 tablets/28 days</td>
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<td>25 mg/packet oral granules</td>
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<td>56 packets/28 days</td>
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<tr>
<td></td>
<td>50 mg/packet oral granules</td>
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<td>56 packets/28 days</td>
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<td></td>
<td>75 mg/packet oral granules</td>
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<tr>
<td>ivacaftor/ lumacaftor (Orkambi)</td>
<td>125/200 mg tablet</td>
<td>Cystic fibrosis, homozygous for F508del mutation</td>
<td>112 tablets/28 days</td>
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<td>125/100 mg tablet</td>
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<td>112 tablets/28 days</td>
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<td>56 packets/28 days</td>
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<td>ivacaftor/tezacaftor (Symdeko)</td>
<td>Kit: (ivacaftor; ivacaftor/tezacaftor) 150mg; 150/100mg</td>
<td>Cystic fibrosis, homozygous F508del mutation or at least one mutation in the CFTR gene that is responsive to ivacaftor/tezacaftor</td>
<td>56 tablets/28 days</td>
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<td>Kit: (ivacaftor; ivacaftor/tezacaftor) 75mg; 75/50 mg</td>
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<td>56 tablets/28 days</td>
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<tr>
<td>elexacaftor/tezacaftor/ivacaftor (Trikafta)</td>
<td>Kit (elexacaftor/tezacaftor/ ivacaftor) 100/50/75mg; 150 mg</td>
<td>Cystic fibrosis, one F508del mutation</td>
<td>84 tablets/28 days</td>
</tr>
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</table>

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

I. Agents listed in this policy may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   B. The medication is not used in combination with other agents in this policy (i.e., use of only one of the following at a given time: Kalydeco, Orkambi, Symdeko, Trikafta) (*please note: if a previous approval has been granted for one of these agents, and criteria is met for another, the previous PA approval will be discontinued*); **AND**
   C. A diagnosis of **cystic fibrosis** when the following are met:
      1. For ivacaftor (Kalydeco):
         i. The member is six **months** of age or older; **AND**
      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**
      4. For elexacaftor/tezacaftor/ivacaftor (Trikafta):
         i. The member is 12 **years** of age or older: **AND**
         ii. The member has at least one copy of the F508del mutation

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.


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.

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 (CI 8.7-13.6); p<0.0001).

• Trial 3 evaluated patients who were heterozygous for F508del mutation and a second mutation not predicted to be responsive to tezacaftor/Ivacaftor (Symdeko). The primary efficacy endpoint, a change in FEV1 compared to baseline, was 1.2 percentage points (CI 0.3-2.6), and was not significant. The study was terminated early.

• The efficacy of ivacaftor/tezacaftor (Symdeko) for patients age six to 12 years was supported by data from a 24-week, open-label treatment period of 70 patients. Observations of safety were noted to be similar to that of the data available for ages 12 years and above.

X. Elexacaftor/tezacaftor/ivacaftor (Trikafta) was evaluated in two trials in subjects 12 years of age and older with a primary outcome of percent predicted forced expiratory volume in one second (ppFEV1):

• Trial 1: 24-week, randomized, double-blind, placebo-controlled trial (n=403). Subjects had an F508del mutation and a second mutation that resulted in no CFTR protein or a CFTR protein that was 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.

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.
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.

October 01, 2020
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<td>Symdeko criteria created.</td>
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<tr>
<td>Criteria update: Excluded samples and updated renewal language to general improvement.</td>
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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

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

Initial Evaluation

I. Dalfampridine ER (Ampyra) may be considered medically necessary when the following criteria below are met:
   A. Member must be 18 years of age or older; **AND**
   B. Must be prescribed by or in consultation with a neurologist; **AND**
   C. A diagnosis of **multiple sclerosis** when the following are met:
      1. Member does **not** have a history of seizures; **AND**
      2. Member has a CrCl >50 mL/min; **AND**
      3. Member must be able to ambulate; **AND**
      4. Member must currently be receiving a disease modifying therapy for multiple sclerosis (i.e. glatiramer acetate, dimethyl fumarate, interferon beta-1a, etc.); **AND**
      5. If request is for brand Ampyra, documentation of treatment with generic dalfampridine ER has been ineffective, contraindicated, or not tolerated.

II. Dalfampridine ER (Ampyra) is considered **investigational** when used for all other conditions, including but **not limited to:**
   A. Acute spinal cord injury
   B. Disorder of neuromuscular transmission
   C. Alzheimer’s disease, dementia
   D. Botulism
   E. Reversal of neuromuscular blockade
   F. Toxicity of calcium channel blockers
   G. Non-ambulating members with multiple sclerosis

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

I. Member has 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

Policy Implementation/Update:

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<tr>
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<td>Last Reviewed</td>
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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

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

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

II. 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.

References


Policy Implementation/Update:

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<th>September 2011, February 2013, April 2018</th>
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<tr>
<td>Last Updated</td>
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Action and Summary of Changes

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

12/2019
requirements for agents in the setting of castration sensitive prostate cancer to streamline policy.
Formatting updates

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<td>Darolutamide (Nubeqa) new agent available, criteria converted to policy, and all agents combined into one policy. Requirement of generic abiraterone added unless contraindicated or not tolerated. Addition of use of GnRH therapy in metastatic castration sensitive disease included. Yonsa brand added. Erleada now FDA approved for castration sensitive disease.</td>
<td>08/2019</td>
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<td>Generic abiraterone requirement added prior to use of branded 250 mg.</td>
<td>12/2018</td>
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<td>Enzalutamide new indication of non-metastatic resistant prostate cancer added. Clinical notes added and appropriate routing through criteria.</td>
<td>08/2018</td>
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<td>Apalutamide (Erleada) criteria created</td>
<td>04/2018</td>
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<tr>
<td>Abiraterone new indication of metastatic, high-risk castration sensitive prostate cancer added. LATITUDE trial information incorporated as well.</td>
<td>02/2018</td>
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<tr>
<td>Enzalutamide (Xtandi) criteria created</td>
<td>02/2013</td>
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<tr>
<td>Abiraterone (Zytiga) criteria created</td>
<td>09/2011</td>
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Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP016

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

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

Quantity limits

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<td>20 mg tablets</td>
<td>Philadelphia chromosome-positive (Ph+) Chronic myeloid leukemia (CML)/Ph+ Acute lymphoblastic leukemia (ALL)</td>
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<td>100 mg tablets</td>
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<td>70 mg tablets</td>
<td>Gastrointestinal Stromal Tumors (GIST)</td>
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Initial Evaluation

I. Dasatinib (Sprycel) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by, or in coordination with, an oncologist; AND
   B. A diagnosis of one of the following:
      1. Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL); AND
         i. Adult member with resistance or intolerance to prior therapy; AND
            a. If resistance to prior TKI therapy:
               i. Member does not have BCR-ABL mutations T315I, V299L, or F317L; OR
               ii. Newly diagnosed pediatric member ≥1 year of age; AND
               iii. Used in combination with chemotherapy; OR
      2. Ph+ Chronic myeloid leukemia (CML); AND
         i. Adult or pediatric member with newly diagnosed Ph+ CML in chronic phase; OR
         ii. Adult or pediatric member with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy; AND
            a. If resistance to prior TKI therapy:
i. Member does not have BCR-ABL mutations T315I, V299L, and F317L; OR

3. Gastrointestinal Stromal Tumors (GIST); AND

   i. BCR-ABL KD mutational status contains PDGFRA D842V mutation; AND
   
   ii. Member has tried and failed imatinib (Gleevec) AND sunitinib (Sutent) AND regorafenib (Stivarga) for the treatment of gastrointestinal stromal tumors

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

   A. Pancreatic cancer - Metastatic

Renewal Evaluation

I. No increase in the rate of disease progression while on therapy

Supporting Evidence

I. Per NCCN guidelines dasatinib (Sprycel) is not active against cells harboring the ABL mutations T315I, V299L, and F317L. Thus for patients with disease resistant to TKI therapy it becomes important to identify potential ABL mutations that may underlie the observed resistance to treatment.

II. The efficacy of Sprycel was investigated in open label trials in adult patients with Ph+ CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib: 1,158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. Overall, 80% of patients had imatinib-resistant disease and 20% of patients were intolerant to imatinib. The primary efficacy endpoint of major cytogenetic response (MCyR) in chronic phase CML was met in 63% of patients. The primary efficacy endpoint of major hematologic response (MaHR) in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was met in 44% of Sprycel patients by 7 years.

III. Prior therapy includes a minimum of 30 to 60 day trial of imatinib 400mg or more per day without a complete hematologic response or discontinuation of imatinib therapy due to toxicity. Dosing may be escalated to 180 mg once daily in patients who do not achieve a hematologic or cytogenic response at the recommended dosage.

IV. In clinical trials imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

V. The approval for Sprycel for pediatric patients with Ph+ ALL was based on findings from a phase II trial (NCT01460160), which demonstrated a 3-year event-free survival (EFS) 64.1% (95% CI, 52.4%-74.7%) in 78 pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. This trial compared dasatinib (Sprycel) plus chemotherapy versus chemotherapy alone in the external historical control trial. Another TKI, Gleevec, was approved for this same patient population in 2013. There is no head to head study comparing Gleevec to Sprycel for Ph+ ALL in pediatric patients. NCCN guidelines recommend all tyrosine kinase inhibitors within the same 2a recommendation.
VI. Dasatinib (Sprycel) in the setting of newly diagnosed chronic phase CML in adults was approved based on the DASISION trial (NCT00481247) an open label, randomized trial comparing Sprycel to imatinib. The primary endpoint of rate of confirmed complete cytogenetic response (CCyR) within 12 months was achieved in 76.8% of Sprycel patients versus 66.2% of imatinib patients. After 60 months follow-up, median time to confirmed complete cytogenetic response was 3.1 months in 215 Sprycel responders and 5.8 months in 204 imatinib responders.

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

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

Investigational or Not Medically Necessary Uses

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

References


Policy Implementation/Update:

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<tr>
<th>Date Created</th>
<th>March 2017</th>
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<tr>
<td>Date Effective</td>
<td>March 2017</td>
</tr>
<tr>
<td>Last Updated</td>
<td>February 2019</td>
</tr>
<tr>
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<td>01/2018, 02/2019</td>
</tr>
<tr>
<td>Action and Summary of Changes</td>
<td>Date</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Updated to new format. Added new indication in pediatric patients with newly diagnosed Ph+ ALL. Added patient specific mutation assessment in the relapsed CML and ALL settings.</td>
<td>02/2019</td>
</tr>
<tr>
<td>Removed pregnancy question and adult only language as this is now approved for pediatric indications. Added regorafenib as an additional prior agent in GIST indication, as well as assessing patient specific mutation that received benefit in GIST in the salvage setting.</td>
<td>01/2018</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferasirox (generic Exjade)</td>
<td>125 mg tablet for suspension</td>
<td>Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome</td>
<td>Monthly quantity to allow for a maximum of 20 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>250 mg tablet for suspension</td>
<td></td>
<td>Setting of transfusions: Monthly quantity to allow for a maximum of 40 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>500 mg tablet for suspension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deferasirox (Exjade)</td>
<td>125 mg tablet for suspension</td>
<td>Hemosiderosis (chronic iron overload) – transfusion thalassemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>250 mg tablet for suspension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>500 mg tablet for suspension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deferasirox (generic Jadenu)</td>
<td>90 mg tablet</td>
<td>Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome</td>
<td>Monthly quantity to allow for a maximum of 14 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>180 mg tablet</td>
<td></td>
<td>Setting of transfusions: Monthly quantity to allow for a maximum of 28 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>360 mg tablet</td>
<td></td>
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</tr>
<tr>
<td>Deferasirox (Jadenu)</td>
<td>90 mg tablet</td>
<td>Hemosiderosis (chronic iron overload) – transfusion thalassemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>180 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>360 mg tablet</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>90 mg granule (sprinkle)</td>
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<tr>
<td></td>
<td>180 mg granule (sprinkle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>360 mg granule (sprinkle)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deferiprone (Ferriprox)</td>
<td>100 mg/1 mL solution</td>
<td>Hemosiderosis (chronic iron overload) – transfusion thalassemia</td>
<td>Monthly quantity to allow for a maximum of 99 mg/kg per day</td>
</tr>
<tr>
<td></td>
<td>500 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000 mg tablet</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 non-transfusion 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 both generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication) (deferiprone [Ferriprox] is not FDA-approved for this indication); OR
      2. **Chronic iron overload due to blood transfusions; 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;
         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 both generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication)

II. Deferasirox (Exjade), deferasirox (Jadenu) and deferiprone (Ferriprox) are considered **not medically necessary** when criteria above are not met and/or when used for:
   A. Plasmodium falciparum parasitemia
III. Deferasirox (Exjade), deferasirox (Jadenu) and deferiprone (Ferriprox) are considered investigational when used for all other conditions, including but not limited to:
   A. Hereditary hemochromatosis
   B. Porphyria cutanea tarda

Renewal Evaluation

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


Policy Implementation/Update:

<table>
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<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
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<td>May 2019</td>
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<tr>
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<td>May 2019</td>
</tr>
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</tr>
<tr>
<td>Last Reviewed</td>
<td>08/2013, 05/2019, 12/2019</td>
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Washington State Rx Services is administered by Moda Health

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
<table>
<thead>
<tr>
<th>Date</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/2019</td>
<td>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.</td>
</tr>
<tr>
<td>05/2019</td>
<td>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.</td>
</tr>
</tbody>
</table>
deflazacort (Emflaza™)
UMP POLICY

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

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

Initial Evaluation

I. Deflazacort (Emflaza) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a neuromuscular specialist or neurologist; AND
   B. The member has a diagnosis of Duchenne Muscular Dystrophy (DMD); AND
      1. Member’s diagnosis has been confirmed by dystrophin genetic testing; AND
      2. Member is two years of age or older; AND
      3. Treatment with oral prednisone for six months or greater has been ineffective, is contraindicated, or not tolerated; AND
      4. Member’s current weight is documented

II. Deflazacort (Emflaza) is considered investigational when used for all other conditions, including, but not limited to:
    A. Dysferlinopathies: including Miyoshi Myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B)

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

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

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

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

i. Central obesity was seen as an adverse event in 25.0% and 24.6% of deflazacort patients compared to 42.9% of prednisone patients and cushingoid appearance was seen in 60.3% and 69.2% of deflazacort patients compared to 77.8% of prednisone patients.

III. Deflazacort (Emflaza) was evaluated in two multicenter, randomized, double-blind, placebo-controlled trials in 225 patients. Study 1 consisted of 196 male pediatric patients, five to 15 years of age with documented mutation of the dystrophin gene, and onset of weakness before five years of age. The primary endpoint was the average change in muscle strength score between baseline and week 12. The average change was 0.15 (95% CI 0.01, 0.28) and -0.10 (95% CI -0.23, 0.03) for the deflazacort (Emflaza) and placebo groups, respectively. Study 2 consisted of 29 male pediatric patients, six to 12 years of age with documented mutation of the dystrophin gene. The primary endpoint was the average muscle strength score at two years. The results were found to not be statistically significant.

Investigational or Not Medically Necessary Uses

I. Dysferlinopathies: including Miyoshi Myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B)
   A. Deflazacort as an ineffective therapy in dysferlinopathies was shown in a double-blinded, placebo-controlled trial. Further evaluation is needed to support use of deflazacort (Emflaza) in this setting.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated initial approval duration to six months, and QLL box with weight-based dosing. Added requirement for neuromuscular specialist or neurologist. Included requirement for confirmation of diagnosis by genetic testing and addition of member weight to confirm dosing. Requires prednisone be tried and failed for six months to be deemed ineffective or have intolerance. Updated renewal criteria to include requirement for previous approval by Moda and not allowing establishing therapy with samples. Added examples of symptom improvement to renewal criteria.</td>
<td>05/2020</td>
</tr>
<tr>
<td>Event</td>
<td>Date</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Revised to policy format, include use in pediatric patients down to two years of age.</td>
<td>07/2019</td>
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<tr>
<td>Update to criteria</td>
<td>01/2017</td>
</tr>
<tr>
<td>Criteria creation</td>
<td>05/2017</td>
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</table>
Diabetic Test Strips and Glucometer

UMP POLICY

Policy Type: PA
Pharmacy Coverage Policy: UMP165

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

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

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meter and Test strips (e.g. Freestyle Lite, Precision Xtra, Contour, Contour USB, Breeze 2)</td>
<td>Meter</td>
<td>Type 1 and type 2 diabetes mellitus</td>
<td>One meter/365 days</td>
</tr>
<tr>
<td></td>
<td>Test Strips</td>
<td></td>
<td>300 test strips/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

Freestyle Lite, Precision Xtra, Contour, Contour USB, and Breeze 2 are the preferred diabetic test strips and glucometers.
- There is no prior authorization required on these preferred agents, unless requesting over the allowed quantity limits noted above.

I. **Non preferred meter and 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. Member uses test strips with a glucometer built into, or communicates with, an insulin pump; **OR**
   C. Member uses a voice meter due to vision impairment; **OR**
   D. There is documentation of medical necessity for a non-formulary glucometer and/or test strips that includes medical rationale and test strips previously tried.

II. Meter and test strips are considered **not medically necessary** when criteria above are not met and/or when used for any condition other than type 1 and 2 diabetes mellitus.

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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.

October 01, 2020
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.

Policy Implementation/Update:

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<table>
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<th>Date</th>
</tr>
</thead>
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<tr>
<td>Criteria transitioned into policy with medically not necessary and</td>
<td>01/2020</td>
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<tr>
<td>renewal evaluation sections added.</td>
<td></td>
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<td>New criteria</td>
<td>01/2016</td>
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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Policy Type: PA/SP  Pharmacy Coverage Policy: 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

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

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 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 (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

**Policy Implementation/Update:**

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<th>September 2015</th>
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<td>12/2019</td>
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**Action and Summary of Changes**

<table>
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<tr>
<th>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.</th>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP104

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

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

Quantity limits

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

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

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

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

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

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

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

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

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

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

Investigational or Not Medically Necessary Uses

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

References

Policy Implementation/Update:

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<tr>
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<td>10/6/2017</td>
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<tr>
<td>Last Updated</td>
<td>11/15/2019</td>
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<td>11/15/2019</td>
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<th>Date</th>
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<tbody>
<tr>
<td>Updated criteria to policy format</td>
<td>11/2019</td>
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</table>
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP122

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

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

Quantity Limits

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

Initial Evaluation
I. 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: orthostatic dizziness, light-headedness, or 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.

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

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.

October 01, 2020
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 (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 (Nothera) 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 Parkinson 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 (Nothera) 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 (Nothera) 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 a) removing aggravating factors (drug-induced hypotension, anemia, dehydration, prolonged bed rest and physical activity), b) restoring intravascular volume, c) increasing cardiovascular responsiveness with low-dose sympathomimetic agents (droxidopa, midodrine, ephedrine, or clonidine), d) improving the patient’s physical fitness, and e) addressing the underlying cause of nOH.
deconditioning), b) 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 c) 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: a) Expanding intravascular volume and b) Increasing peripheral vascular resistance. Medications used for the treatment of nOH consist of the following: dihydroergotamine, ephedrine, fludrocortisone, midodrine, erythropoetin, 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 (Nothera) in conditions other than nOH.

References


Policy Implementation/Update:

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<tr>
<th>Date Created</th>
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<td>Last Updated</td>
<td>November 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>11/2019</td>
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</table>
Updated criteria to policy format; Added age limit, added attempted at least one non-pharmacologic intervention criteria

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October 01, 2020
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP019

Description
Dupilumab (Dupixent) is an injectable human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling, which inhibits the release of proinflammatory cytokines, chemokines and IgE.

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

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
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</table>
| dupilumab (Dupixent)| 200 mg/1.14mL | Atopic Dermatitis (moderate to severe) | Initial: 4 (300mg) syringes (8 mL) per a 42-day supply  
Maintenance: 2 (300mg) syringes (4 mL) per 28 day supply | 197463 |
|                    | 300 mg/2mL  | Asthma (moderate to severe)         | Initial: 4 (200mg OR 300mg) syringes (8 mL) per a 42-day supply  
Maintenance: 2 (200mg OR 300mg) syringes (4 mL) per 28 day supply | 197463 |
|                    |             | Chronic rhinosinusitis with nasal polyposis | Initial & Maintenance: 2 (300mg) syringes (4 mL) per 28 day supply | 197463 |

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. A diagnosis of one of the following:
      1. **Atopic dermatitis (moderate to severe); AND**
         i. Member is 12 years of age or older; **AND**
         ii. Minimum body surface area (BSA) involvement of at least 10%; **OR**
         iii. Physician Global Assessment (PGA) score of three or greater; **AND**
         iv. Prior treatment with at least two agents from two different groups has been ineffective or not tolerated, unless ALL are contraindicated.

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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.

2. **Asthma (moderate to severe); AND**
   - i. Member is 12 years of age or older; **AND**
   - ii. Member has one of the following:
     - a. Moderate-to-severe persistent asthma of an eosinophilic phenotype; **OR**
     - b. Moderate-to-severe persistent asthma that is dependent on oral corticosteroids; **AND**
   - iii. Environmental triggers of asthma have been addressed, including, but not limited to smoking cessation or allergen limitations; **AND**
   - iv. Member is currently being treated with:
     - a. A medium- to high-dose inhaled corticosteroid; **AND**
     - b. Two additional controller medications (e.g., long-acting beta-2 agonist, leukotriene receptor antagonist); **AND**
   - v. Background controller medications will be continued with the use of Dupixent, unless contraindicated; **OR**

3. **Chronic rhinosinusitis with nasal polyposis; AND**
   - i. Member is 18 years of age or older; **AND**
   - ii. Member has a diagnosis of bilateral sinonasal polyposis via endoscopy or computed tomography (CT); **AND**
   - iii. Member has ongoing nasal congestion/blockage/obstruction with moderate to severe symptom severity; **AND**
   - iv. Member has nasal discharge; **OR**
   - v. Member has facial pain or pressure; **OR**
   - vi. Member has reduction or loss of smell; **AND**
   - vii. Prior treatment with two intranasal corticosteroid has been ineffective or not tolerated, unless contraindicated; **AND**
   - viii. Background intranasal corticosteroid will be continued with the use of Dupixent, unless contraindicated.

II. **Dupilumab (Dupixent) is considered investigational when used for all other conditions, including but not limited to:**
   - A. Pediatric (6 to 11 years of age) asthma
   - B. Pediatric (6 months to 5 years of age) atopic dermatitis
   - C. Eosinophilic esophagitis
   - D. Chronic obstructive pulmonary disease (COPD)
   - E. Food and environmental allergies

**Renewal Evaluation**
I. The member has an absence of unacceptable toxicity from the medication; **AND**
II. Documentation of disease improvement or stabilization; **AND**
   A. **Atopic dermatitis (moderate to severe); OR**
   B. **Asthma (moderate to severe); AND**
      1. Environmental triggers of asthma have been addressed, including, but not limited to smoking cessation or allergen limitations; **AND**
      2. Background controller medications will be continued with the use of Dupixent, unless contraindicated; **OR**
   C. **Chronic rhinosinusitis with nasal polyposis; AND**
      1. Background intranasal corticosteroid will be continued with the use of Dupixent, unless contraindicated.

**Supporting Evidence**

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

II. The FDA approval of dupilumab (Dupixent) in the setting of moderate to severe atopic dermatitis was based on the results from three randomized, double-blind, placebo-controlled trials. In all three trials, patients in the dupilumab (Dupixent) arm achieved statistically significant improvement when compared to the placebo arm. See table below for details.

<table>
<thead>
<tr>
<th></th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of subjects randomized (EAS)</strong></td>
<td>224</td>
<td>233</td>
<td>106</td>
</tr>
<tr>
<td><strong>IGA 0 or 1</strong></td>
<td>38%</td>
<td>36%</td>
<td>39%</td>
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<tr>
<td><strong>EASI-75</strong></td>
<td>51%</td>
<td>44%</td>
<td>69%</td>
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</table>

III. The FDA approval of dupilumab (Dupixent) in the setting of moderate to severe asthma was based on the results of three randomized, placebo-controlled, multicenter trials.
   - In both Trials 1 and 2, patients receiving either dupilumab (Dupixent) 200 mg or 300 mg every two weeks experienced a significant reduction in the rate of asthma exacerbations when compared with placebo.
   - In Trial 3, the primary endpoint was the percent of reduction from baseline of the final oral corticosteroid dose at week 24 while maintaining asthma control. Patients in the dupilumab (Dupixent) arm (70%) achieved greater mean percent reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control when compared to placebo arm (42%).

IV. The FDA approval of dupilumab (Dupixent) in the setting of chronic rhinosinusitis with nasal polyposis was based on the results from two phase 3 pivotal trials SINUS-24 and SINUS-52. SINUS-24 was a 24-week study, while SINUS-52 was a 52-week study; both trials evaluated dupilumab (Dupixent) 300mg administered every two weeks combined with standard-of-care mometasone furoate nasal spray (MFNS), and compared to placebo injection plus MFNS. In both
trials, there were two co-primary endpoints, improvement in nasal congestion/obstruction severity and reduction in nasal polyps. At 24 weeks, patients in the dupilumab (Dupixent) arm achieved statistically significant improvements when compared to the placebo arm.

- 57% 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
- 33% and 27% reduction in their nasal polyps score compared to a 7% and 4% increase with placebo in SINUS-24 and SINUS-52, respectively

Investigational or Not Medically Necessary Uses

1. 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 FDA approved indications.

References


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<tr>
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<td>July 2017</td>
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<tr>
<td>Last Updated</td>
<td>December 2018</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>04/2017, 01/2018, 12/2018</td>
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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

October 01, 2020
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<thead>
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<th>Date</th>
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<td>Criteria update: excluded samples and updated renewal language to general improvement</td>
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</tr>
<tr>
<td>Updated format and added the renewal approval duration</td>
<td>01/2018</td>
</tr>
<tr>
<td>Criteria update: Incorporated new diagnosis of moderate to severe asthma and appropriate criteria</td>
<td>12/2018</td>
</tr>
<tr>
<td>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.</td>
<td>08/2019</td>
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Policy Type: PA          Pharmacy Coverage Policy: UMP021

Description
Elagolix (Orilissa), elagolix/estradiol/norethindrone acetate (Oriahnn) are oral gonadotropin-releasing hormone (GnRH) antagonists.

Length of Authorization
- Initial: Three months
- Renewal:
  1. Elagolix (Orilissa) 150 mg: Up to 12 months, maximum total fills should not exceed 24 months
  2. Elagolix (Orilissa) 200 mg: Up to three months, maximum total fills should not exceed 6 months
  3. Elagolix/estradiol/norethindrone acetate (Oriahnn): Up to 12 months, maximum total fills should not exceed 24 months

Quantity limits

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

Initial Evaluation
I. Elagolix (Orilissa), 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 must be premenopausal; AND
   C. Member does not have history of osteoporosis (defined as a T-score less than or equal to -2.5 or Z-score less than -1.5 at the lumbar spine, femoral neck or total hip); AND
   D. Provider attests the member is not pregnant and does not have plans to become pregnant; AND
   E. A diagnosis of one of the following:
      1. Moderate-to-severe pain associated with endometriosis; AND
i.  Request is for elagolix (Orilissa); of note, elagolix/estradiol/norethindrone acetate (Oriahnn) should not be used for moderate-to-severe pain associated with endometriosis; AND

ii. Treatment with 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 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); of note, elagolix (Orilissa) should not be used for heavy menstrual bleeding associated with uterine fibroids; AND

   ii. Must be used in combination with a estradiol/norethindrone acetate product (Activella, CombiPatch, Mimvey Lo, etc.); AND

   iii. Treatment with hormonal contraceptives (oral, IUD, implant, etc.) has been ineffective, contraindicated, or not tolerated

Renewal Evaluation

I.  Member has received a previous prior authorization approval for this agent through this health plan; 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 drug, such as, fractures due to loss of bone mineral density; AND

IV. Provider attests the member is not pregnant and does not have plans to become pregnant; AND

V.  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 of disease symptoms (significant/sustained reduction in menstrual blood loss per cycle, improved quality of life, etc.); 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 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, Mifeprrex), GnRH agonists (leuprolide depot (Lupron), nafarelin acetate (Synarel), goserelin acetate (Zoladex), etc.), raloxifene (Evista), and danazol. GnRH agonists are the most effective medical therapy but due to side effects are primarily used selectively as preoperative therapy. Surgical treatment options are available, but often cause patients to become incapable of reproduction.

VI. 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). Hormonal therapy...
used in combination with elagolix was estradiol/norethidone (Activella, Amabelz, CombiPatch, Lopreeza, Mimvey Lo, and Mimvey).

VII. The most common adverse events noted for elagolix/estradiol/norethindrone acetate (Oriahnn) were hot flushes, night sweats, nausea, and headache; however, elagolix/estradiol/norethindrone acetate (Oriahnn) had lower rates of hot flushes and night sweats compared to elagolix alone. Elagolix/estradiol/norethindrone acetate (Oriahnn) also had a reduced change from baseline in bone mineral density compared to elagolix alone. Elaris UF-1 had similar rates of discontinuation due to adverse events across all treatment arms; however, in Elaris UF-2, elagolix alone 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.

VIII. 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, Oriahnn) in combination with bone loss prevention treatments.

IX. Elagolix (Orilissa, Oriahnn) is contraindicated in pregnant patients due to an increased risk of early pregnancy loss.

References


Policy Implementation/Update:

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<th>Date</th>
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<td>Added criteria for treatment of heavy menstrual bleeding associated with uterine fibroids, added requirements for premenopause and confirmation member is not pregnant. Also added NSAIDS as an option for trial and failure for pain associated with endometriosis.</td>
<td>12/2019</td>
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<td>Date</td>
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<tr>
<td>------------------------------</td>
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<tr>
<td>Transition from criteria to policy</td>
<td>09/2019</td>
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<tr>
<td>Criteria created</td>
<td>10/2018</td>
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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Policy Type: PA

Pharmacy Coverage Policy: UMP179

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

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

Quantity Limits

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

Initial Evaluation

I. Eluxadoline (Viberzi) may be considered medically necessary when the following criteria are met:
   A. A diagnosis of Irritable Bowel Syndrome with Diarrhea (IBS-D); AND
      1. The member is 18 year of age or older; AND
      2. Prescribed by, or in consultation with, a gastroenterologist; AND
      3. Treatment with at least three therapies from three different groups have been ineffective, not tolerated, or ALL are contraindicated (please note, if one or more groups is contraindicated, a trial of three agents from the remaining groups will be required):
         a. Group 1: antidiarrheal (e.g. loperamide, bismuth subsalicylate, diphenoxylate/atropine, or paregoric)
         b. Group 2: bile acid sequestrant (e.g. cholestyramine and colestipol)
         c. Group 3: antispasmodic (e.g. dicyclomine and hyoscyamine)
         d. Group 4: Tricyclic serotonergic agent: (e.g. amitriptyline, nortriptyline, imipramine, or desipramine)

II. Eluxadoline (Viberzi) is considered investigational when used for all other conditions, including but not limited to:
   A. Diabetic diarrhea
   B. Diarrhea associated with fecal incontinence
   C. Pediatric IBS-D
   D. Mixed IBS or IBS with constipation
Renewal Evaluation

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

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

III. The medication is prescribed by, or in consultation with, a gastroenterologist; AND

IV. The member has demonstrated a beneficial response to therapy [e.g., symptomatic improvement, improvement in pain associated with IBS-D, a decrease in score for the Bristol Stool Scale (BSS) for stool consistency]

Supporting Evidence

I. The efficacy and safety of eluxadoline (Viberzi) for IBS-D was evaluated in two randomized, double-blind, placebo-controlled trials. Treatment arms were 75 mg, 100 mg or placebo, all administered twice daily. Patients were 18-80 years of age, and all met ROME III criteria for IBS-D. Patients, on average, had a pain score of 3 (0-10) in abdominal pain due to IBS-D, an average daily stool consistency of 5.5 or greater, and at least five days with a BSS score of 5 or greater (1-7). The BSS for stool consistency is rated on a scale of 1-7, with 1 being hard to pass or lumpy stool, and 7 being entirely liquid stool. Efficacy was assessed via a responder composite endpoint of simultaneous improvement in the daily worse abdominal pain score by 30% or greater compared to baseline AND a reduction in BSS to less than 5 for at least half of the days within a 12-week timeframe.

• Study 1: A 26-week study of 1281 patients, with an additional 26 weeks for safety evaluation. Eluxadoline (Viberzi) showed a 23-29% response rate compared to 17% for placebo. Composite response rates were statistically significant at 12 weeks for both strengths, and the 26-week endpoint was statistically significant for the 100 mg.

• Study 2: A 26-week study of 1145 patients. This study also included a 4-week withdrawal period upon completion of the 26-week phase. During the withdrawal period, patients were permitted to take rescue loperamide therapy for uncontrolled diarrhea. Eluxadoline (Viberzi) showed a 29-33% response rate compared to 16-20% for placebo. Composite response rates were statistically significant for both strengths at week 12 and 26.

II. Conventional treatment options for IBS-D include antidiarrheals, antibiotics, antispasmodics, antidepressants, and bile acid sequestrants; all of which, the American College of Gastroenterology gave moderate or weak recommendations because of poor quality of evidence and applicability to patient groups. However, due to insufficient comparative evidence for efficacy, conventional treatment options still provide a better value over eluxadoline (Viberzi). Notably, Of the antidepressants, tricyclic agents have been shown to slow intestinal transit; however, SSRI/SNRI agents have less published data and the data available is inconsistent in showing benefit in IBS.
Investigational or Not Medically Necessary Uses

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

References


Policy Implementation/Update:

<table>
<thead>
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<th>Date</th>
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<tr>
<td>Prior authorization criteria transitioned to policy format. Update to three conventional therapies required prior to coverage. Update to require specialist prescriber.</td>
<td>04/2020</td>
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<td>Policy Created</td>
<td>02/2019</td>
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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

<table>
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<tr>
<th>Product Name</th>
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<th>Indication</th>
<th>Quantity Limit*‡</th>
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<tr>
<td>Emicizumab-kxwh</td>
<td>30 mg</td>
<td>Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A with or without factor VIII inhibitors</td>
<td>Up to 690 mg every 28 days</td>
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<td>60 mg</td>
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<td></td>
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<td></td>
<td>150 mg</td>
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</table>

* 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

Washington State Rx Services is administered by Moda Health

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

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<th>August 2019</th>
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<td>August 2019</td>
</tr>
<tr>
<td>Last Updated</td>
<td>August 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>08/2019</td>
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</tbody>
</table>

**Action and Summary of Changes**

| New policy created for emicizumab-kxwh (Hemlibra) | 08/2019 |

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

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<td>encorafenib (Braftovi)</td>
<td>50 mg capsule</td>
<td>Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy;</td>
<td>180 capsules/30 days</td>
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<td>75 mg capsule</td>
<td>Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy</td>
<td>180 capsules/30 days</td>
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<tr>
<td>binimetinib (Mektovi)</td>
<td>15 mg tablet</td>
<td>Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy</td>
<td>180 tablets/30 days</td>
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Initial Evaluation
I. Encorafenib (Braftovi) and binimetinib (Mektovi) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; AND
   B. Medications are prescribed by, or in consultation with, an oncologist, dermatologist, or gastroenterologist; AND
   C. Encorafenib (Braftovi) and binimetinib (Mektovi) will not be used in combination with any other oncolytic agent unless specified below (e.g. encorafenib (Braftovi) and cetuximab (Erbitux) for the treatment of colorectal cancer); AND
   D. The member has not progressed on prior BRAF-inhibitor therapy (e.g., dabrafenib, vemurafenib); AND

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October 01, 2020
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

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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 in combination with cetuximab and 14 months for vemurafenib in combination with cetuximab. The combination therapy showed a statistically significant improvement in OS compared to vemurafenib alone (16.2 months vs 9.3 months, *p*<0.0001).
(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

1. 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


Washington State Rx Services is administered by modahealth.

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October 01, 2020

Policy Implementation/Update:

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<th>Date</th>
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<td>Updated with new indication for Braftovi for metastatic colorectal cancer in combination with cetuximab. Updated language to state not for combination use besides agents listed in the criteria. Removed exclusions for colorectal cancer and V600-mutated cancer besides melanoma.</td>
<td>06/2020</td>
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<td>Prior authorization criteria transitioned to policy, updated criteria with the following: age edit, allowance of dermatologist prescribing, specialist requirement on renewal.</td>
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entrectinib (Rozlytrek®)
UMP POLICY

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

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<td>Neurotrophic receptor tyrosine kinase gene fusion positive solid tumors</td>
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<td>200 mg capsules</td>
<td>Non-small cell lung cancer, metastatic, ROS1-positive</td>
<td>90 capsules/30 days</td>
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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.

References

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

Policy Implementation/Update:

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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), Gilotrif (afatinib), and gefitinib (Iressa) are orally administered EGFR TKIs.

Length of Authorization
- Initial: Three months; split fill applies to dacomitinib (Vizimpro) and erlotinib (Tarceva) only
- Renewal: 12 months

Quantity limits

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Initial Evaluation

I. Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), Gilotrif (afatinib), 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. 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 after use of another agent in this policy; **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 listed in this policy (previous use of any of the other agents in this policy); **AND**
      i. The tumor is 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 inhibitor 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 the member has tried and failed, has a contraindication or intolerance to the generic; and is being used 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 documented disease progression on prior EGFR inhibitor 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); one of the following (i or ii)**
   i. Metastatic (stage IV) non-small cell lung cancer; **AND**
a. The member has not had documented disease progression on prior EGFR inhibitor therapy (no previous use of any other agent listed in this policy); \textbf{AND}

b. The treatment will be used for first-line treatment in metastatic setting; \textbf{AND}

c. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated, or has L861Q, G719X, or S768I mutation; \textbf{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.)

\textbf{5. For gefitinib (Iressa)}

i. Metastatic (stage IV) non-small cell lung cancer; \textbf{AND}

ii. The member has not had disease progression on prior EGFR inhibitor therapy (no previous use of any other agent listed in this policy); \textbf{AND}

iii. The treatment will be used for first-line treatment in the locally advanced or metastatic setting; \textbf{AND}

iv. The tumor is confirmed to be EGFR exon 19 deletion or exon 21 L858R substitution mutated; \textbf{AND}

\textbf{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

\textbf{III. Osimertinib (Tagrisso), dacomitinib (Vizimpro), erlotinib (Tarceva), Gilotrif (afatinib), 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 or locally advanced stage EGFR NSCLC, 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

\textbf{Renewal Evaluation}

I. The medication is prescribed by or in consultation with an oncologist; \textbf{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 with the exception of erlotinib (Tarceva) in combination with gemcitabine for the treatment of pancreatic cancer; \textbf{AND}

III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; \textbf{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.

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 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 a 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), afatinib (Gilotrif) 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, a difference in efficacy was not indicated.
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 or locally advanced stage EGFR NSCLC, 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

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References


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Action and Summary of Changes

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<td>Criteria update and policy creation: All EGFR TKI agents combined into one policy, streamline quantity limits, renewal criteria, duration or approval upon initial and renewal request. Update Tagrisso criteria to allow for use in the first line setting. Addtion of age requirement and prescriber requirement for all agents.</td>
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<td>Gilotrif criteria update: updated criteria to include L861Q, G719X, or S768I mutations and metastatic, squamous NSCLC that has progressed after treatment with platinum-based chemotherapy. Due to the statement that afatinib is not recommended as second-line therapy for squamous cell carcinoma from National Comprehensive Cancer Network (NCCN), a clinical note has been added to address the request for afatinib in members who are diagnosed with squamous NSCLC that has progressed on platinum-based chemotherapy.</td>
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<td>Tagrisso criteria update: Include clinical note regarding the Flaura trial and recent NCCN NSCLC Guidelines. Also, a route for approval if patient has a contraindication to erlotinib, afatinib and gefitinib.</td>
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<td>Gilotrif criteria update: updated criteria to new format, deleted renal and hepatic function questions, and deleted female contraception questions as this is properly managed by providers</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: 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

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<td>5 mg tablets</td>
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*Total daily dose should not exceed 9 mg per day. This may be achieved by 5 mg plus 4 mg, or by three 3mg tablets.

Initial Evaluation

I. Erdafitinib (Balversa) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; AND
   B. The medication is prescribed by or in consultation with an oncologist or urologist; AND
   C. Not to be used in combination with other oncolytic medications (i.e., must be used as a monotherapy for the conditions listed below); AND
   D. The provider attests that the member will be treated with a maximum of 8 mg per day for at least two weeks to assess for tolerability before considering a total daily dose of 9 mg per day; AND
   E. A diagnosis of urothelial carcinoma when the following are met:
      1. Disease is considered advanced or metastatic; AND
      2. Genetic alteration is FGFR3 point mutation or fusion as detected by an FDA-approved test; AND (one of i or ii)
         i. The member has previously progressed during or following at least one line of prior platinum-containing chemotherapy (e.g., cisplatin, carboplatin); OR
ii. The member previously progressed during or following neoadjuvant or adjuvant platinum-containing chemotherapy (e.g., cisplatin, carboplatin); AND
   a. The platinum-containing chemotherapy was administered within the last 12 months

II. Erdafitinib (Balversa) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Urothelial carcinoma that has FGFR2 genetic alteration (e.g., fusion or point mutation)

III. Erdafitinib (Balversa) is considered investigational when used for all other conditions, including, but not limited to:
   A. Urothelial carcinoma prior to the advanced or metastatic setting
   B. Urothelial carcinoma without FGFR mutation, or without previous treatment with platinum-based chemotherapy
   C. For urothelial carcinoma, or otherwise, treatment with a dose greater than 9 mg per day
   D. Conditions outside of urothelial carcinoma (e.g., Non-Hodgkin Lymphoma, gliomas, osteosarcoma, histiocytosis, soft tissue sarcoma, etc.)

Renewal Evaluation
I. The medication is prescribed by, or in consultation with, an oncologist or urologist; AND
II. The medication is not used in combination with other oncolytic medications (i.e., erdafitinib [Balversa] is used as monotherapy); AND
III. Tumor response is documented with stabilization of disease or decrease in size of tumor or tumor spread; AND
IV. The member has an absence of unacceptable toxicity from the drug (e.g., ophthalmic disturbances, hyperphosphatemia).

Supporting Evidence
I. Erdafitinib (Balversa) was evaluated in one, single-arm, open-label trial. Eighty-seven subjects (n=87) had advanced or metastatic urothelial carcinoma with FGFR2 or FGFR3 genetic alterations. Additionally, subjects must have progressed on or after at least one line of prior platinum-containing chemotherapy. This included those that had received neoadjuvant or adjuvant platinum-containing chemotherapy in the past 12 months.
II. No pediatric patients were included in the trial. Subjects assessed were between the ages of 36 and 87. Ninety-seven percent of subjects had received prior cisplatin or carboplatin, and 10% had received both. Twenty-four percent of subjects had received prior anti-PD-L1/PD-1 therapy (immunotherapy). No concomitant oncolytic medications were allowed during the trial.
III. The study assessed for objective response rate (ORR), including both partial and complete response (PR and CR), and duration of response (DoR). Thirty-two percent of subjects met the ORR (2 patients showed CR), and the median duration of response was 5.4 months.
IV. High rates of dose-reduction and dose-interruption were observed, at 53% and 68% respectively. Serious adverse events including, but not limited to, ophthalmic disturbances, hyperphosphatemia, and fatal myocardial infarction, occurred during the trial (1-20%).

Investigational or Not Medically Necessary Uses
I. The pivotal trial evaluated for the FDA-approved indication of urothelial carcinoma included six patients with a FGFR2 fusion genetic alteration, and no patients that had FGFR2 point mutation. None of these six patients showed an ORR on or after treatment with erdafitinib (Balversa). As of April 2019, there is no evidence that this population has responded to therapy.

II. Currently, the available outcomes data for erdafitinib (Balversa) was based on a maximum dose of 9 mg per day. No subjects were on concurrent oncolytic therapies. All subjects were verified to be with FGFR-mutation, and with advanced or metastatic urothelial carcinoma. Safety and efficacy outcomes in patients not previously progressed on or after platinum-containing chemotherapy is unknown at the time of this writing.

III. Erdafitinib (Balversa) is currently in clinical trials for a variety of other conditions (e.g. Non-Hodgkin Lymphoma, gliomas, osteosarcoma, histiocytosis, soft tissue sarcoma, etc.).

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

References


Policy Implementation/Update:

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<tr>
<td>Date Effective</td>
<td>August 2019</td>
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<th>Date</th>
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Washington State Rx Services is administered by Moda Health

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October 01, 2020
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP025

Description
Erenumab (Aimovig), galcanezumab (Emgality), and fremanezumab (Ajovy) are subcutaneous injections of monoclonal antibodies that bind to the calcitonin gene-related peptide (CGRP) receptor or ligand.

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

Quantity limits

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<tr>
<td>erenumab (Aimovig)</td>
<td>70 mg/1 mL autoinjector</td>
<td>Migraine prophylaxis</td>
<td>1 mL/30 days</td>
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<td>140 mg/1 mL autoinjector</td>
<td></td>
<td></td>
</tr>
<tr>
<td>galcanezumab (Emgality)</td>
<td>120 mg/1 mL autoinjector</td>
<td>Migraine prophylaxis</td>
<td>Initial: 2 mL (240 mg)/30 days for one fill</td>
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<td></td>
<td>120 mg/1 mL prefilled syringe</td>
<td></td>
<td>Maintenance: 1 mL (120mg)/30 days</td>
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<tr>
<td></td>
<td>100 mg/1 mL</td>
<td>Episodic cluster headache</td>
<td>3 mL/30 days</td>
</tr>
<tr>
<td>fremanezumab (Ajovy)</td>
<td>225 mg/1.5 mL prefilled syringe</td>
<td>Migraine prophylaxis</td>
<td>1.5 mL/30 days OR 4.5 mL per 90-day supply</td>
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<tr>
<td></td>
<td>225 mg/1.5 mL autoinjector</td>
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</tbody>
</table>

Initial Evaluation

Migraine

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

A. A diagnosis of migraine; **AND**
B. The member is 18 years of age or older; **AND**
C. The medications in this policy will not be used in combination with each other; **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; 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

II. Erenumab (Aimovig) and fremanezumab (Ajovy) may be considered medically necessary when the following criteria below are met:
   A. Criteria I(A) – I(J) above are met; AND
   B. Treatment with galcanezumab (Emgality) has been ineffective, contraindicated, or not tolerated

Cluster Headache

I. Galcanezumab (Emgality) may be considered medically necessary when the following criteria below 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.)

II. Erenumab (Aimovig), galcanezumab (Emgality), and fremanezumab (Ajovy) are considered investigational when used for all other conditions, including but not limited to:
   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
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 medications in this policy will not be used in combination with each other; AND

IV. The provider has attested that the member has not received onabotulinum toxin (e.g., Botox, etc.) within the past three months; AND

V. The member will not receive onabotulinum toxin (e.g., Botox, etc.) concurrently with any agent in this policy; AND

A. Diagnosis of Migraine prophylaxis; AND
   1. 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
   2. Upon subsequent renewals the member has maintained the initial response or gained further response to therapy; OR

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:
      a. A reduction in four weekly cluster headache attacks compared to baseline; OR
      b. 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 the agents in the policy are used concurrently. 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. The agents in this policy shall 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 shall be
discontinued. Another therapy should be initiated after a washout period to ensure the member and provider are realizing baseline migraine frequency and severity.

IV. In the pivotal trials for the agents listed in this policy, members had a history of four or more monthly migraine days for at least one year. Migraine 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 injectable CGRP agents.

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

VI. Guidelines recommend select beta blockers, antidepressants, anticonvulsants and onabotulinum toxin A as efficacious or probably efficacious (Level A and B, respectively) for the prophylactic treatment of migraine in adults. If onabotulinum toxin A has been listed as a therapy that has been tried and failed, 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 benzdiazepines. Specifically, nortriptyline does not have the same level of efficacy supporting use for migraine prophylaxis as amitriptyline and shall not be considered for adequate trials of prophylactic therapy.

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

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

IX. 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.

X. 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

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


• Prophylactic therapies: Level A evidence: suboccipital steroid injection as a transitional but not long term therapy. Several other therapies have been evaluated; however, available evidence coupled with expert opinion recommendations state verapamil and lithium shall be first-line therapy; however, due to the 1-2 week onset of efficacy, transitional therapy is recommended with oral or subcutaneous steroids.

XII. Galcanezumab (Emgality) was evaluated for safety and efficacy in episodic cluster headache. One Phase 3, RCT of 106 adult patients was conducted over eight weeks. This included those with episodic cluster headache in patients not on other therapies for headache prophylaxis. Patients were allowed to use acute/abortive headache treatment regimens (triptans, oxygen, APAP, NSAIDS). Patients with MOH were excluded. Outcomes included mean change from baseline in weekly cluster headache 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, percentage of participants with suicidal behaviors assessed by C-SSRS.

XIII. 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 shall 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
References


Policy Implementation/Update:

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<tr>
<td>Added Ajovy autoinjector to policy</td>
<td>04/2020</td>
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<tr>
<td>Removed PFS and 2-pack of Aimovig from policy as it is no longer available one the market</td>
<td>02/2020</td>
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<tr>
<td>Criteria update: update to reflect preferred galcanezumab (Emgality)</td>
<td>11/2019</td>
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<tr>
<td>Criteria update: Transition from criteria to policy and compilation of all injectable CGRP therapies into one policy. Updated Aimovig quantity limit to 30 days vs 28 to align with other agents. Added comment that these therapies will not be used in combination with one another, clarified prophylactic requirement for migraine indication, reworded renewal criteria. Added Emgality new indication of cluster headache.</td>
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<td>01/2019</td>
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<td>Criteria update: Changed onabotulinum toxin requirement to three months versus previous four months of washout. Updated renewal questions to specify a reduction in monthly migraine days by two.</td>
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<td>Criteria created</td>
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Policy Type: PA/SP Pharmacy Coverage Policy: UMP124

Description
Epoetin alfa (Retacrit, Procrit, Epogen) is a glycoprotein that stimulates red blood cell production; whereas, darbepoetin alfa (Aranesp) stimulates erythropoiesis by the same mechanism as endogenous erythropoietin.

Length of Authorization

Initial and Renewal:
- Epoetin alfa (Procrit, Epogen):
  - Chronic kidney disease with or without dialysis – Three months
  - Cancer chemotherapy – 12 months
  - Anemia due to zidovudine therapy – 12 months
  - Allogeneic blood transfusion in surgery patients – 14-days

- Darbepoetin alfa (Aranesp):
  - Chronic kidney disease with or without dialysis – Three months
  - Cancer chemotherapy – 12 months

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>darbepoetin alfa (Aranesp)</td>
<td>25 mcg/mL vial</td>
<td>Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy</td>
<td>4 vials/syringes per 30 days</td>
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<td>60 mcg/mL vial</td>
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<td>150 mcg/mL vial</td>
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<td>200 mcg/0.75 mL vial</td>
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<td>300 mcg/mL vial</td>
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<td></td>
<td>10 mcg/0.4 mL syringe</td>
<td>Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy</td>
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<td>25 mcg/0.42 mL syringe</td>
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<td>500 mcg/mL syringe</td>
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<td>epoetin alfa (Retacrit)</td>
<td>2000 units/mL vial</td>
<td>Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy; Anemia due to</td>
<td>2,000U, 3,000U, 4,000U and 10,000U vials: 12 vials per 30 days</td>
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<td>3000 units/mL vial</td>
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<tr>
<td></td>
<td>10000 units/mL vial</td>
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<table>
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<tr>
<th>Epogen alfa (Procrit)</th>
<th>40000 units/mL vial</th>
<th>zidovudine therapy; Allogeneic blood transfusion</th>
<th>20,000U and 40,000U vials: 4 vials per 30 days</th>
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<tr>
<td></td>
<td>2000 units/mL vial</td>
<td>Chronic Kidney Disease With or Without Dialysis; Cancer chemotherapy; Anemia due to zidovudine therapy; Allogeneic blood transfusion</td>
<td>2,000U, 3,000U, 4,000U and 10,000U vials: 12 vials per 30 days</td>
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<td>3000 units/mL vial</td>
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<td>20,000U and 40,000U vials: 4 vials per 30 days</td>
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<td>20000 units/2 mL vial</td>
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**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 $\geq 100$ ng/mL (mcg/L) and transferrin saturation (TSAT) $\geq 20\%$ measured within the previous 3 months; **AND**

III. Documentation of continued need for therapy indicated by Hemoglobin (Hb) and/or Hematocrit (Hct) as follows:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Hb and/or Hct Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia secondary to myelodysplastic syndrome (MDS)</td>
<td>Hemoglobin (Hb) $&lt;12$ g/dL and/or Hematocrit (Hct) $&lt;36%$</td>
</tr>
<tr>
<td>Anemia secondary to myeloproliferative neoplasms (MF, post-PV myelofibrosis, post-ET myelofibrosis)</td>
<td>Hemoglobin (Hb) $&lt;10$ g/dL and/or Hematocrit (Hct) $&lt;30%$</td>
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<tr>
<td>Reduction of allogeneic blood transfusions in elective, non-cardiac, non-vascular surgery</td>
<td>Hemoglobin (Hb) between $10$ g/dL and $13$ g/dL and/or Hematocrit (Hct) between $30%$ and $39%$</td>
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<tr>
<td>Anemia secondary to chemotherapy treatment</td>
<td>Hemoglobin (Hb) $&lt;10$ g/dL and/or Hematocrit (Hct) $&lt;30%$</td>
</tr>
<tr>
<td>Anemia secondary to zidovudine treated, HIV-infected patients</td>
<td>Hemoglobin (Hb) $&lt;12$ g/dL and/or Hematocrit (Hct) $&lt;36%$</td>
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<tr>
<td>Anemia secondary to chronic kidney disease</td>
<td><strong>Pediatric patients:</strong> Hemoglobin (Hb) $&lt;12$ g/dL and/or Hematocrit (Hct) $&lt;36%$; <strong>Adults:</strong> Hemoglobin (Hb) $&lt;11$ g/dL and/or Hematocrit (Hct) $&lt;33%$</td>
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<tr>
<td>All other indications</td>
<td>Hemoglobin (Hb) $&lt;11$ g/dL and/or Hematocrit (Hct) $&lt;33%$</td>
</tr>
</tbody>
</table>

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated renewal section criteria point III to read as “Documentation of continued need for therapy indicated by Hemoglobin (Hb) and/or Hematocrit (Hct) as follows:”</td>
<td>04/2020</td>
</tr>
<tr>
<td>• Transitioned to policy format</td>
<td></td>
</tr>
<tr>
<td>• Added language regarding preferred product, Retacrit and removal of PA requirement</td>
<td></td>
</tr>
<tr>
<td>• Aligned criteria with medical benefit for consistency across benefits, which included clarifying initial requirements (e.g. labs obtained within 30 days, adequate iron stores, Hg/Hct levels)</td>
<td>12/2019</td>
</tr>
<tr>
<td>• Added coverage criteria for anemia associated with rheumatoid arthritis, anemia secondary to MDS, and anemia secondary to myelofibrosis</td>
<td></td>
</tr>
<tr>
<td>• Added specific renewal criteria</td>
<td></td>
</tr>
</tbody>
</table>

Previous reviews

10/2018, 11/2012, 08/2012

Policy created

06/2011
Policy Type: PA/SP

Pharmacy Coverage Policy: UMP026

Description
Esketamine (Spravato) is an intranasal N-methyl-D-aspartate (NMDA) receptor antagonist. The mechanism by which esketamine (Spravato) exerts its antidepressant effect is unknown.

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

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>esketamine (Spravato)</td>
<td>56 mg dose kit</td>
<td>Treatment resistant depression (TRD) in conjunction with an oral antidepressant</td>
<td>Initial (two months): PA #1‡: 56 mg – 2 devices per 3 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PA #2: 35 devices per 56 days (to allow for 56mg or 84mg)</td>
</tr>
<tr>
<td></td>
<td>84 mg dose kit</td>
<td></td>
<td>Renewal*: 6 devices per 28 days (to allow for 56mg or 84mg at bi-weekly dosing)</td>
</tr>
</tbody>
</table>

‡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. 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. Treatment with ALL of the following has been ineffective, contraindicated, or not tolerated:
   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 two antidepressants from 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
   v. Electroconvulsive therapy (ECT) or repetitive transcranial magnetic stimulation (rTMS) or documentation of contraindication to BOTH; AND
3. The member does not have a contraindication to and has not previously failed ketamine; AND
4. Documentation of ongoing use of antidepressant to be used concurrently with esketamine (Spravato); AND
5. 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)].

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. Major Depressive Disorder symptoms, including suicidal ideation in patients who are at imminent risk for suicide (active suicidal ideation with intent)
   B. Pain management
   C. 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 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). They are not currently being studied for the treatment with esketamine (Spravato). The known adverse events include dissociative or perceptual changes (including distortion of time, space and illusions), 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. 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.
VI. 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.

VII. 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.

VIII. 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.

IX. 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.

X. 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.

XI. 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.

XII. 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.

XIII. 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.

XIV. 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.

XV. 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; high scores are associated with significant functional impairment. Sensitivity is 83% and specificity 69%.

XVI. 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. Major Depressive Disorder symptoms, including suicidal ideation in patients who are at imminent risk for suicide (active suicidal ideation with intent)
   A. A proof-of-concept study was conducted to explore the hypothesis that standard-of-care treatment plus intranasal esketamine would rapidly reduce depressive symptoms, including suicidality, among individuals with major depression who were assessed to be at imminent risk for suicide compared to placebo. The findings from this trial led to follow up trials ASPIRE I & II, which evaluated reduction in depressive symptoms at 24 hours after the first dose of esketamine (Spravato) in patients who were admitted for acute psychiatric hospitalization due to their suicide risk. Trial data has not yet been published and thus not commercially available.
   B. There is insufficient safety and efficacy data to support the use of esketamine (Spravato) in any indication other than treatment resistant depression (TRD) in conjunction with an oral antidepressant.

II. 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**

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

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

<table>
<thead>
<tr>
<th>Selective Serotonin Reuptake Inhibitors</th>
<th>Serotonin and Norepinephrine Reuptake Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• paroxetine</td>
<td>• sertraline</td>
</tr>
<tr>
<td>• fluvoxamine</td>
<td>• fluoxetine</td>
</tr>
<tr>
<td>• escitalopram</td>
<td>• citalopram</td>
</tr>
<tr>
<td>• duloxetine</td>
<td>• milnacipran</td>
</tr>
<tr>
<td>• venlafaxine</td>
<td>• levomilnacipran</td>
</tr>
<tr>
<td>• desvenlafaxine</td>
<td></td>
</tr>
</tbody>
</table>

| Tricyclic antidepressant               |                                                  |
| • amitriptyline                        |                                                  |
| • clomipram                             |                                                  |
| • nortriptyline                         |                                                  |

| Other                                   |                                                  |
| • bupropion                             | • vilazodone                                      |
| • mirtazapine                           | • vortioxetine                                     |
|                                         | • nefazodone                                      |

**References**


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Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Added major depressive disorder (MDD) symptoms, including suicidal ideation in patients who are at imminent risk for suicide as an investigational indication</td>
<td>03/2020</td>
</tr>
<tr>
<td>• Added criteria:</td>
<td></td>
</tr>
<tr>
<td>o Documentation of improvement from baseline assessment by 50% or more, indicating clinical benefit for treatment resistant depression or documentation attesting member is in remission (MADRS total score ≤12, HRSD or HAM-D score less than 10, PHQ-9 score less than 5 or SDS score of less than 6 at day 28);</td>
<td></td>
</tr>
<tr>
<td>o The member does not have a contraindication to and has not previously failed ketamine treatment in conjunction with antidepressant treatment [e.g. cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT), problem-solving therapy (PST) etc.] and ECT (Electroconvulsive therapy) or repetitive transcranial magnetic stimulation (rTMS) unless all are contraindicated has been ineffective, contraindicated, or not tolerated</td>
<td></td>
</tr>
<tr>
<td>o Diagnoses of major depressive disorder (MDD) was made following Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria and member is experiencing a persistent MDD episode (duration greater than or equal to two years) or member is experiencing recurrent MDD (an interval of at least two consecutive months between separate episodes during which criteria are not met for a major depressive episode)</td>
<td></td>
</tr>
</tbody>
</table>
- 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
- Policy effective: 05/2019
- Policy created: 03/2019

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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/northern acet, Fyavolv, Jinteli, Lopreeza, Mimvey, Mimivey Lo, or norethindrone ac-eth estradiol has been ineffective, contraindicated, or not tolerated.
everolimus (Afinitor®, Afinitor Disperz®)
UMP POLICY

Policy Type: PA/SP
Pharmacy Coverage Policy: UMP125

Split Fill Management*

Description
Everolimus (Afinitor, Afinitor Disperz) is an orally administered mammalian target of rapamycin (mTOR) inhibitor to reduce cell proliferation, angiogenesis, and glucose uptake.

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

Quantity Limits

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

Washington State Rx Services is administered by

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October 01, 2020
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

III. Brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg is requested; **AND**

1. 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 had treatment failure with sunitinib (Sutent) and/or sorafenib (Nexavar); **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. Brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg is requested;
         **AND**
         i. 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. Brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg is requested; **AND**
      a. The member has a contraindication to generic everolimus [Note: everolimus (Afinitor Disperz) is not FDA-approved in this setting]; **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 (i.e., 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. Brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg is requested; **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. Brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg is requested; **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. Brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg is requested; **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. The request is for everolimus (Afinitor) 10 mg; **OR**

Washington State Rx Services is administered by **Moda Health**

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

October 01, 2020
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

ii. The request is for generic everolimus 2.5 mg, 5 mg, or 7.5 mg; OR
iii. Brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg is requested; 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. Brand everolimus (Afinitor) 2.5 mg, 5 mg, or 7.5 mg is requested; 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. 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) has been evaluated in combination with exemestane for HR+, HER2-, advanced or metastatic breast cancer; however, it has not been sufficiently evaluated as part of a combination regimen for the remaining indications. In clinical trials, subjects had previously progressed on or after an aromatase inhibitor, 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.

III. 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 and in comparison to placebo. Overall survival was not statistically different between the treatment arms.

IV. Everolimus (Afinitor) has been evaluated for safety and efficacy in renal cell carcinoma in those that have previously received sunitinib (Sutent), sorafenib (Nexavar), or both sequentially. Subjects may also have had bevacizumab (Avastin), interleukin 2, or interferon alpha. Progression-free survival was shown to be statistically significant in favor of everolimus
(Afinitor); however, OS was not statistically different compared to placebo. Results may have been confounded by high rates of crossover from placebo to active therapy (80%).

V. Everolimus (Afinitor) was evaluated for safety and efficacy in renal angiomyolipomas – tuberous sclerosis complex associated. Response rate was statistically significant in favor of everolimus (Afinitor), as well as the time to progression compared to placebo.

VI. 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).

VII. 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.

VIII. Everolimus is the AB-rated generic of everolimus (Afinitor) as of December 2019, the 2.5 mg, 5 mg, and 7.5 mg strengths had generic availability. Medical necessity for brand will be indicated by a contraindication to generic. Intolerance to the generic is a likely indicator of intolerance to brand, given the therapeutic equivalence.

Investigational or Not Medically Necessary Uses

I. Carcinoid tumor
   A. Everolimus (Afinitor) was evaluated in a clinical trial for safety and efficacy for carcinoid tumor. The primary efficacy outcome was not reached, and overall survival outcomes favored placebo. At this time efficacy of everolimus (Afinitor) in this setting is not known to be clinically beneficial.

II. Everolimus (Afinitor, Afinitor Disperz) has not been sufficiently evaluated for safety and/or efficacy, and/or is in clinical trials for the following indications:
   A. Graft-versus-host disease
   B. Ependymoma
   C. Hodgkin Lymphoma or Non-Hodgkin Lymphoma
   D. Central nervous system cancers
   E. Kaposi’s sarcoma
   F. Thymoma and thymic carcinoma
   G. Endometrial, ovarian, uterine cancers
   H. Prostate cancer
   I. Gastroesophageal carcinomas
   J. Waldenstrom macroglobulinemia

* The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>March 2012</th>
</tr>
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<tbody>
<tr>
<td>Date Effective</td>
<td>May 2012</td>
</tr>
<tr>
<td>Last Updated</td>
<td>January 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>05/2012, 05/2018, 12/2019, 01/2020</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic everolimus 2.5 mg, 5 mg, and 7.5 mg added to the policy, with brand coverage only if medical necessity established for brand over generic.</td>
<td>01/2020</td>
</tr>
<tr>
<td>Prior authorization criteria transitioned to policy format, specialist providers updated to include neurologist, Addition of trial of conventional antiepileptic therapies prior to payment consideration for everolimus (Afinitor Disperz), addition of age requirement for everolimus (Afinitor), updated QLL for everolimus (Afinitor Disperz) to be calculated upon clinical review.</td>
<td>12/2019</td>
</tr>
<tr>
<td>Afinitor Disperz with indications added to criteria, formatting update and quantity limits changed to mirror available package sizes.</td>
<td>05/2018</td>
</tr>
</tbody>
</table>
Extended Half-Life Factor IX Products – Hemophilia B
UMP POLICY

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprolix, coagulation factor IX (recombinant, Fc fusion protein)</td>
<td>250, 500, 1000, 2000, 3000, 4000 IU</td>
<td><strong>On-demand Treatment</strong>: Up to 100 IU/dL for the first dose, then again every 6 to 10 hours for another dose. Dosing is then every 24 hours for three days, then every 48 hours until healing is achieved</td>
<td><strong>On-demand Treatment</strong>: Up to the number of doses requested every 28 days</td>
</tr>
</tbody>
</table>
| | | **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 | **Routine Prophylaxis**:  
  - ≥12 years: Up to 315 IU/kg every 28 days  
  - <12 years: Up to 255 IU/kg every 28 days |
| | | **Perioperative Management**:  
  - **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 | **Perioperative Management**: Up to the number of doses requested for 28 days |
### Idelvion, coagulation factor IX (recombinant, albumin fusion protein)

<table>
<thead>
<tr>
<th>Dosage (IU)</th>
<th>On-demand Treatment*</th>
<th>Routine Prophylaxis:</th>
</tr>
</thead>
</table>
| 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 | **≥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

<table>
<thead>
<tr>
<th>On-demand Treatment: Up to the number of doses requested every 28 days</th>
<th>Routine Prophylaxis:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≥12 years</strong>: Up to 170 IU/kg every 28 days</td>
<td><strong>&lt;12 years</strong>: Up to 230 IU/kg every 28 days</td>
</tr>
</tbody>
</table>

### Rebinyn, coagulation factor IX (recombinant, GlycoPEGylated)

<table>
<thead>
<tr>
<th>Dosage (IU)</th>
<th>On-demand Treatment: Up to 80 IU/kg for the initial dose. Additional doses of 40 IU/kg can be given.</th>
<th>Perioperative Management:</th>
</tr>
</thead>
</table>
| 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. | **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. |

<table>
<thead>
<tr>
<th>On-demand Treatment: Up to the number of doses requested every 28 days</th>
<th>Perioperative Management: Up to the number of doses requested for 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On-demand Treatment</strong>: Up to the number of doses requested every 28 days</td>
<td><strong>Perioperative Management</strong>: Up to the number of doses requested for 28 days</td>
</tr>
</tbody>
</table>

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*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). 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

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October 01, 2020
Supporting Evidence

I. Hemophilia B (factor IX deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. The availability of factor replacement products has dramatically improved care for those with hemophilia B.

II. There are varying severities of hemophilia B depending on the level of factor produced by the patient. Hemophilia B is divided into the following categories based on severity:
   i. **Severe**: <1% factor activity (<0.01 IU/mL)
   ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
   iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)

III. There are three general approaches to bleeding management in those with hemophilia B:
   - Episodic (“on demand”) treatment that is given at the time of clinically evident bleeding
   - Perioperative management of bleeding for those undergoing elective surgery/procedures
   - Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia B is to replace the deficient coagulation factor either through episodic (“on demand”) treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor IX products are the treatment of choice for hemophilia B as recommended by The National Hemophilia Foundation’s Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia B. Therapy should be initiated early with the goal of keeping the trough factor IX level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. The safety and efficacy of the extended half-life products were established based on open-label, non-randomized trials. Alprolix and Idelvion demonstrated effectiveness in reducing annualized bleeding rates when used prophylactically compared to on-demand treatment. Rebinyn has been shown to stop or prevent bleeding in the on-demand and perioperative settings.

VI. Extended half-life factor IX products were developed to extend the half-life and allow for longer infusion intervals. The majority of published clinical trial evidence evaluating extended half-life products have included previously treated patients with a minimum of 50 exposure days and no history of inhibitors.

VII. There is no evidence that extended half-life factor replacement products are safer or more effective than standard half-life products. There are no head-to-head trials comparing extended half-life products and standard half-life products to definitively establish superior safety or efficacy.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of extended half-life factor IX products in any other condition.

References
1. Alprolix® [Prescribing Information]. Waltham, MA: Bioverativ; July 2019
2. Idelvion® [Prescribing Information]. Kankakee, IL: CSL Behring; May 2018

Policy Implementation/Update:

<table>
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<tr>
<th>Date Created</th>
<th>August 2019</th>
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<tbody>
<tr>
<td>Date Effective</td>
<td>August 2019</td>
</tr>
<tr>
<td>Last Updated</td>
<td>August 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>08/2019</td>
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<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>New policy created for extended half-life factor products</td>
<td>08/2019</td>
</tr>
</tbody>
</table>
### Policy Type: PA/SP

**Pharmacy Coverage Policy: UMP029**

#### Description
Adynovate, Eloctate, Esperoct and Jivi are extended half-life factor VIII products for the treatment and prevention of bleeding in patients with hemophilia A.

#### Length of Authorization
- **Initial:** 6 months (for on-demand and prophylaxis); 1 month (for perioperative)
- **Renewal:** 12 months (for prophylaxis); 6 months (for on-demand)

#### Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adynovate, antihemophilic factor (recombinant), PEGylated</td>
<td>250, 500, 750, 1000, 1500, 2000, 3000 IU</td>
<td><strong>On-demand Treatment:</strong> Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved&lt;br&gt;&lt;br&gt;<strong>Routine Prophylaxis:</strong>&lt;br&gt;• ≥12 years: Up to 50 IU/kg two times per week&lt;br&gt;• &lt;12 years: 55 IU/kg two times per week with a maximum of 70 IU/kg&lt;br&gt;&lt;br&gt;<strong>Perioperative Management:</strong>&lt;br&gt;• <em>Minor</em> (e.g. tooth extraction): Up to 50 IU/kg within one hour before surgery; Repeat after 24 hours as needed until bleeding is resolved&lt;br&gt;• <em>Major</em> (e.g. intracranial, intra-abdominal, or intrathoracic, or joint-replacement): Up to 60 IU/kg within one hour before operation; Repeat every 8-24 hours (6 to 24 hours for patients &lt;12 years of age) until adequate round healing</td>
<td><strong>On-demand Treatment:</strong> Up to the number of doses requested every 28 days&lt;br&gt;&lt;br&gt;<strong>Routine Prophylaxis:</strong>&lt;br&gt;• ≥12 years: Up to 420 IU/kg every 28 days&lt;br&gt;• &lt;12 years: Up to 590 IU/kg every 28 days&lt;br&gt;&lt;br&gt;<strong>Perioperative Management:</strong>&lt;br&gt;Up to the number of doses requested for 28 days</td>
</tr>
<tr>
<td>Drug</td>
<td>On-demand Treatment</td>
<td>Routine Prophylaxis</td>
<td>Perioperative Management</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>Eloctate</strong>, antihemophilic factor (recombinant), Fc fusion protein</td>
<td>Up to 50 IU/kg every 12 to 24 hours (every 8 to 24 hours in patients &lt;6 years of age) until bleeding is resolved</td>
<td>≥6 years: Up to 65 IU/kg every three to five days&lt;br&gt; &lt;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</td>
<td><strong>Minor</strong> (e.g. tooth extraction): Up to 40 IU/kg every 24 hours (every 12-24 hours for patients &lt;6 years of age) for at least 1 day until healing is achieved&lt;br&gt; <strong>Major</strong> (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 &lt;6 years of age) and then every 24 hours until adequate wound healing (at least 7 days)</td>
</tr>
<tr>
<td><strong>Esperoct</strong>, antihemophilic factor (recombinant), glycopegylated</td>
<td>Up to the number of doses requested every 28 days</td>
<td>≥6 years: Up to 820 IU/kg every 28 days&lt;br&gt; &lt;6 years: Up to 1,010 IU/kg every 28 days</td>
<td><strong>Minor and Major surgery</strong>: Up to 50 IU/kg for those ≥12 years of age and up to 65 IU/kg for those &lt;12 years of age&lt;br&gt; <strong>Minor and Major surgery</strong>: Up to 368 IU/kg every 28 days&lt;br&gt; <strong>Minor and Major surgery</strong>: Up to 546 IU/kg every 28 days</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Jivi, antihemophilic factor (recombinant), PEGylated</th>
<th>On-demand Treatment: Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>500, 1000, 2000, 3000 IU</td>
<td>Routine Prophylaxis:</td>
</tr>
<tr>
<td></td>
<td>• ≥12 years: Up to 40 IU/kg two times per week</td>
</tr>
<tr>
<td></td>
<td>• &lt;12 years: Not FDA approved</td>
</tr>
<tr>
<td></td>
<td>Perioperative Management:</td>
</tr>
<tr>
<td></td>
<td>• Minor (e.g. tooth extraction): Up to 30 IU/kg within every 24 hours for at least 1 day until healing as achieved</td>
</tr>
<tr>
<td></td>
<td>• 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</td>
</tr>
<tr>
<td></td>
<td>On-demand Treatment: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td></td>
<td>Routine Prophylaxis:</td>
</tr>
<tr>
<td></td>
<td>• ≥12 years: Up to 340 IU/kg every 28 days</td>
</tr>
<tr>
<td></td>
<td>• &lt;12 years: Not FDA approved</td>
</tr>
<tr>
<td></td>
<td>Perioperative Management: Up to the number of doses requested for 28 days</td>
</tr>
</tbody>
</table>

† Allows for +5% to account for assay and vial availability

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3. Prior treatment with a standard half-life factor VIII product administered at the FDA approved dose for at least 50 exposure days was ineffective for the treatment or prevention of bleeding episodes; OR
   i. There is clinical documentation that all available standard half-life factor VIII products are inappropriate; AND
4. Documentation that inhibitor testing has been performed within the last 12 months; AND
   i. if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; AND
5. If the request is for Jivi, the member is 12 years of age or older and has been previously treated with another factor VIII product

II. Extended half-life factor VIII products are considered investigational when used for all other conditions.

Renewal Evaluation

I. For on-demand treatment and routine prophylaxis:
   i. Documentation of clinical benefit, including decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline; AND
   ii. Documentation that inhibitor testing has been performed within the last 12 months; AND
      1. If inhibitor titers are high (≥5 Bethesda units), there is documented plan to address inhibitors; AND
   iii. For on-demand treatment only, the dose and frequency are not greater than the routine prophylactic dose outlined in the Quantity Limit Table above

Supporting Evidence

I. Hemophilia A (factor VIII deficiency) is an X-linked inherited coagulation factor deficiency that results in lifelong bleeding disorders. The availability of factor replacement products has dramatically improved care for those with hemophilia A.
II. There are varying severities of hemophilia A depending on the level of factor produced by the patient, these are divided into the following:
   i. Severe: <1% factor activity (<0.01 IU/mL)
   ii. Moderate: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
   iii. Mild: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)
III. There are three general approaches to bleeding management in those with hemophilia A:
   - Episodic (“on demand”) treatment that is given at the time of clinically evident bleeding
   - Perioperative management of bleeding for those undergoing elective surgery/procedures
   - Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)
II. The current standard of care for hemophilia A is to replace the deficient coagulation factor either through episodic (“on demand”) treatment given at the time of bleeding or through continuous prophylaxis to prevent bleeding. Recombinant factor VIII products are the treatment of choice for hemophilia A as recommended by The National Hemophilia Foundation’s Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia A. Therapy should be initiated early with the goal of keeping the trough factor VIII level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. The safety and efficacy of the extended half-life products were established based on open-label, non-randomized trials. All are effective for reduction in annualized bleeding rates when used prophylactically compared to on-demand treatment.

VI. Extended half-life factor VIII products were developed to extend the half-life and allow for longer infusion intervals. The majority of published clinical trial evidence evaluating extended half-life products have included previously treated patients with a minimum of 50 exposure days and no history of inhibitors.

VII. There is no evidence that extended half-life factor replacement products are safer or more efficacious than standard half-life products. However, there are no head-to-head trials comparing extended half-life products and standard half-life products to definitively establish superior safety or efficacy.

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
4. Eloctate® [Prescribing Information]. Waltham, MA: Bioverativ Therapeutics; December 2017
5. Jivi® [Prescribing Information]. Whippany, NJ: Bayer; August 2018
**Policy Implementation/Update:**

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<td>New policy created for extended half-life factor products</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit‡</th>
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<tbody>
<tr>
<td>Alphanate, antihemophilic factor/von Willebrand factor complex (human)</td>
<td>250, 500, 1000, 1500, 2000 IU FVIII</td>
<td>Control and prevention of bleeding – hemophilia A*: Up to 50 IU factor VIII/kg twice daily for at least three to five days. Following this, factor VIII levels should be maintained at 25 IU factor VIII/kg twice daily until healing has been achieved. Major hemorrhages may require treatment for up to ten days. Intracranial hemorrhages may require prophylaxis therapy for up to six months.</td>
<td>Control and prevention of bleeding in hemophilia A: Up to the number of doses requested every 28 days</td>
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<td>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</td>
<td>Perioperative management in hemophilia A: Up to the number of doses requested for 28 days</td>
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<tr>
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<td>Control and prevention of bleeding and perioperative management – vWD*: Pre-operative/pre-procedure dose:</td>
<td>Control and prevention of bleeding and perioperative management in vWD: Up to the number of doses requested for 28 days</td>
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<tr>
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<td>• Adults: Up to 60 IU VWF:RCo/kg body weight</td>
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<td>• Pediatrics: Up to 75 IU VWF:RCo/kg body weight</td>
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<td>Maintenance:</td>
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<td></td>
<td>• 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</td>
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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
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<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit¹</th>
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</table>
| Humate-P, antihemophilic factor/von Willebrand factor complex (human) | 600, 1200, 2400 IU vWF:RCo | **Control and prevention of bleeding – hemophilia A**:  
- Minor: Up to 15 IU factor VIII:C/kg to achieve a factor VIII:C plasma level of approximately 30% of normal. One infusion may be sufficient. If needed, half of the loading dose may be given one or twice daily for one to two days  
- Moderate: Up to 25 15 IU factor VIII:C/kg to achieve a factor VIII:C plasma level of approximately 50% of normal, followed by 15 IU factor VIII:C/kg every eight to 12 hours for the first one to two days to maintain the factor VIII:C plasma level at 30% of normal. Continue the same dose one or twice for up to seven days or until adequate wound healing is achieved  
- Major: Initially up to 50 IU factor VIII:C/kg, followed by up to 25 IU factor VIII:C/kg every eight hours to maintain the factor VIII:C plasma level at 80-100% of normal for seven days. Continue the same dose one or twice daily for another seven days to maintain the factor VIII:C level at 30-50% of normal  
**Control and prevention of bleeding – vWD**: Up to 80 IU vWF:RCo (corresponding to 17 to 33 IU factor VIII in Humate-P) per kg body weight every eight to 12 hours. Adjust as needed based on the extent and location of bleeding. Repeat doses as long as necessary.  
**Perioperative management – vWD**:  
- Loading: vWF:RCo target peak plasma level – 100 IU/dL; Target factor VIII:C activity – 80-100 IU/dL  
**Control and prevention of bleeding – 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  

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<tr>
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<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit‡</th>
</tr>
</thead>
</table>
|             |             | • Minor: vWF:RCo target peak plasma level – 50-60 IU/dL; Target factor VIII:C activity – 40-50 IU/dL  
• Emergency: vWF:RCo target peak plasma level – 100 IU/dL; Target factor VIII:C activity – 80-100 IU/dL. Administer a dose of 50-60 IU vWF:RCo/kg body weight | Maintenance: Initial maintenance dose should be half the loading dose, irrespective of additional dosing required to meet factor VIII:C targets. Subsequent doses should be based on the patient’s vWF:RCo and factor VIII levels |        |
| Wilate, von Willebrand factor/coagulation factor VIII complex (human) |             | Control of bleeding episodes – vWD⁶: 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)  
γ The ratio of VWF:RCo to factor VIII varies by lot, so with each new lot, check the IU vWF:RCo/Vial to ensure accurate dosing  
* One IU of factor VIII activity per kg body weight will increase the circulating factor VIII level by approximately 2 IU/dL  
⁺ Target peak plasma vWF:RCo level – baseline plasma vWF:RCo level) – body weight (kg)/in vivo recovery. If the in vivo recovery is not available, assume an in vivo recovery of 2 IU/dL per IU/kg and calculate the loading dose as follows: (100 – baseline plasma vWF:RCo) x body weight (kg)/2  
€ The ratio between vWF:RCo and factor VIII activities is approximately 1:1. The dosage should be adjusted according to the extent and location of the bleeding.

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October 01, 2020
Initial Evaluation

von Willebrand Disease

I. **Alphanate** or **Humate-P** may be considered medically necessary when the following criteria below are met:
   
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
   
   C. Use is planned for one of the following indications:
      
      1. Treatment of spontaneous and trauma-induced bleeding episodes; **OR**
      
      2. Used as surgical bleeding prophylaxis during major or minor procedures when desmopressin (DDAVP) is either ineffective or contraindicated; **AND**
      
      3. **Alphanate** will **not** be used for severe (type 3) vWD undergoing major surgery

II. **Wilate** may be considered medically necessary when the following criteria below are met:
   
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   
   B. A diagnosis of von Willebrand disease (vWD) has been confirmed by blood coagulation and von Willebrand factor testing; **AND**
   
   C. Use is planned for one of the following indications:
      
      1. Perioperative management of bleeding; **OR**
      
      2. For the treatment of spontaneous and trauma-induced bleeding episodes when one of the following is met:
         
         i. Member has severe vWD; **OR**
         
         ii. Member has mild or moderate vWD and the use of desmopressin (DDAVP) is known or suspected to be ineffective or contraindicated; **AND**
      
      D. **Wilate** will not be used for the routine prophylactic treatment of spontaneous bleeding episodes; **AND**
   
   E. Wilate is not being used for hemophilia A

Hemophilia A (congenital factor VIII deficiency)

I. **Alphanate** or **Humate-P** may be considered medically necessary when the following criteria below are met:
   
   A. Treatment is prescribed by or in consultation with a hematologist; **AND**
   
   B. A diagnosis of hemophilia A has been confirmed by blood coagulation testing; **AND**
   
   C. Use is planned for one of the following indications:
      
      1. On-demand treatment and control of bleeding episodes **AND** the number of factor VIII/VWF units requested does **not** exceed those outlined in the Quantity Limits table above for routine prophylaxis; **OR**
      
      2. Routine prophylaxis to reduce the frequency of bleeding episodes when one of the following is met:
         
         i. Member has severe hemophilia A (defined as factor VIII level of <1%); **OR**
         
         ii. Member has had more than one documented episode of spontaneous bleeding; **OR**
      
      3. Perioperative management of bleeding; **AND**
D. Documentation that inhibitor testing has been performed within the last 12 months AND if inhibitor titers are high (≥5 Bethesda units), there is a documented plan to address inhibitors; AND

E. Dose and frequency does not exceed those outlined in the Quantity Limit Table above, unless documented clinical reasoning for higher dosing and/or frequency is supported by a half-life study to determine the appropriate dose and dosing interval

II. Alphanate, Humate-P, and Wilate are considered investigational when used for any other condition.

Renewal Evaluation

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

Supporting Evidence

von Willebrand Disease

I. Von Willebrand disease (vWD) is the most common of the inherited bleeding disorders. Although vWD is common, only a fraction of patients seek medical attention due to bleeding symptoms due to the mild nature of the disease in many patients, and to the lack of bleeding challenges.

II. There are three types of inherited vWD:
   - Type 1 – The most common type that accounts for about 70% of cases. It reflects a quantitative deficiency of von Willebrand factor (vWF). The clinical presentation varies from mild to moderately severe.
   - Type 2 – Accounts for 25-30% of cases and is characterized by several qualitative abnormalities of vWF (e.g. altered size ratios or biologic properties).
   - Type 3 – The most severe type of disease with very low or undetectable levels of vWF. Patients typically present with severe bleeding involving both the skin and mucous membrane surfaces and soft tissues and joints. Replacement therapy with vWF is usually required.

III. Choice of therapy begins with an accurate and complete diagnosis of vWD, plus patient-specific factors must be taken to account (e.g. history of bleeding, response to prior therapies).

IV. A trial of desmopressin (DDAVP) should be considered in all patients with type 1 and most with type 2, but not in patients with type 3 vWD. Typically, minor bleeding episodes can be treated with DDAVP without further therapeutic intervention. Major surgery typically requires replacement with vWF. However, Alphanate is not indicated for patients with severe vWD undergoing major surgery.

V. Patients with type 3 vWD, those with more severe type 1, and many of those with certain subtypes of type 2 disease often require replacement therapy with a vWF-containing product to control bleeding. However, vWF is not generally given as long-term prophylaxis like is done in patients with hemophilia A.
VI. The safety and efficacy of factor VIII/vWF complex products were established based on open-label, non-randomized trails. All replacement are effective in restoring hemostasis.

Hemophilia A

I. Hemophilia A (factor VIII deficiency) is an X-linked inherited coagulation factor deficiency that results in a lifelong bleeding disorder. The availability of factor replacement products has dramatically improved care for those with hemophilia A.

II. There are varying severities of hemophilia A depending on the level of factor produced by the patient. Hemophilia A is divided into the following categories based on severity:

   i. **Severe**: <1% factor activity (<0.01 IU/mL)
   ii. **Moderate**: Factor activity level ≥ 1% of normal and ≤ 5% of normal (≥ 0.01 and ≤ 0.05 IU/mL)
   iii. **Mild**: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)

III. There are three general approaches to bleeding management in those with hemophilia A:

   i. Episodic (“on demand”) treatment that is given at the time of clinically evident bleeding
   ii. Perioperative management of bleeding for those undergoing elective surgery/procedures
   iii. Routine prophylaxis is administered in the absence of bleeding to reduce bleeding and long-term complications of bleeding (e.g. arthropathy)

II. The current standard of care for hemophilia A is to replace the deficient coagulation factor either through episodic (“on demand”) treatment given at the time of bleeding, or through continuous prophylaxis to prevent bleeding. Recombinant factor VIII products are the treatment of choice for hemophilia A as recommended by The National Hemophilia Foundation’s Medical and Scientific Advisory Council (MASAC).

III. MASAC recommends that prophylaxis be considered optimal therapy for individuals age one and older with severe hemophilia A. Therapy should be initiated early with the goal of keeping the trough factor VIII level above 1% between doses.

IV. For individuals who have had more than one bleeding episode (e.g. two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level.

V. The safety and efficacy of the standard half-life products were established based on open-label, non-randomized trails. All replacement products can produce satisfactory hemostasis.

Investigational or Not Medically Necessary Uses

There is no evidence to support the use of factor VIII/vWF complex products in any other condition.

References

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

Washington State Rx Services is administered by Moda Health

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

October 01, 2020


Policy Implementation/Update:

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<td>New policy created for factor VIII/vWF complex products</td>
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fedratinib (Inrebic®)
UMP POLICY

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

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<td>fedratinib</td>
<td>100 mg tablets</td>
<td>Myelofibrosis</td>
<td>120 tablets/30 days</td>
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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 investigational when used for all other conditions, including but not limited to:
   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

Policy Implementation/Update:

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Washington State Rx Services is administered by

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®)

UPM POLICY

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

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<tr>
<td></td>
<td>800 mcg sublingual tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td>fentanyl citrate</td>
<td>200 mcg lozenge handle</td>
<td>Chronic pain associated with cancer</td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td>(Actiq)</td>
<td>400 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>600 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>800 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>1200 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>1600 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td>fentanyl citrate</td>
<td>100 mcg buccal tablet</td>
<td>Chronic pain associated with cancer</td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td>(Fentora)</td>
<td>200 mcg buccal tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>400 mcg buccal tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>600 mcg buccal tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>800 mcg buccal tablet</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td>fentanyl citrate</td>
<td>100 mcg nasal spray</td>
<td>Chronic pain associated with cancer</td>
<td>15 bottles/30 days</td>
</tr>
<tr>
<td>(Lazanda)</td>
<td>400 mcg nasal spray</td>
<td></td>
<td>15 bottles/30 days</td>
</tr>
<tr>
<td>fentanyl citrate</td>
<td>100 mcg sublingual spray</td>
<td>Chronic pain associated with cancer</td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td>(Subsys)</td>
<td>200 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>400 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>600 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>800 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>1200 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td></td>
<td>1600 mcg sublingual spray</td>
<td></td>
<td>4 cartons/30 days</td>
</tr>
<tr>
<td>fentanyl citrate</td>
<td>200 mcg lozenge handle</td>
<td>Chronic pain associated with cancer</td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td>(fentanyl citrate)</td>
<td>400 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
<tr>
<td></td>
<td>600 mcg lozenge handle</td>
<td></td>
<td>120 lozenges/30 days</td>
</tr>
</tbody>
</table>
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

### Initial Evaluation

I. Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, fentanyl citrate) may be considered medically necessary when the following criteria are met:
   A. Member has a diagnosis of **chronic pain associated with cancer**; AND
   B. Member is enrolled into the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) program; AND
   C. Member is 18 years of age or older; OR
      1. If request is for fentanyl citrate (Actiq), member is 16 years of age or older; AND
   D. Medication is prescribed by, or in consultation with, an oncologist or pain specialist; AND
   E. Member is opioid tolerant; AND
   F. Member is **currently experiencing** breakthrough cancer pain, for which fentanyl citrate is being prescribed to treat; AND
   G. The provider has recorded baseline and ongoing assessments of measurable, objective pain scores and function scores. These should be tracked serially in order to demonstrate clinically meaningful improvements in pain and function; AND
   H. The patient has been screened for mental health disorders, substance use disorder, naloxone use; AND
   I. The provider has checked the Prescription Drug Monitoring Program (PDMP) for any other opioid use and concurrent use of benzodiazepines and other sedatives

II. Fentanyl Citrate (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, fentanyl citrate) is considered **not medically necessary** when criteria above are not met and/or when used for:
   A. Non-tolerant opioid members
   B. Any indication that is not for treatment of breakthrough pain in patients experiencing chronic pain associated with cancer

### Renewal Evaluation

I. See initial evaluation section.

### Supporting Evidence

I. Based off clinical trials, there is currently no evidence to support the use of fentanyl citrate (Abstral®, Fentora®, Lazanda®, Subsys®, fentanyl citrate) in any age group below 18 years of age, with the exception of fentanyl citrate (Actiq®, fentanyl citrate) which was studied in those aged 16 years and older.
II. Due to the FDA indication, Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS), and strict dosing guidelines, these agents are not to be prescribed without the consultation or direct supervision of a pain specialist or oncologist.

III. All fentanyl citrate products, and the parties involved in their use (i.e., outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors) are required to be enrolled into the TIRF REMS program, in accordance with FDA guidelines.

IV. The policy aligns with recommendations of the Centers for Disease Control, the Washington State Agency Medical Directors Group, and the Bree Collaborative around safe and appropriate opioid prescribing.

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

VI. This policy applies to all groups under UMP, including Public Employees Benefit Board (PEBB) and School Employees Benefits Board (SEBB).

Investigational or Not Medically Necessary Uses

I. Fentanyl citrate (Abstral) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraines dental pain, or use in the emergency department

II. Fentanyl citrate (Actiq)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraines and dental pain

III. Fentanyl citrate (Fentora)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain, including headache/migraine and dental pain

IV. Fentanyl citrate (Lazanda)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraine and dental pain, or in emergency department

V. Fentanyl citrate (Subsys)
   A. Opioid non-tolerant patients
   B. Management of acute or postoperative pain including headache/migraine and dental pain, or in emergency department

Appendix

I. Table 1: Product dosing schedule and conversion from lozenge (Actiq) to other formulation

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Titration Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>fentanyl citrate (Abstral)</td>
<td>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</td>
</tr>
</tbody>
</table>
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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.

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

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

**Start:** 100mcg, if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher.

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

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

For patients converting from ACTIQ doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg FENTORA tablet and should proceed using multiples of this tablet strength.

### fentanyl citrate (Lazanda)

**Start:** 100mcg (one spray in each nostril) if adequate pain control is seen with this dose within 30 minutes continue with this dose. If not seen, try administering another dose of 100mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher.

*Due to differences in pharmacokinetic properties and individual variability, do not switch patients on a mcg per mcg basis from any other fentanyl product to Lazanda as Lazanda is not equivalent with any other fentanyl product, nor is Lazanda a generic version of any other fentanyl product.*

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Titration Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mcg nasal spray</td>
<td>2 x 100 mcg spray (1 in each nostril)</td>
</tr>
<tr>
<td>400 mcg nasal spray</td>
<td>1 x 400 mcg</td>
</tr>
<tr>
<td>800 mcg nasal spray</td>
<td>2 x 400 mg (1 in each nostril)</td>
</tr>
</tbody>
</table>

---

Washington State Rx Services is administered by moda HEALTH

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

October 01, 2020
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.

---

**fentanyl citrate (Subsys)**

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

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

---

**Initial Dosing Recommendations for Patients on ACTIQ**

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

a. For patients converting from Actiq doses 400 mcg and below, titration should be initiated with 100 mcg SUBSYS and should proceed using multiples of this strength.
b. For patients converting from Actiq doses of 600 and 800 mcg, titration should be initiated with 200 mcg SUBSYS and should proceed using multiples of this strength.
c. For patients converting from Actiq doses of 1200 and 1600 mcg, titration should be initiated with 400 mcg SUBSYS and should proceed using multiples of this strength.

---

**Product Name**

<table>
<thead>
<tr>
<th>Fentanyl Citrate (Fentanyl Citrate)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start:</strong> 200 mcg 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 200 mcg a half hour after first dose, and if pain control is still not seen discontinue any additional doses for at least four hours and consider titrating higher.</td>
</tr>
<tr>
<td><em>Note: No more than six units is allowed to be dispensed at one time until maintenance dose is found.</em></td>
</tr>
</tbody>
</table>

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

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**References**

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Removed attestation criteria following UMP guidance, as cancer is exempt diagnosis for the attestation requirement. Per UMP guidance, left in baseline and ongoing pain assessments, mental health and substance abuse screening, and provider check of Prescription Drug Monitoring Program (PDMP) for any other opioid use and concurrent use of benzodiazepines and other sedatives.</td>
<td>06/2020</td>
</tr>
<tr>
<td>Converted to policy, added in REMS question, age limitation question, and clarified prescribing provider specialty needed for approval.</td>
<td>04/2020</td>
</tr>
<tr>
<td>Previous reviews</td>
<td>11/15/13, 12/28/17</td>
</tr>
<tr>
<td>Criteria created</td>
<td>12/2011</td>
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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

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neupogen (filgrastim)</td>
<td>• Bone marrow transplant</td>
<td>15 prefilled syringes or 15 vials per 30-day supply</td>
</tr>
<tr>
<td></td>
<td>• Peripheral progenitor cell (PBPC) mobilization and transplant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Prophylactic use in patients with non-myeloid malignancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Treatment of chemotherapy-induced febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Neutropenic complications from prior cycle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Acute myeloid leukemia (AML) patient following induction or consolidation chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bone marrow transplantation failure or engraftment delay</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Severe chronic neutropenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Myelodysplastic syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Exposure to myelosuppressive doses of radiation</td>
<td></td>
</tr>
<tr>
<td>Zarxio (filgrastim-sndz)*</td>
<td>300mcg/0.5mL; 480/0.8mL Syringe</td>
<td>15 prefilled syringes or 15 vials per 30-day supply</td>
</tr>
<tr>
<td>Nivestym (filgrastim-aafi)</td>
<td>300mcg/mL; 480mcg/1.6mL Vial;</td>
<td>15 prefilled syringes or 15 vials per 30-day supply</td>
</tr>
<tr>
<td></td>
<td>300mcg/0.5mL; 480/0.8mL Syringe</td>
<td></td>
</tr>
<tr>
<td>Granix (tbo-filgrastim)</td>
<td>300mcg/mL; 480mcg/1.6mL Vial;</td>
<td>15 prefilled syringes or 15 vials per 30-day supply</td>
</tr>
<tr>
<td></td>
<td>300mcg/0.5mL; 480/0.8mL Syringe</td>
<td></td>
</tr>
<tr>
<td>Leukine (sargramostim)</td>
<td>250mcg; 500mcg/mL vial</td>
<td>15 vials per 30-day supply</td>
</tr>
</tbody>
</table>

*No PA required*
Initial Evaluation

I. Products may be considered medically necessary when the following criteria below are met:

<table>
<thead>
<tr>
<th>Zarxio is the preferred short-acting G-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patients must have failed, have contraindication to, or intolerance of Zarxio prior to the consideration of any other short-acting G-CSF.</td>
</tr>
<tr>
<td>o There is no prior authorization required for Zarxio unless requesting above the quantity limit noted above.</td>
</tr>
</tbody>
</table>

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. tisagenlecleucel (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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>February 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>February 2017</td>
</tr>
<tr>
<td>Last Updated</td>
<td>December 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>12/28/2018, 10/15/2019, 12/2019</td>
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<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated quantity level limit to allow 15 doses per 30 day supply</td>
<td>12/2019</td>
</tr>
<tr>
<td>Policy title change, designate Zarxio as a preferred product, add “No PA Required” to Initial Evaluation Section 1 boxed information</td>
<td>10/2019</td>
</tr>
</tbody>
</table>
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added Nivestym, biosimilar to Neupogen</td>
<td>10/2018</td>
</tr>
<tr>
<td>Added Fulphila, biosimilar to Neulasta</td>
<td>07/2018</td>
</tr>
<tr>
<td>Criteria update. Zarxio is the preferred short-acting G-CSF</td>
<td>02/2017</td>
</tr>
<tr>
<td>Zarxio, Udenyca, Neulasta, Neulasta Onpro preferred GCSF</td>
<td>12/2018</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>gilteritinib (Xospata)</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg tablets</td>
<td>Relapse/Refractory FLT3 AML</td>
<td>90 tablets/30 days</td>
<td>204950</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Gilteritinib (Xospata) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Prescribed by, or in consultation with, an oncologist or hematologist; **AND**
   C. A diagnosis of *relapsed/refractory FLT3-mutated acute myeloid leukemia* and all of the following are met:
      1. Relapsed/refractory defined as those that fail to attain a complete remission (CR) with intensive induction chemotherapy; **AND**
      2. Xospata (gilteritinib) will be used as monotherapy; **AND**
      3. FLT3 mutation status has been detected by an FDA-approved test (LeukoStrat CDx FLT3 mutation Assay by Invivoscribe Technologies, Inc.)

II. Gilteritinib (Xospata) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Newly diagnosed AML
   B. AML in the absence of FLT3 mutation
   C. AML in combination with other therapies in the relapsed/refractory setting

Renewal Evaluation

I. Relapsed/refractory FLT3-mutated AML
   A. Clinical documentation of response to treatment, such as stabilization or improvement in disease; **AND**
   B. Absence of disease progression after six months; **AND**
   C. Absence of unacceptable toxicity from the medication; **AND**
   D. Gilteritinib (Xospata) continues to be used as monotherapy

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Supporting Evidence

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

II. Subjects included were adults with confirmed FLT3-mutated AML as detected by an FDA-approved test. Use of gilteritinib (Xospata) in assigned subjects was as monotherapy only. Currently, there are no literature available on safety and efficacy outside of this setting.

Investigational or Not Medically Necessary Uses

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

II. AML in the absence of FLT3 mutation
   A. Clinical trials have only evaluated gilteritinib (Xospata) in patients that have a confirmed FLT3 mutation by an FDA-approved test.

III. AML in combination with other therapies in the relapsed/refractory setting
   A. There is a lack of evidence for the safety and efficacy of gilteritinib (Xospata) outside of the monotherapy setting. Clinical trials evaluated monotherapy only.

References

4. ClinicalTrials.gov

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>January 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>February 2019</td>
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<tr>
<td>Last Updated</td>
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</tr>
<tr>
<td>Last Reviewed</td>
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Action and Summary of Changes

<table>
<thead>
<tr>
<th>Date</th>
</tr>
</thead>
</table>
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

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

Initial Evaluation
I. Glasdegib (Daurismo) may be considered medically necessary when the following criteria are met:
   A. Prescribed by an oncologist or hematologist; **AND**
   B. A diagnosis of newly-diagnosed acute myeloid leukemia (AML) when the following are met:
      1. Age 75 years and older **OR**
      2. Have comorbidities that preclude use of intensive induction chemotherapy such as:
         i. Baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2
         ii. Severe cardiac comorbidity (i.e. LEVF <45%)
         iii. Baseline Scr >1.3 (CrCl ≥30 to <45 mL/min) **AND**
      3. Does not have hepatic or severe renal impairment (CrCl <30 mL/min); **AND**
      4. Used in combination with low-dose cytarabine (LDAC)

II. Glasdegib (Daurismo) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Acute Myeloid Leukemia – Previously treated
   B. Monotherapy use or used in combination with azacitidine or decitabine

Renewal Evaluation
I. Clinical documentation of response to treatment, such as stabilization or improvement of disease; **AND**
II. Absence of unacceptable toxicity from the medication

Supporting Evidence

Washington State Rx Services is administered by

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
I. Glasdegib (Daurismo) is FDA-approved, in combination with LDAC, for the treatment of newly-diagnosed AML in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.

II. Patients included in the trial were 55 years and older and met one of the following: at least 75 years old, severe cardiac disease, baseline Eastern Cooperative Oncology Group performance stats (ECOG PS) of 2, or a baseline serum creatinine > 1.3 mg/dL. The study did not include patients with an ECOG PS of 3, severe renal, or hepatic impairment, all of which are comorbidities that would preclude use of intensive chemotherapy.

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

Investigational or Not Medically Necessary Uses

I. Acute Myeloid Leukemia – Previously treated
   A. Pivotal trials leading to FDA approval were specifically in the previously untreated setting. Use in the relapsed/refractory setting is not supported by clinical trials nor cited within NCCN AML guidelines.

II. Monotherapy use or used in combination with azacitidine or decitabine
   A. Monotherapy use or use in combination with azacitidine or decitabine is not supported within guidelines or clinical evidence. Trials are currently underway evaluating the use in combination with azacitidine or decitabine, data has not yet been published.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>January 2019</th>
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<tbody>
<tr>
<td>Date Effective</td>
<td>February 2019</td>
</tr>
<tr>
<td>Last Updated</td>
<td></td>
</tr>
<tr>
<td>Last Reviewed</td>
<td></td>
</tr>
<tr>
<td>Action and Summary of Changes</td>
<td>Date</td>
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<tr>
<td>-------------------------------</td>
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</tbody>
</table>

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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

<table>
<thead>
<tr>
<th>Glycerol phenylbutyrate (Ravicti)</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 g/mL (25 mL bottle)</td>
<td>Urea Cycle Disorder</td>
<td>500 mL (20 bottles)/30 days</td>
<td>177929</td>
</tr>
</tbody>
</table>

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 phenylbutyrate (Ravicti).

References


Policy Implementation/Update:

<table>
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<tr>
<th>Date Created</th>
<th>July 2013</th>
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<tbody>
<tr>
<td>Date Effective</td>
<td>August 2013</td>
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<tr>
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<td>January 2019</td>
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<td>Last Reviewed</td>
<td></td>
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</table>

**Action and Summary of Changes**

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.

<table>
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<th>Date</th>
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<tbody>
<tr>
<td>01/2019</td>
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</table>
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

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

Initial Evaluation
I. Glycopyrronium (Qbrexza) may be considered medically necessary when the following criteria below are met:
   A. Member is nine years of age or older; AND
   B. The medication is prescribed by or in consultation with a dermatologist; AND
   C. Member has a confirmed diagnosis of primary axillary hyperhidrosis; AND
   D. Member has a history of medical complications such as skin infections or significant functional impairments due to condition; OR
   E. Member has a significant impact to activities of daily living due to condition; AND
   F. Member has tried and failed or have a contraindication to both of the following:
      1. Over-the-counter topical antiperspirant therapy (e.g. Drysol Solution, Hypercare Solution, or Aluminum Chloride Hexahydrate 20% Solution); AND
      2. Oral anticholinergics (e.g. oxybutynin tablet, 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
Washington State Rx Services is administered by moda HEALTH
I. Glycopyrronium (Qbrexza) is the first topical anticholinergic agent FDA-approved for treatment of axillary hyperhidrosis. The drug was studied in two, phase III, randomized, double-blind, vehicle controlled, parallel group trials, ATMOS-1 (N=344) and ATMOS-2 (N=353) evaluating daily glycopyrronium (Qbrexza) application to each axilla over 4 weeks. ASDD responder rate at week 4 was significantly greater for glycopyrronium (Qbrexza) versus vehicle in both trials.
   - ATMOS-1: 52.8% vs 28.3%; \( P<0.001 \)
   - ATMOS-2: 66.1% vs 26.9%; \( P<0.001 \)

II. Safety and efficacy of glycopyrronium (Qbrexza) has been established in patients older than nine years of age.

III. Glycopyrronium (Qbrexza) is FDA approved in the setting of primary hyperhidrosis. Secondary causes of hyperhidrosis should be ruled out. Patients with generalized, secondary hyperhidrosis usually present as adults and report sweating that occurs both while awake and sleeping. Medications should be carefully reviewed, as many can cause generalized sweating.

IV. Topical antiperspirants offer a localized treatment approach with a favorable side effect profile compared to other therapies. Although glycopyrronium (Qbrexza) is a topical formulation, it carries a similar side effect profile to oral anticholinergics (e.g. oxybutynin).

References

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>October 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>November 2018</td>
</tr>
<tr>
<td>Last Updated</td>
<td>September 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>09/2019</td>
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<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transition from criteria to policy</td>
<td>09/2019</td>
</tr>
<tr>
<td>Criteria created</td>
<td>10/2018</td>
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</table>
**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**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>Duration of approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>naferlin (Synarel)</td>
<td>2 mg/mL nasal spray</td>
<td>Endometriosis</td>
<td>16 mL/30 days</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Central Precocious Puberty</td>
<td>40 mL/30 days</td>
<td>6 months</td>
</tr>
<tr>
<td>Leuprolide acetate (Lupron)</td>
<td>1 mg/0.2mL kit</td>
<td>Central Precocious Puberty</td>
<td>1 kit/14 days</td>
<td>6 months</td>
</tr>
<tr>
<td>Leuprolide acetate (Lupron Depot)</td>
<td>3.75 mg/syringe kit</td>
<td>Endometriosis, Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria</td>
<td>1 syringe kit/30 days</td>
<td>6 months for all indications EXCEPT - 3 months for uterine leiomyoma -2 months for Endometrial Thickness</td>
</tr>
<tr>
<td></td>
<td>7.5 mg/syringe kit</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/30 days</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>11.25 mg/syringe kit</td>
<td>Advanced Prostate Cancer, Advanced Breast Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria</td>
<td>1 syringe kit/90 days</td>
<td>6 months for all indications EXCEPT - 3 months for Uterine Leiomyoma -2 months for Endometrial Thickness</td>
</tr>
<tr>
<td></td>
<td>22.5 mg/syringe kit</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/90 days</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>30 mg/syringe kit</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/120 days</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>45 mg/syringe kit</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/180 days</td>
<td>6 months</td>
</tr>
<tr>
<td>Leuprolide acetate (Lupron Depot-Ped)</td>
<td>7.5 mg/syringe kit</td>
<td>Central Precocious Puberty</td>
<td>1 syringe kit/30 days</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>11.25 mg/syringe kit</td>
<td>Central Precocious Puberty</td>
<td>1 syringe kit/30 days OR 1 syringe kit/90 days</td>
<td>6 months</td>
</tr>
</tbody>
</table>

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October 01, 2020
<table>
<thead>
<tr>
<th>Leuprolide acetate (Eligard)</th>
<th>15 mg/syringe kit</th>
<th>Central Precocious Puberty</th>
<th>1 syringe kit/30 days</th>
<th>6 months</th>
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</thead>
<tbody>
<tr>
<td>30 mg/syringe kit</td>
<td>Central Precocious Puberty</td>
<td>1 syringe kit/90 days</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>7.5 mg/syringe kit</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/30 days</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>22.5 mg/syringe kit</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/90 days</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>30 mg/syringe kit</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/120 days</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>45 mg/syringe kit</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/180 days</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>Leuprolide-norethindrone (Lupaneta)</td>
<td>3.75-5 mg/syringe</td>
<td>Endometriosis</td>
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<tr>
<td>11.25-5 mg/syringe</td>
<td>Endometriosis</td>
<td>1 syringe kit/90 days</td>
<td>6 months</td>
<td></td>
</tr>
<tr>
<td>Renewal</td>
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<tr>
<td>naferlin (Synarel)</td>
<td>2 mg/mL nasal spray</td>
<td>Central Precocious Puberty</td>
<td>40 mL/30 days</td>
<td>6 months</td>
</tr>
<tr>
<td>Leuprolide acetate</td>
<td>1 mg/0.2mL kit (each kit contains 2.8 mL of leuprolide acetate and 14 disposable syringes)</td>
<td>Central Precocious Puberty</td>
<td>1 kit/14 days</td>
<td>6 months</td>
</tr>
<tr>
<td>Leuprolide acetate (Lupron Depot)</td>
<td>3.75 mg/syringe kit</td>
<td>Endometriosis, Advanced Breast Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria</td>
<td>1 syringe kit/30 days</td>
<td>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</td>
</tr>
<tr>
<td>7.5 mg/syringe kit</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/30 days</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>11.25 mg/syringe kit</td>
<td>Advanced Prostate Cancer, Endometrial Thickness, Uterine leiomyoma, Gender Dysphoria</td>
<td>1 syringe kit/90 days</td>
<td>12 months for Advanced Breast Cancer and Gender Dysphoria EXCEPT - 6 months for Endometriosis (MAX #1 renewal)</td>
<td></td>
</tr>
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<table>
<thead>
<tr>
<th>Drug</th>
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<th>Condition</th>
<th>Cycle Duration</th>
<th>Notes</th>
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</thead>
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<tr>
<td>Leuprolide acetate (Lupron Depot-Ped)</td>
<td>7.5 mg/syringe</td>
<td>Central Precocious Puberty</td>
<td>1 syringe kit/30 days</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>kit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.25 mg/syringe</td>
<td>Central Precocious Puberty</td>
<td>1 syringe kit/30 days OR 1 syringe kit/90 days</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>kit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 mg/syringe</td>
<td>Central Precocious Puberty</td>
<td>1 syringe kit/30 days</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>kit</td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>30 mg/syringe</td>
<td>Central Precocious Puberty</td>
<td>1 syringe kit/90 days</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>kit</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Leuprolide acetate (Eligard)</td>
<td>7.5 mg/syringe</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/30 days</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>kit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.5 mg/syringe</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/90 days</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>kit</td>
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<tr>
<td></td>
<td>30 mg/syringe</td>
<td>Advanced Prostate Cancer</td>
<td>1 syringe kit/120 days</td>
<td>12 months</td>
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<tr>
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<tr>
<td></td>
<td>45 mg/syringe</td>
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<td>Leuprolide-norethindrone (Lupaneta)</td>
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**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 **not medically necessary** when criteria above are not met and/or when used for:
   A. In vitro fertilization
   B. Premenstrual syndrome
Renewal Evaluation

I. Member 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 mcg twice daily.
followed by a second-look laparoscopy (n=28) or no initial surgical procedure with nafarelin (Synarel) 200 mcg twice daily followed by a second-look laparoscopy with appropriate surgery (n=25). There was no difference in efficacy. Additionally, per label 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 leiomyoma 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.

References

Policy Implementation/Update:

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<tr>
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**Action and Summary of Changes**

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Criteria transitioned into policy format. With the following updates made: added supporting evidence, added indications that are medically not necessary, added renewal criteria, limit renewal for endometriosis to a total duration of 12 months, limit initial approval for uterine leiomyoma to 3 months per FDA max, require bone mineral density evaluation upon renewal for the treatment of endometriosis, require concomitant iron therapy for uterine leiomyoma indication, updated Lupron-depot strength for advanced breast cancer, and no renewal for uterine leiomyoma and endometrial thickness.
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP126

Description
Somatropin and somatrem are purified polypeptide hormones of recombinant DNA origin. Somatropin is comprised of amino acids in a sequence identical to that of human growth hormone. Somatrem includes the addition of methionine, another amino acid, to an otherwise 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
  - AIDS wasting syndrome: three months only
  - Short bowel syndrome: 1 month only
  - All others: Six months
- Renewal: 12 months
  - AIDS wasting syndrome: three months only
  - Short bowel syndrome: no renewal allowed
  - All others: 12 months

Quantity limits

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| somatropin (Norditropin FlexPro) | 5 mg/1.5 mL pen injector | * Idiopathic short stature  
|                             | 10 mg/1.5 mL pen injector | * Noonan syndrome  
|                             | 15 mg/1.5 mL pen injector | * Prader-Willi syndrome  
|                             | 30 mg/3 mL pen injector | * Turner syndrome  
|                             |                       | * Growth failure in children  
|                             |                       | * Growth hormone deficiency, adults  
|                             |                       | * Idiopathic short stature  
| somatropin (Nutropin AQ)    | 5 mg/2 mL pen injector | * Growth failure associated with chronic renal insufficiency (CRI)  
|                             | 10 mg/2 mL pen injector | * Turner syndrome  
|                             | 20 mg/2 mL pen injector | * Growth failure in children  
|                             |                       | * Growth hormone deficiency, adults  
|                             |                       | * Idiopathic short stature  
| somatropin (Omnitrope)      | 5.8 mg vial           | * Prader-Willi syndrome  
|                             | 5 mg/1.5 mL cartridge | * Turner syndrome  
|                             | 10 mg/1.5 mL cartridge | * Growth failure in children  
|                             |                       | * Growth hormone deficiency, adults  
|                             |                       | * Idiopathic short stature  
| somatropin (Saizen)         | 5 mg vial             | * Growth failure in children  
|                             | 8.8 mg vial           | * Growth hormone deficiency, adults  
| somatropin (Saizen Click Easy) | 8.8 mg/1.5 mL cartridge | * Wasting or cachexia associated with HIV  
| somatropin (Saizenprep)     | 8.8 mg cartridge      | * Turner syndrome  
| somatropin (Serostim)       | 4 mg vial             | * Growth failure in children  
|                             | 5 mg vial             | * Growth hormone deficiency, adults  
|                             | 6 mg vial             | * Idiopathic short stature  
|                             |                       | * Short stature homeobox-containing gene (SHOX) deficiency  
| somatropin (Zomacton)       | 5 mg vial             | * Turner syndrome  
|                             | 10 mg vial            | * Growth failure in children  
|                             |                       | * Growth hormone deficiency, adults  
|                             |                       | * Idiopathic short stature  
| somatropin (Zorbtive)       | 8.8 mg vial           | * Short bowel syndrome  

*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.*
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**
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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 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:

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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.

a. Adult onset from one of the following: hypopituitarism due to pituitary disease, hypothalamic disease, pituitary surgery, cranial radiation therapy, or traumatic brain injury; AND
   i. A subnormal response (less than 10 ng/ml) to any TWO of the following provocative growth hormone (GH) stimulation tests:
      1. Arginine
      2. Clonidine
      3. Glucagon
      4. Insulin induced hypoglycemia
      5. L-dopa
      6. Propranolol; OR

b. Childhood-onset growth hormone deficiency; AND
   i. Serum insulin-like growth factor-1 (IGF-1) concentration lower than the age- and gender appropriate reference range; OR

c. Idiopathic GH deficiency diagnosis; AND
   i. Diagnosis been confirmed by BOTH of the following:
      1. A subnormal response (less than 10 ng/ml) to any TWO of the following provocative growth hormone (GH) stimulation tests:
         a. Arginine
         b. Clonidine
         c. Glucagon
         d. Insulin induced hypoglycemia
         e. L-dopa
         f. Propranolol; AND
      2. Serum insulin-like growth factor-1 (IGF-1) concentration lower than the age- and gender appropriate reference range
   ii. Treatment with Omnitrope has been ineffective, contraindicated, or not tolerated

II. Growth hormone is considered not medically necessary when used for all other conditions, including but not limited to:
   A. Idiopathic (i.e. of unknown origin) short stature, also called non-growth hormone deficient short stature in children
   B. Increased athletic performance in adults

III. Growth hormone is considered investigational when used for all other conditions, including but not limited to:
   A. Growth hormone insensitivity (Laron Syndrome)
   B. Constitutional growth delay
C. Children with growth failure caused by glucocorticoids  
D. Children who are not growth hormone deficient but have short stature associated with chronic disease  
E. Children with chromosomal and genetic disorders (except Turner’s and Prader Willi Syndromes) or familial short stature  
F. Russell Silver syndrome  
G. Altered body habitus or lipodystrophy associated with antiviral therapy  
H. Precocious puberty  
I. Obesity  
J. Cystic fibrosis  
K. Idiopathic dilated cardiomyopathy  
L. Juvenile idiopathic arthritis

Renewal Evaluation

I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; AND  
II. Member has received a previous prior authorization approval for this agent through this health plan; AND  
III. A diagnosis of one of the following:  
A. Children with 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); 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. 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 are somatropin and they are administered by subcutaneous injection and bioequivalent since they are the same chemical structure. Other than device and FDA approved indications, there is little to no differentiation of products. There are seven somatropin products that compete in the setting of GH deficiency and aside from innovative delivery devices, there is no clinical data to differentiate them.

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. As stated earlier 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 should not be used for growth promotion in pediatric patients with closed epiphyses.

VI. Zortrave 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.

VIII. Guidelines for Use of Growth Hormone in Clinical Practice: Patients with childhood-onset GH deficiency previously treated with GH replacement in childhood should be retested after final height is achieved and GH therapy discontinued for at least 1 month to ascertain their GH status before considering restarting GH therapy. Exceptions include those with known mutations, those with embryopathic/congenital defects, those with irreversible hypothalamic-pituitary structural lesions, and those with evidence of panhypopituitarism (at least 3 pituitary hormone deficiencies) and serum IGF-I levels below the age- and sex-appropriate reference range off GH therapy.

- For childhood GH treatment of conditions other than GHD, such as Turner’s syndrome and idiopathic short stature, there is no proven benefit to continuing GH treatment in adulthood; hence, there is no indication to retest these patients when final height is achieved.

IX. The Endocrine Society’s clinical guidelines now recommend GH for use in idiopathic adult GH deficiency although this diagnosis is rare. Significant false-positive error rates occur in response
to a single GH stimulation test, therefore use of two tests is recommended before making a
diagnosis. The presence of a low IGF-I also increases the likelihood that this diagnosis is correct.

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<td>Zorbtive</td>
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</table>

GHD = Growth Hormone Deficiency (Ch = Children, Ad = Adult)
TS = Turner Syndrome
ISS = Idiopathic Short Stature
SGA = Growth failure in children born Small for Gestational Age
PWS = Prader-Willi Syndrome in children
CKD = Growth failure due to chronic kidney disease
NS = Noonan Syndrome
SHOX = Short stature homeobox-containing gene deficiency
HIV = HIV-associated Wasting or Cachexia
SBS = Short Bowel Syndrome

Investigational or Not Medically Necessary Uses

I. Idiopathic short stature
   A. Growth hormone therapy for certain conditions may not be approved when 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

References

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

Policy Implementation/Update:

<table>
<thead>
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<th>Date</th>
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<tr>
<td>Date Created</td>
<td>September 2014</td>
</tr>
<tr>
<td>Date Effective</td>
<td>August 2014</td>
</tr>
<tr>
<td>Last Updated</td>
<td>November 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>03/2018, 11/2019</td>
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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
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.

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.

<table>
<thead>
<tr>
<th>Date</th>
<th>Notes</th>
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<tr>
<td>11/2019</td>
<td>Updated growth hormone stimulation requirements to align with guideline recommendations (Molitch 2011 and Grimberg 2016). Added requirement of treatment to be prescribed by specialist. Removed route for coverage in the setting of idiopathic short stature as growth hormone therapy for certain conditions may not be approved when growth hormone use is not expected to correct a significant functional deficit OR when reduced growth is not due to an underlying medical condition.</td>
</tr>
<tr>
<td>03/2018</td>
<td>Criteria update: updated criteria to new format, deleted question defining HIV wasting, added routing questions for growth failure in children born small for gestational age added clinical notes to questions.</td>
</tr>
</tbody>
</table>
**Hepatitis C**

**UMP POLICY**

**Policy Type: PA/SP**  
**Pharmacy Coverage Policy: UMP036**

**Description**
The listed treatments for Hepatitis C are for orally administered Direct-Acting Antiviral (DAA) therapies.

**Length of Authorization**
- Initial: 8-16 weeks based on liver status*
- Renewal: none

**Quantity limits**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit*</th>
</tr>
</thead>
<tbody>
<tr>
<td>glecaprevir/pibrentasvir (Mavyret)</td>
<td>100 mg/40 mg tablet</td>
<td>HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced</td>
<td>84 tablets/28 days</td>
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<tr>
<td>sofobuvir (Sovaldi)</td>
<td>150 mg oral pellets</td>
<td>HCV Genotype 2 or 3 Treatment naïve or experienced</td>
<td>28 pellets/28 days</td>
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<tr>
<td></td>
<td>200 mg oral pellets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mg oral tablet</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>400 mg oral tablet</td>
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<tr>
<td>ledipasvir/sofosbuvir (Harvoni)</td>
<td>45 mg /200 mg tablet</td>
<td>HCV Genotype 1, 4, 5, 6 Treatment naïve or experienced</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>90 mg /400 mg tablet</td>
<td>HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced</td>
<td></td>
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<tr>
<td>ledipasvir/sofosbuvir (authorized generic)</td>
<td>45 mg /200 mg tablet</td>
<td>HCV Genotype 1, 4, 5, 6 Treatment naïve or experienced</td>
<td>28 tablets/28 days</td>
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<tr>
<td></td>
<td>90 mg /400 mg tablet</td>
<td>HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced</td>
<td></td>
</tr>
<tr>
<td>velpatasvir/sofosbuvir (Epclusa)</td>
<td>100 mg/400 mg tablet</td>
<td>HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td>velpatasvir/sofosbuvir (authorized generic)</td>
<td>100 mg/400 mg tablet</td>
<td>HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td>daclatasvir (Daklinza)</td>
<td>30 mg, 60 mg, 90 mg tablet</td>
<td>HCV Genotype 1, 3</td>
<td>28 tablets/28 days</td>
</tr>
</tbody>
</table>

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October 01, 2020
<table>
<thead>
<tr>
<th>Treatment Name</th>
<th>Dosage</th>
<th>Genotype(s)</th>
<th>Duration</th>
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</thead>
<tbody>
<tr>
<td>elbasvir/grazoprevir (Zepatier)</td>
<td>50 mg /100 mg tablet</td>
<td>HCV Genotype 1, 4</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td>velpatasvir/sofosbuvir/voxilaprevir (Vosevi)</td>
<td>100 mg/400 mg/100 mg tablet</td>
<td>HCV Genotype 1, 2, 3, 4, 5, 6 Treatment experienced</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td>simeprevir (Olysio)</td>
<td>150 mg capsule</td>
<td>HCV Genotype 1 Treatment naïve or experienced</td>
<td>28 capsules/28 days</td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak)</td>
<td>12.5/75/50 mg oral tablet and dasabuvir 250 mg tablet</td>
<td>HCV Genotype 1a, 1b Treatment naïve or experienced</td>
<td>1 box/28 days</td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira XR)</td>
<td>12.5/75/50 mg oral tablet and dasabuvir 250 mg tablet</td>
<td>HCV Genotype 1a, 1b Treatment naïve or experienced</td>
<td>1 box/28 days</td>
</tr>
<tr>
<td>ombitasvir/paritaprevir/ritonavir (Technivie)</td>
<td>12.5/75/50 mg tablet</td>
<td>HCV Genotype 4</td>
<td>1 box/28 days</td>
</tr>
</tbody>
</table>

*See appendix for specific treatment durations

**Initial Evaluation**

I. Patient has confirmed diagnosis of Hepatitis C and a quantifiable HCV RNA test >15 IU/mL within the last 12 months.

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
   F. Documentation, if available, of presence or absence of resistant mutations in treatment experienced patients.

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

References

12. Guidance from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) Recommendations for Testing, Managing, and Treating hepatitis C. Available online at [link].
14. Center for Disease Control Website [link]. Accessed 8/17/16


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tbody>
<tr>
<td>Appendix updated to follow Mavyret label update indicating an 8 week treatment duration in treatment naive, compensated cirrhosis patients. Add newly available lower doses of Sovaldi and Harvoni.</td>
<td>10/2019</td>
</tr>
<tr>
<td>Updated to remove provider specialty and F0 requirements</td>
<td>06/2019</td>
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<tr>
<td>Updated preferred products to only include Mavyret, sofosbuvir/velpatasvir (authorized generic to Eclusa), and Vosevi.</td>
<td>04/2019</td>
</tr>
<tr>
<td>Previous reviews</td>
<td>02/2018, 11/2017, 06/2017, 09/2016, 08/2016,</td>
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</table>
Appendix:
Please note, Mavyret is the preferred agent for Uniform Medical Plan.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Regimen</th>
<th>Please select:</th>
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<tbody>
<tr>
<td><strong>Genotype 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment naïve + No cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment naïve + Cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>velpatasvir/sofosbuvir (authorized generic to Epclusa) x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced^ + No cirrhosis</td>
<td>Mavyret x 16 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced^ + Cirrhosis</td>
<td>Mavyret x 16 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced^ + No cirrhosis</td>
<td>Mavyret x 12 weeks</td>
<td>velpatasvir/sofosbuvir (authorized generic to Epclusa) x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced^ + Cirrhosis</td>
<td>Mavyret x 12 weeks</td>
<td>velpatasvir/sofosbuvir (authorized generic to Epclusa) x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced^ + No cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced^ + Cirrhosis</td>
<td>Mavyret x 12 weeks</td>
<td>velpatasvir/sofosbuvir (authorized generic to Epclusa) x 12 weeks</td>
</tr>
<tr>
<td>Genotype 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment naïve + No cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment naïve + Cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>velpatasvir/sofosbuvir (authorized generic to Epclusa) x 12 weeks</td>
</tr>
<tr>
<td>Treatment experienced^ + No cirrhosis</td>
<td>Vosevi x 12 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced^ + Cirrhosis</td>
<td>Vosevi x 12 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced</td>
<td>Other:</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Treatment experienced + No cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Treatment experienced + Cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Treatment experienced + No cirrhosis</td>
<td>Mavyret x 8 weeks</td>
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</tr>
<tr>
<td>Treatment experienced + Cirrhosis</td>
<td>Mavyret x 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Treatment experienced + No cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Treatment experienced + No cirrhosis</td>
<td>Vosevi x 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Treatment experienced + Cirrhosis</td>
<td>Vosevi x 12 weeks</td>
<td></td>
</tr>
<tr>
<td>Treatment experienced + No cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
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<tr>
<td>Treatment experienced + No cirrhosis</td>
<td>Mavyret x 16 weeks</td>
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</tr>
<tr>
<td>Treatment experienced + Cirrhosis</td>
<td>Mavyret x 16 weeks</td>
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<tr>
<td>Treatment experienced + No cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
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<tr>
<td>Treatment experienced + Cirrhosis</td>
<td>sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks</td>
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</tbody>
</table>

**Genotype 3**

| Treatment naïve + No cirrhosis | Mavyret x 8 weeks |
| Treatment naïve + Cirrhosis | Mavyret x 8 weeks |
| Treatment experienced + No cirrhosis | Vosevi x 12 weeks |
| Treatment experienced + cirrhosis | Vosevi x 12 weeks |
| Treatment experienced + No cirrhosis | sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks |
| Treatment experienced + cirrhosis | sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks |
| Treatment experienced + No cirrhosis | Mavyret x 16 weeks |
| Treatment experienced + Cirrhosis | Mavyret x 16 weeks |
| Treatment experienced + No cirrhosis | sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks |
| Treatment experienced + Cirrhosis | sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks |

**Genotype 4**

| Treatment naïve + No cirrhosis | Mavyret x 8 weeks |
| Treatment naïve + Cirrhosis | Mavyret x 8 weeks |
| Treatment experienced + No cirrhosis | Vosevi x 12 weeks |

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| Treatment experienced^ + cirrhosis | Vosevi x 12 weeks |
| Treatment experienced^ + No cirrhosis | sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks |
| Treatment experienced^ + Cirrhosis | sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks |
| Treatment experienced' + No cirrhosis | Mavyret x 8 weeks |
| Treatment experienced' + Cirrhosis | Mavyret x 12 weeks |

**Genotype 5**

| Treatment naïve + No cirrhosis | Mavyret x 8 weeks |
| Treatment naïve + Cirrhosis | Mavyret x 8 weeks |
| Treatment experienced^+ No cirrhosis | Vosevi x 12 weeks |
| Treatment experienced^ + cirrhosis | Vosevi x 12 weeks |
| Treatment experienced^ + No cirrhosis | sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks |
| Treatment experienced^ + Cirrhosis | sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks |
| Treatment experienced' + No cirrhosis | Mavyret x 8 weeks |
| Treatment experienced' + Cirrhosis | Mavyret x 12 weeks |

**Genotype 6**

<p>| Treatment naïve + No cirrhosis | Mavyret x 8 weeks |
| Treatment naïve + Cirrhosis | Mavyret x 8 weeks |
| Treatment experienced^+ No cirrhosis | Vosevi x 12 weeks |
| Treatment experienced^ + cirrhosis | Vosevi x 12 weeks |
| Treatment experienced^ + No cirrhosis | sofosbuvir/velpatasvir |</p>
<table>
<thead>
<tr>
<th>Treatment experienced + Cirrhosis</th>
<th>Mavyret x 12 weeks</th>
<th>Other:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(authorized generic to Epclusa) x 12 weeks</td>
<td>sofosbuvir/velpatasvir</td>
<td></td>
</tr>
<tr>
<td>Other:</td>
<td>sofosbuvir/velpatasvir</td>
<td></td>
</tr>
<tr>
<td>Treatment experienced + No cirrhosis</td>
<td>Mavyret x 8 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>Treatment experienced† + Cirrhosis</td>
<td>Mavyret x 12 weeks</td>
<td>Other:</td>
</tr>
<tr>
<td>(authorized generic to Epclusa) x 12 weeks</td>
<td>sofosbuvir/velpatasvir</td>
<td></td>
</tr>
</tbody>
</table>

^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

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP075

Description
C1 esterase inhibitor (Cinryze, Berinert, Haegarda, Ruconest), lanadelumab (Takhzyro), and icatibant (Firazyr) are injectable medications for the treatment of hereditary angioedema (HAE).

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

Quantity limits

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<th>Product Name</th>
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<th>Quantity Limit</th>
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<tr>
<td>C1 esterase inhibitor (Cinryze)</td>
<td>500 unit single use vial for IV administration</td>
<td>HAE prophylaxis</td>
<td>20 vials/30 days</td>
</tr>
<tr>
<td>C1 esterase inhibitor (Haegarda)</td>
<td>2000 unit single use vial for SQ administration</td>
<td>HAE prophylaxis</td>
<td>Weight based, refer to chart below</td>
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<tr>
<td></td>
<td>3000 unit single use vial for SQ administration</td>
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<tr>
<td>lanadelumab (Takhzyro)</td>
<td>300 mg/2 mL single dose vial for SQ administration</td>
<td></td>
<td>4 mL/28 days</td>
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<td>500 unit single use vial for IV administration</td>
<td>Treatment of acute HAE attacks</td>
<td>Weight based, refer to chart below</td>
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<tr>
<td>C1 esterase inhibitor (Ruconest)</td>
<td>2100 unit single use vial for IV administration</td>
<td></td>
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<tr>
<td>icatibant (Firazyr)</td>
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<td>9 syringes (36 mL)/30 days</td>
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<table>
<thead>
<tr>
<th>Medication</th>
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<th>Vial Configuration</th>
<th>Vials per Dose</th>
<th>Number of Vials per 30 days</th>
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<td>20-33</td>
<td>2000 unit</td>
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<td>8</td>
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<tr>
<td></td>
<td>34-50</td>
<td>3000 unit</td>
<td>1</td>
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<td></td>
<td>51-67</td>
<td>2000 unit</td>
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<td>134-150</td>
<td>3000 unit</td>
<td>3</td>
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<td>Berinert</td>
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<td>25 - 50 kg</td>
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<td>50 - 75 kg</td>
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<td>12</td>
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<td>75 - 100 kg</td>
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<td>100-125 kg</td>
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<td></td>
<td>125-150 kg</td>
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</tbody>
</table>
Initial Evaluation (All information must be supported by documentation and chart notes that have been reviewed by a Moda clinical pharmacist)

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, OR Takhzyro are requested; AND
            a. The member is not prescribed more than one agent FDA-approved for prophylaxis (e.g., Cinryze, Haegarda, Takhzyro); AND
            b. The member has a history of at least one of the following criteria for long-term 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 danazol, aminocaproic acid, or tranexamic acid, or has a contraindication to all; AND
            d. “On demand” therapy (e.g., Firazyr, Ruconest, Berinert) has been ineffective, contraindicated, or not tolerated; AND
            e. For Cinryze: the member is ≥ 6 years of age; OR
            f. For Takhzyro: The member is ≥ 12 years of age; OR
            g. For Haegarda: the member is ≥ 12 years of age; AND
               i. 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

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

a. Ruconest is requested; **AND**
b. Treatment with Berinert AND Firazyr 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, ecallantide (Kalbitor), etc.); **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 three months, to calculate appropriate dose); **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**

vii. For brand Firazyr: the member is ≥ 18 years of age; **AND**
   a. 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 (Berinert, Ruconest, icatibant (Firazyr), Kalbitor)
   B. Combination use of prophylactic therapies (Cinryze, Haegarda, Takhzyro)
   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 that have been reviewed by a Moda clinical pharmacist)

I. The medication is prescribed by, or in consultation with one of the following specialists: allergist, immunologist, dermatologist, hematologist, pulmonologist, medical geneticist; **AND**

II. The member continues to be evaluated for potentially treatable triggers of HAE attacks and is being managed to avoid triggers; **AND**

III. The member has been seen and evaluated for medication efficacy and safety in the past 12 months; **AND**

IV. 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**

V. The member has not been prescribed more than one medication FDA approved for HAE prophylaxis (Berinert, Ruconest, icatibant (Firazyr), etc.); **AND**

VI. Documentation of improvement in the number, severity, or duration of attacks, and the member has experienced functional improvement; **AND**
• **For brand Firazyr:** the member has tried and failed, not tolerated, or has contraindication to generic icatibant; **OR**

• **For Berinert and Haegarda:** documentation of current weight (within the last three months, to calculate appropriate dose); **OR**

• **For Takhzyro:** Documentation that 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.

**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. Other forms of HAE show normal complement lab measurements and prevalence of these types are rare. Clinical trials have 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 reduces the number of disabling attacks and medication requirement. Common triggers include stress, NSAIDS, ACE inhibitors, antibiotics, trauma, illness, dental work, hormonal fluctuations, food sensitivities, and potentially many other patient specific triggers. Additionally, allergic/anaphylactic reactions and adverse effects of these foods and medications shall 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 number of attacks, severity, comorbid conditions, emergency department visits, inadequate response or control using acute treatments, and/or where severe, debilitating, or laryngeal attacks are recurrent. Options include androgens (danazol), antifibrinolytics (aminocaproic acid, tranexamic acid), C1 esterase inhibitors (Cinryze, Haegarda) and kallikrein inhibitor (Takhzyro).

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.
Investigational or Not Medically Necessary Uses

I. Use of two or more therapies for the same indication (e.g., acute or prophylactic) has not been evaluated for safety and efficacy.

II. The medications listed in this policy have not been sufficiently evaluated for safety and efficacy outside of hereditary angioedema.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added age restriction to Takzyro of ≥ 12 years of age</td>
<td>03/2020</td>
</tr>
<tr>
<td>Policy created and criteria added to initial and renewal portions. Takzyro combined with other agents. Specification on inappropriateness of dual therapy use, medical necessity of therapy, and addition of generic icatibant to the policy and use required prior to brand payment consideration.</td>
<td>10/2019</td>
</tr>
<tr>
<td>Takhzyro criteria created for P&amp;T.</td>
<td>10/2018</td>
</tr>
<tr>
<td>Criteria updated to include Cinryze prophylactic therapy for patients six years of age and older, a new FDA approved age range.</td>
<td>01/2018</td>
</tr>
<tr>
<td>HAE indication review completed, agents included in policy were updated and questions added to align with clinical appropriateness and medical criteria.</td>
<td>11/2017</td>
</tr>
<tr>
<td>Criteria created</td>
<td>10/2016</td>
</tr>
</tbody>
</table>
Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP127

**Description**
Human chorionic gonadotropin (hCG) stimulates production of gonadal steroid hormones by causing production of androgen by the testes and the development of secondary sex characteristics in males. In females, hCG acts as a substitute for luteinizing hormone (LH) to stimulate ovulation.

**Length of Authorization**
- Initial: 12 months (for hypogonadotropic hypogonadism); six months (for cryptorchidism)
- Renewal: 12 months (for hypogonadotropic hypogonadism)*
  * Other indications are not eligible for renewal

**Quantity Limits**

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

*Drugs used in the treatment of fertility are excluded from coverage. Please refer to the member handbook/certificate of coverage for further information.

**Initial Evaluation**

I. Human chorionic gonadotropin (Novarel; Pregnyl) may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of one of the following:
      1. **Hypogonadotropic hypogonadism; AND**
         i. Two sub-normal testosterone concentration levels taken on two separate mornings while fasting; **AND**
         ii. Treatment with all of the following has been ineffective, contraindicated, or not tolerated:
            a. Generic injectable testosterone (i.e. testosterone cypionate, testosterone enanthate); **AND**
            b. Generic topical testosterone (i.e. generic testosterone 1% gel); **OR**
      2. **Prepubertal cryptorchidism; AND**
         i. Not due to anatomical obstruction

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
II. Human chorionic gonadotropin (Novarel; Pregnyl) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Men with low testosterone concentration and without clinical symptoms and signs consistent with testosterone deficiency. The routine assessment of testosterone level in the absence of hypogonadal symptoms is not advised.
   B. Men with a single, sub-normal testosterone concentration that is not repeatable per the U.S. Endocrine Society.
   C. Men with symptoms of hypogonadism; however, current testosterone level is within normal range.

III. Human chorionic gonadotropin (Novarel; Pregnyl) is considered investigational when used for all other conditions including but not limited to:
   A. Age-related hypogonadism
   B. Men with type 2 diabetes mellitus with low testosterone for the purpose of improving glycemic control
   C. Obesity

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

Supporting Evidence
   I. Human chorionic gonadotropin (Novarel; Pregnyl) is FDA approved for the treatment of hypogonadotropic hypogonadism, prepubertal cryptorchidism, and ovulation induction. Coverage of medications used in the treatment of fertility is an excluded benefit; thus, criteria for coverage in the setting of ovulation induction is unrepresented within this policy.
   II. There are several dosing regimen options in the setting of prepubertal cryptorchidism; however the label only supports a six week course with the potential of another series given one month later if the initial course was not successful.
   III. Per the 2018 AUA guidelines, diagnosis of hypogonadism should be confirmed prior to initiating testosterone replacement therapy. Testosterone levels should be drawn ideally between 8 and 10 AM while fasting due to the diurnal fluctuation of testosterone and its sensitivity to glucose ingestion. A separate, confirmatory measurement is recommended.
   IV. Thirty percent of men with an initial testosterone concentration in the hypogonadal range can have a measurement within the normal range on repeat measurement.
   V. The Endocrine Society strongly advises against “trial periods” of testosterone in men with a single sub-normal testosterone concentration and vague symptoms of deficiency.
VI. In patients within normal range, or have low testosterone concentration due to age, obesity or otherwise, the benefit of increased testosterone has not been shown. Rather, in this patient population with low testosterone and an intact gonadal system, increasing testosterone is associated with an increase of certain health risks, including cardiovascular disease. Because of this, the FDA has required manufacturers to label testosterone products warning of the increased risk for heart attack and stroke.

Investigational or Not Medically Necessary Uses

I. All of the aforementioned conditions listed in the not medically necessary section are considered to be excluded from coverage.

II. In the conditions listed, there is insufficient information, or, information reports inconclusive evidence, to support the safety and efficacy of using human chorionic gonadotropin (Novarel; Pregnyl).

References


Policy Implementation/Update:

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<thead>
<tr>
<th>Date Created</th>
<th>December 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>December 2019</td>
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<tr>
<td>Last Updated</td>
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<tr>
<td>Last Reviewed</td>
<td>12/2019</td>
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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Policy Type: PA/SP

Pharmacy Coverage Policy: 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

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<tr>
<th>Product Name</th>
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<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>hydroxyprogesterone caproate (Makena, hydroxyprogesterone caproate)</td>
<td>Intramuscular solution: 250 mg/mL, 1250 mg/5 mL</td>
<td>Preterm birth</td>
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<td>Subcutaneous auto-injector: 275 mg/1.1mL</td>
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<td>Subcutaneous auto-injector*: 4 auto-injectors/30 days</td>
</tr>
</tbody>
</table>

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:

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

Supporting Evidence

I. Hydroxyprogesterone caproate (Makena) was initially approved based on the data from the NICHD-MFMU Network trial. The NICHD-MFMU Network trial was acquired by a pharmaceutical company (Adeza, Sunnyvale, CA) and submitted as part of a new drug application (NDA) to the Food and Drug Administration (FDA) in April 2006. An FDA Advisory Committee in August 2006 voted unanimously that an additional confirmatory clinical trial was required to further assess safety and efficacy.

II. Based on the FDA ruling, the NDA sponsor initiated the confirmatory clinical trial (PROLONG), enrolling 5% of the overall subjects prior to FDA approval. The study was designed to have the power to show a direct clinical benefit (i.e., a reduction in a prespecified neonatal morbidity and mortality index).

III. PROLONG is a Phase 3B, randomized double-blind parallel group study with a 2:1 ratio of active drug: vehicle, assigned randomly by a global telephone-based interactive registration system. The inclusion criteria was: at least 18 years of age, pregnant with a singleton gestation, has a documented history (chart notations from previous pregnancy and not just oral history) of singleton spontaneous PTB between 200/7 and 366/7 weeks, after spontaneous PTB, or premature rupture of membranes. The primary safety outcome was fetal/early infant death defined as any of the following: spontaneous abortion/miscarriage (delivery from 160/7–196/7 weeks of gestation), stillbirth delivering after 200/7 weeks through term, or early infant death. The results of the PROLONG trial: fetal/early infant death rates were lower than expected and not different between treatment groups (17-OHPC 1.7 vs. placebo 1.9%; RR=0.87 [95% CI: 0.4–1.81]). No statistically significant difference in the frequency of stillbirth (17-OHPC 1.1% vs placebo 0.5%; RR 2.07 [95% CI 0.59–7.29]).

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

Not Medically Necessary Uses

I. Hydroxyprogesterone caproate (Makena) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. There is limited clinical evidence to suggest that hydroxyprogesterone caproate (Makena) is safe and efficacious in the setting of: multifetal gestation, major fetal anomalies, maternal complications (current or planned cerclage, hypertension requiring medication, or seizure disorder), uterine anomalies, pediatric population (< 16 years of age), and therapy initiated after 21 weeks of gestation
   B. Although there may be a role for generic hydroxyprogesterone caproate in the setting of breast cancer, adenocarcinoma of uterus, amenorrhea and endometrial disorder (production of secretory endometrium and desquamation); for the purpose of this hydroxyprogesterone caproate (Makena) policy, only the indication of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth/premature rupture of membranes at less than 37 weeks would be considered medically necessary.

References


Policy Implementation/Update:

<table>
<thead>
<tr>
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<th>Date</th>
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<tr>
<td>Criteria transitioned into policy format</td>
<td>02/2020</td>
</tr>
<tr>
<td>Criteria updated to remove question around contraindication, included package insert clinical notes, and new subcutaneous autoinjector formulation</td>
<td>04/2018</td>
</tr>
<tr>
<td>Criteria updated to truncate approval table to 20 weeks based on the most recent guideline from The Society for Maternal-Fetal Medicine.</td>
<td>10/2017</td>
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| Previous reviews                                                                           | 09/2013, 10/2012,
ibrutinib (IMBRUVICA®)  
UMP POLICY

Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP037

Split Fill Management*

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

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

Quantity limits

<table>
<thead>
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<th>ibritinib (Imbruvica)</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>560 mg tablets</td>
<td>Mantle Cell Lymphoma, previously treated; Marginal Zone Lymphoma, relapsed/refractory</td>
<td>30 tablets/30 days</td>
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<tr>
<td>420 mg tablets</td>
<td>Chronic Graft versus Host Disease (refractory); Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; Waldenström Macroglobulinemia</td>
<td>30 tablets/30 days</td>
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<td>280 mg tablet</td>
<td>Dose modification</td>
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<td>140 mg tablet</td>
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<td>140 mg capsule</td>
<td>Dose modification</td>
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<tr>
<td>70 mg capsule</td>
<td>Dose modification</td>
<td>30 capsules/30 days</td>
</tr>
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</table>

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 not have a 17p deletion or TP53 mutation confirmed by testing; AND
      a. Ibrutinib (Imbruvica) will be used as monotherapy; OR
      b. The request is for use in combination with bendamustine and rituximab in the relapsed/refractory setting; OR
      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)
      a. Ibrutinib (Imbruvica) will be used as monotherapy; OR

II. **Ibrutinib (Imbruvica) is considered not medically necessary when criteria above are not met and/or when used for:**
   A. Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia in combination with rituximab only

III. **Ibrutinib (Imbruvica) is considered investigational when used for all other conditions, including but not limited to:**
   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. Esophagealgastric carcinoma
   J. Glioblastoma
   K. Non-small-cell lung carcinoma
   L. T-cell Lymphoma

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

I. 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 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. Glioblastoma
   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


Policy Implementation/Update:

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<th>Date</th>
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<td>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.</td>
<td>06/2020</td>
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<td>Updated criteria to policy format, specified combination therapy in CLL/SLL patients to be used in members without 17p deletion/TP53 mutation, addition of trial and failure of 140mg capsules prior to use of 140 mg or 280 mg tablets. In MCL, marginal zone lymphoma, and graft versus host disease, added more detail on</td>
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type of prior therapy required. For Waldenström macroglobulinemia added use to be as monotherapy or with rituximab.

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Policy Type: PA/SP Pharmacy Coverage Policy: UMP168

Description
Idelalisib (Zydelig) is an orally administered PI3Kδ kinase inhibitor.

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

Quantity Limits

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<td>idelalisib (Zydelig)</td>
<td>100 mg tablets</td>
<td>Relapsed Chronic Lymphocytic Leukemia; Relapsed Follicular B-cell non-Hodgkin Lymphoma; Relapsed Small Lymphocytic Lymphoma</td>
<td>60 tablets/30 days</td>
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Initial Evaluation

I. Idelalisib (Zydelig) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; AND
   C. A diagnosis of one of the following:
      1. Relapsed Chronic Lymphocytic Leukemia (CLL); AND
         i. Documentation of use of at least one prior therapy; AND
         ii. Use is in combination with rituximab; AND
         iii. Will not be used with any other oncology therapy; OR
      2. Relapsed Small Lymphocytic Lymphoma (SLL); AND
         i. Treatment with two 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 two prior therapies for FL has been ineffective, contraindicated, or not tolerated; AND
         ii. Medication will be used as monotherapy.

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

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.
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-Hodgkin’s 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 naive or first line therapy for any indication
   B. In combination with other medications for any indication outside of dual therapy with rituximab for the indication of relapsed CLL.
   C. Marginal zone lymphoma
   D. Lymphoplasmacytic lymphoma with or without Waldenstrom’s macroglobulinemia
   E. Immunoglobulin M (IgM) associated primary amyloidosis
   F. Hodgkin Lymphoma
   G. Acute Lymphoblastic Leukemia
   H. Non-Small Cell Lung Cancer

References

1. Zydelig (idelalisib) [prescribing information]. Gilead Science, Inc, Foster City(CA). 2014
2. ClinicalTrials.gov. A Randomized, Double-Blind, Placebo-Controlled Study of Idelalisib in Combination With Rituximab for Previously Treated Chronic Lymphocytic Leukemia (CLL). NCT01539512.

Policy Implementation/Update:

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<td>02/2020</td>
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<td>Previous reviews</td>
<td>11/2014</td>
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**Policy Type:** PA/SP  
**Pharmacy Coverage Policy:** UMP128

**Description**
Imatinib (Gleevec) is an orally administered protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase to suppress proliferation and promote apoptosis of cancer cells.

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

**Quantity limits**

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<td>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;</td>
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<td>imatinib</td>
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<td>Systemic mast cell disease, aggressive, D816V c-Kit mutation negative or unknown</td>
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**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**

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<td>Generic imatinib preferred therapy indicated for initial and continuation of therapy, unless medical necessity for brand met.</td>
<td>11/2018</td>
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<tr>
<td>Criteria questions rearranged and clarified.</td>
<td>08/2017</td>
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<tr>
<td>Criteria updated to prefer generic imatinib for initial approval.</td>
<td>05/2017</td>
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<tr>
<td>Criteria updated for new disease states.</td>
<td>02/2016</td>
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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Policy Type: PA/SP  

Pharmacy Coverage Policy: UMP039

Description

Inotersen (Tegsedi) is a subcutaneously administered antisense oligonucleotide inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

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<tr>
<th>Inotersen (Tegsedi)</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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<tr>
<td>284 mg/1.5 mL syringe</td>
<td>hereditary transthyretin-mediated amyloidosis</td>
<td>6 mL/28 days</td>
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Initial Evaluation

I. Inotersen (Tegsedi) may be considered medically necessary when the following criteria are met:
   A. Prescribed by or in consultation with a neurologist or cardiologist; AND
   B. A diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) when the following are met:
      1. Age 18 years and older; AND
      2. Documented transthyretin variant (TTR mutation) by genotyping (e.g., V30M); AND
      3. Documented amyloid deposit by biopsy; AND
      4. Patient has a platelet count > 100 × 109/L; AND
      5. Documentation of one of the following:
         i. Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb
         ii. Patient has a baseline FAP Stage 1 or 2
         iii. Patient has a baseline neuropathy impairment (NIS) score ≥ 10 and ≤ 130 AND
      6. Presence of clinical signs and symptoms of the disease (e.g., peripheral sensorimotor polyneuropathy, autonomic neuropathy, motor disability, etc.); AND
      7. No prior liver transplant or anticipated liver transplant; AND
      8. New York Heart Association (NYHA) functional classification of <3; AND
      9. Does not have presence of known type 1 or type 2 diabetes mellitus; AND
      10. Does not have renal insufficiency (defined as CrCl <60 mL/min); AND
      11. Patient has tried and failed or has a contraindication to patisiran (Onpattro); AND
      12. Inotersen (Tegsedi) will not be used in combination with patisiran (Onpattro) or tafamidis meglumine (Vyndaqel)
II. inotersen (Tegsedi) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Cardiac amyloidosis due to wild-type or mutant TTR

**Renewal Evaluation**

I. Patient has previously received treatment with inotersen (Tegsedi); **AND**

II. Documentation of one of the following:
   A. Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb; **OR**
   B. Patient has a baseline FAP Stage 1 or 2; **OR**
   C. Patient has a baseline neuropathy impairment (NIS) score ≥ 10 and ≤ 130 **AND**

III. Documentation that the patient has experienced a positive clinical response to inotersen (Tegsedi) (e.g., improved neurologic impairment, motor function, quality of life, slowing of disease progression, etc.); **AND**

IV. Inotersen (Tegsedi) will not be used in combination with patisiran (Onpattro) or tafamidis meglumine (Vyndaqel); **AND**

V. Absence of unacceptable toxicity from the medication

**Supporting Evidence**

I. In the pivotal NEURO-TTR trial leading to approval, inotersen (Tegsedi) was studied in adults with stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) hereditary transthyretin amyloidosis with polyneuropathy.

II. Diagnosis of the hereditary form of ATTR requires demonstration of a TTR gene mutation. Although mass spectrometry can demonstrate a mass difference between wild-type and TTR protein variants in serum, it does not specify the site and kind of amino acid substitution in a number of disease-related TTR gene mutations; thus, DNA sequencing is usually required.

III. Use of inotersen (Tegsedi) is contraindicated in patients with platelet count less than 100 x 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**

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

**Policy Implementation/Update:**

| Date Created | January 2019 |
| Date Effective | February 2019 |
| Last Updated | January 2019 |
| Last Reviewed | 01/2019 |

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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP084

Description
Istradefylline (Nourianz™) is an orally administered adenosine receptor antagonist.

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

Quantity limits

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<td>Parkinson’s disease</td>
<td>30 tablets/30 days</td>
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<td>(Nourianz)</td>
<td>40 mg tablets</td>
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<td>30 tablets/30 days</td>
<td>207955</td>
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Initial Evaluation

I. Istradefylline (Nourianz™) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by or in consultation with a neurologist; AND
   B. A diagnosis of Parkinson’s Disease when the following are met:
      1. Member is currently on an oral levodopa regimen at least four times per day; AND
      2. Member is experiencing at least two hours of daily OFF time; AND
      3. Prescriber attests that member will be using istradefylline (Nourianz™) in combination with carbidopa/levodopa; AND
      4. Treatment with one the following has been ineffective, contraindicated or not tolerated:
         i. Carbidopa/levodopa IR up to five times a day; OR
         ii. Carbidopa/levodopa XR; AND
      5. Current or previous treatment with at least TWO of the following agents used as adjunctive treatment to levodopa/carbidopa has been ineffective, contraindicated, or not tolerated:
         i. Dopamine agonist (e.g., ropinirole, pramipexole)
         ii. COMT inhibitor (e.g., entacapone, tolcapone)
         iii. MAO-B inhibitor (e.g., rasagiline, safinamide, selegiline)

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

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
A. Parkinson’s disease WITHOUT documentation of motor fluctuations, “wearing off”

Renewal Evaluation

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

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

III. Prescriber attests that member will be using istradefylline (Nourianz) in combination with carbidopa/levodopa; **AND**

IV. Documentation that member has a reduction in wearing off period from baseline.

Supporting Evidence

I. The efficacy of istradefylline (Nourianz) as adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes was shown in four 12-week placebo-controlled trials that included a total of 1,143 patients. In all four studies, patients treated with istradefylline (Nourianz) experienced a statistically significant decrease from baseline in daily “off” time compared to patients receiving a placebo. In these pivotal clinical trials, patients were experiencing at least two hours of daily OFF time and were receiving the following concomitant therapies: dopamine agonists (85%), COMT inhibitors (38%), MAO-B inhibitors (40%), anticholinergics (13%), and/or amantadine (33%).

II. Levodopa, administered in oral carbidopa/levodopa formulations, is the mainstay and most effective medication for management of PD motor symptom management. Currently, motor fluctuations are managed by increasing the patient’s levodopa dose, reducing intake of dietary protein with levodopa administration, using longer acting carbidopa/levodopa formulations, and adding other agents that can be clinically useful in extending “on” time (e.g., dopamine agonists, COMT inhibitors, and MAO-B inhibitors).

III. The 2018 International Parkinson and Movement Disorder Society Evidence-Based Medicine Review reported istradefylline (Nourianz) to be “likely efficacious” and “possibly useful” for clinical practice due to conflicting evidence but generally positive outcomes. Guidelines don’t recommend one adjunctive therapy approach over another.

Investigational or Not Medically Necessary Uses

I. Parkinson’s disease WITHOUT documentation of motor fluctuations, “wearing off”
   
   A. Istradefylline (Nourianz) has not been studied in patients with Parkinson’s disease who aren’t experiencing motor fluctuations; therefore, it would be considered investigational when requested in this setting.

References


Policy Implementation/Update:

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<th>September 2019</th>
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<tr>
<td>Date Effective</td>
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Action and Summary of Changes

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Ivabradine (Corlanor®)
UMP POLICY

Policy Type: PA
Pharmacy Coverage Policy: UMP040

Description
Ivabradine (Corlanor) is an orally administered direct and selective inhibitor of the hyperpolarization-activated cyclic nucleotide-gated (HCN-gated) channels, or the f-channels that are located in the cardiac sinoatrial node which results in a lowering of the heart rate.

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

Quantity limits

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<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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<td>ivabradine (Corlanor)</td>
<td>5 mg tablets</td>
<td>Heart Failure in Adult Patients</td>
<td>60 tablets/30 days</td>
<td>188210</td>
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<td></td>
<td>7.5 mg tablets</td>
<td></td>
<td>60 tablets/30 days</td>
<td>188211</td>
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<tr>
<td></td>
<td>5 mg/5 mL solution</td>
<td>Heart Failure in Pediatric Patients</td>
<td>450 mL/30 days</td>
<td>Not available yet</td>
</tr>
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Initial Evaluation
I. Ivabradine (Corlanor) may be considered medically necessary when the following criteria below are met:
   A. Prescribed by or in consultation with a cardiologist; **AND**
   B. A diagnosis of one of the following:
      1. **Heart Failure in Adult Patients; AND**
         i. Prescribed by or in consultation with a cardiologist; **AND**
         ii. The member have stable, symptomatic chronic heart failure; **AND**
         iii. The member have left ventricular ejection fraction ≤ 35%; **AND**
         iv. The member is in sinus rhythm with resting heart rate ≥ 70 beats per minute; **AND**
         v. Treatment with maximally tolerated beta-blockers have been ineffective, contraindicated, or not tolerated; **AND**
         vi. The member does not have any of the following contraindications:
            a. Acute decompensated heart failure
            b. Blood pressure less than 90/50 mmHg
            c. Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
            d. Resting heart rate less than 60 bpm prior to treatment
            e. Severe hepatic impairment
            f. Pacemaker dependence

Washington State Rx Services is administered by moda HEALTH

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
g. Concomitant use of strong cytochrome CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors);

**OR**

2. **Heart Failure in Pediatric Patients; AND**
   i. Member is ≥ 6 months years of age; **AND**
   ii. The member has stable symptomatic heart failure due to dilated cardiomyopathy; **AND**
   iii. The member is in sinus rhythm with elevated heart rate; **AND**
   iv. The member does not have any of the following contraindications:
      a. Acute decompensated heart failure
      b. Blood pressure less than 90/50 mmHg
      c. Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
      d. Resting heart rate less than 60 bpm prior to treatment
      e. Severe hepatic impairment
      f. Pacemaker dependence
      g. Concomitant use of strong cytochrome CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors);

**OR**

3. **Inappropriate Sinus Tachycardia; AND**
   i. The member has inappropriate sinus tachycardia; **AND**
   ii. The member does not have any of the following contraindications:
      a. Acute decompensated heart failure
      b. Blood pressure less than 90/50 mmHg
      c. Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
      d. Resting heart rate less than 60 bpm prior to treatment
      e. Severe hepatic impairment
      f. Pacemaker dependence
      g. Concomitant use of strong cytochrome CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors)

II. **Ivabradine (Corlanor) is considered not medically necessary** when criteria above are not met and/or when used for:
   A. Coronary artery disease with or without heart failure

III. **Ivabradine (Corlanor) is considered investigational** when used for all other conditions, including but not limited to:
   A. Non-stable, asymptomatic chronic heart failure
   B. Pediatric heart failure not due to dilated cardiomyopathy

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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.

October 01, 2020
Renewal Evaluation

I. **Heart Failure in adults, heart failure in pediatrics, inappropriate sinus tachycardia; AND**
   A. Member has previously received treatment with ivabradine (Corlanor); **AND**
   B. Continues to meet criteria identified in section I of the initial Evaluation; **AND**
   C. Provider attest to stabilization of disease (e.g. heart rate reduction, reduction in hospitalization due to worsening heart failure); **AND**
   D. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. Ivabradine (Corlanor) is indicated to reduce the risk of hospitalization for worsening heart failure in adult patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction $\leq 35\%$, who are in sinus rhythm with resting heart rate $\geq 70$ beats per minute and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use.


Investigational or Not Medically Necessary Uses

I. Coronary artery disease
   A. In the BEAUTIFUL and SIGNIFY trials, no benefits were found in patients with stable coronary artery disease with or without stable heart failure, who were given ivabradine (Corlanor).

II. Non-stable, asymptomatic chronic heart failure
   A. Ivabradine (Corlanor) has not been studied in patients with non-stable, asymptomatic chronic heart failure; therefore, it would be considered investigational when Corlanor is requested in that setting.

III. Pediatric heart failure not due to dilated cardiomyopathy
   A. Ivabradine (Corlanor) has not been studied in pediatric patients with heart failure that is not due to dilated cardiomyopathy; therefore, it would be considered investigational when Corlanor is requested in that setting.

References

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

Washington State Rx Services is administered by Moda Health

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
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<td>Transitioned criteria to policy. In this transition, the following updates were made: added new indication for pediatric heart failure due to dilated cardiomyopathy, incorporated the approvable off-label indication of inappropriate sinus tachycardia, and added renewal criteria.</td>
<td>06/2019</td>
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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

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<td>enasidenib</td>
<td>50 mg tablets</td>
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<td>(Idhifa)</td>
<td>100 mg tablets</td>
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<td>ivosidenib</td>
<td>250 mg capsule</td>
<td>Acute myeloid leukemia, relapsed/refractory</td>
<td>60 capsules/30 days</td>
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<tr>
<td>(Tibsovo)</td>
<td></td>
<td>Acute myeloid leukemia, newly diagnosed</td>
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Initial Evaluation
I. Enasidenib (Idhifa) or ivosidenib (Tibsovo) may be considered medically necessary when the following criteria are met:
   A. 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

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
2. **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.

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**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


Policy Implementation/Update:

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<td>Criteria update: To improve the clinical flow of the policy, the indication of relapse/refractory AML was separated from newly diagnosed AML. For clinical appropriateness and standard of practice, the requirement for both chemotherapy “AND” allogenic stem cell transplant for relapsed or refractory AML, was changed to an “OR,” therefore, either one prior regimen would satisfy that requirement. For the newly diagnosed AML diagnosis, additional information around comorbidities has been included in the policy to help better determine the comorbidities that may preclude newly diagnosed AML patients from intensive induction chemotherapy. Based on current clinical trials that are being conducted, myelodysplastic syndrome (MDS) has been added to the investigation/experimental section of this policy and supporting evidence has been updated to reflect the rationale for the addition. The supporting evidence in this whole policy has been updated to reflect the pivotal trials. The references section has been updated to include the pivotal trials and NCCN guideline for AML.</td>
<td>02/2020</td>
</tr>
<tr>
<td>Policy created. Tibsovo and Idhifa was combined into one policy.</td>
<td>12/2019</td>
</tr>
</tbody>
</table>
ixazomib (Ninlaro®)  
UMP POLICY

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ixazomib (Ninlaro)</td>
<td>2.3 mg capsule</td>
<td>Previously treated multiple myeloma, in combination with lenalidomide and dexamethasone</td>
<td>3 capsules/28 days</td>
</tr>
<tr>
<td></td>
<td>3 mg capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 mg capsule</td>
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<td></td>
</tr>
</tbody>
</table>

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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<th>Date Created</th>
<th>December 2015</th>
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<td>February, 2016</td>
</tr>
<tr>
<td>Last Updated</td>
<td>November 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>11/2019</td>
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Action and Summary of Changes

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.  

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<thead>
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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

<table>
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<th>Product Name</th>
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<th>Quantity Limit</th>
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<tbody>
<tr>
<td>lapatinib (Tykerb)</td>
<td>250 mg tablets</td>
<td>Breast cancer, HER2 overexpression, advanced or metastatic in combination with capecitabine after prior therapy</td>
<td>105 tablets/28 days</td>
<td>125759</td>
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<tr>
<td></td>
<td></td>
<td>Breast cancer, HR-positive, HER2 overexpression, in postmenopausal women, in combination with letrozole</td>
<td>168 tablets/28 days</td>
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Initial Evaluation

I. Lapatinib (Tykerb) may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Lapatinib (Tykerb) will not be used in combination with any other oncolytic medication with the exception of capecitabine (Xeloda), letrozole, or trastuzumab; **AND**
   D. A diagnosis of **breast cancer** when the following are met:
      1. The tumor is positive for HER2(+) gene expression; **AND**
      2. The breast cancer is advanced (stage III) or metastatic (stage IV); **AND**
      3. The medication will be used in one of the following settings:
         i. Progression following ALL of the following therapies: anthracycline therapy (e.g., doxorubicin), taxane therapy (e.g., paclitaxel, docetaxel), trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.); **AND**
            a. Will be used in combination with capecitabine; **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.).

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
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. Lapatinib (Tykerb) was evaluated in in combination with capecitabine for HER2(+), metastatic breast cancer. The trial was a Phase 3, randomized study versus capecitabine monotherapy in subjects that had previous exposure to anthracyclines, taxanes, and trastuzumab. The primary endpoint was time to progression and the results were statistically significant in favor of lapatinib (Tykerb).
II. Overall survival data was not mature at time of assessment, and future results are likely to be confounded as subjects on placebo were allowed to cross over to active therapy during the trial.
III. In two randomized trials, lapatinib (Tykerb) showed to be less effective than trastuzumab-based chemotherapy regimens. The package label indicates subjects should have disease progression
on trastuzumab prior to initiation of lapatinib (Tykerb) when used in combination with capecitabine for those with advanced or metastatic, HER2(+) disease.

IV. Lapatinib (Tykerb) in combination with letrozole was evaluated in a double-blind, placebo-controlled study. The trial included women with HR+, HER2(+), metastatic breast cancer who had not received prior therapy for metastatic disease. The primary outcome was progression-free survival (PFS) which was statistically significant in favor of lapatinib (Tykerb).

V. Another trial evaluated lapatinib (Tykerb) in combination with an aromatase inhibitor, again evaluating in HR+, HER2(+), metastatic disease. These subjects had progressed after trastuzumab chemotherapy and endocrine therapies. The treatment arms included lapatinib (Tykerb) + trastuzumab + Al, trastuzumab + Al, or lapatinib (Tykerb) + Al. The results were statistically significant in PFS for the triple therapy, followed by lapatinib (Tykerb) + Al, then trastuzumab + Al. Additionally, lapatinib (Tykerb) has demonstrated a statistically significant improvement in PFS in HER2(+) breast cancer when added to trastuzumab compared to lapatinib (Tykerb) alone.

Investigational or Not Medically Necessary Uses

I. Lapatinib (Tykerb) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. HER2(−) breast cancer
   B. Concurrent use with therapies outside of those listed above
   C. Ovarian, uterine, endometrial cancer
   D. Peritoneal cancer
   E. Pancreatic cancer
   F. Melanoma
   G. Central nervous system cancers
   H. Head and neck cancer
   I. Gastrointestinal cancer
   J. Bladder, urothelial, renal cancer

References

Policy Implementation/Update:

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<th>September 2008</th>
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<tr>
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<td>October 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>08/2011, 08/2013, 09/2013, 10/2019</td>
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<tr>
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<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria transitioned to policy. Policy updated to include the following requirement: specialist prescriber,</td>
<td>10/19</td>
</tr>
<tr>
<td>age, concurrent therapies, specified place in therapy</td>
<td></td>
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</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>larotrectinib</td>
<td>25 mg capsule</td>
<td>Neurontrophic receptor tyrosine kinase gene fusion positive solid tumor, metastatic</td>
<td>180 tablets/30 days</td>
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<tr>
<td>(Vitrakvi)</td>
<td>100 mg capsule</td>
<td></td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>20 mg/1 mL solution</td>
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<td>Quantity calculated to 100 mg/m2 of body surface area</td>
</tr>
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</table>

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; \textbf{AND}
   B. Medication will \textbf{not} be used in combination with any other oncolytic medication; \textbf{AND}
   C. The member has \textbf{not} previously progressed on other NTRK gene fusion medications (e.g., entrectinib [Rozlytrek]); \textbf{AND}
   D. A diagnosis of solid tumor with confirmed NTRK gene fusion; \textbf{AND}
   E. Member has metastatic disease, or surgical resection is likely to result in severe morbidity (i.e., tumor is unresectable); \textbf{AND}
   F. The member does \textbf{not} have an acquired resistance mutation (resistant mutations include, but may not be limited to: G595R, G623R, G696A, F617L); \textbf{AND}
   G. \textbf{All} alternative therapies for diagnosis and stage of cancer have been exhausted, as defined by:
      1. Progression following all appropriate treatments; \textbf{OR}
      2. Nonresponse to all available therapies; \textbf{OR}
      3. All available therapies are contraindicated or not tolerated; \textbf{OR}
      4. No standard or satisfactory treatments exist; \textbf{AND}
   H. The member has intolerance to or contraindication to entrectinib (Rozlytrek); \textbf{OR}
1. Member is less than 12 years of age

II. Larotrectinib (Vitrakvi) is considered **not medically necessary** when criteria above are not met and/or when used for the following:
   A. When used for a resistance mutation (resistant mutations include, but may not be limited to G595R, G623R, G696A, F617L)

III. Larotrectinib (Vitrakvi) is considered **investigational** when used for all other conditions, including but **not limited to**:
   A. Oncolytic indications as an adjunct therapy
   B. Non-small cell lung cancer without NTRK fusion gene rearrangements
   C. Solid tumors that do not harbor NTRK gene fusions
   D. Leukemias or lymphomas

**Renewal Evaluation**

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

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

III. Prescribed by, or in consultation with, an oncologist; **AND**

IV. Medication will **not** be used in combination with any other oncolytic medication; **AND**

V. Response to therapy as indicated by stabilization of disease or decrease in tumor size or spread; **AND**

VI. Member does **not** have unacceptable medication toxicity (e.g., hepatotoxicity, severe delirium or gait disturbances, etc.); **AND**

VII. Documentation of absence of acquired resistance

**Supporting Evidence**

I. Per the landmark trials LOXO-TRK-14001 (SCOUT and NAVIGATE): All subjects were diagnosed with measurable or evaluable metastatic or locally advanced solid tumors, had progressed beyond all effective and available therapies per the National Comprehensive Cancer Network (NCCN), had no therapies available for the diagnosis per NCCN guidelines, or surgical resection would result in significant morbidity.

II. Subjects were without acquired resistance mutations to NTRK-inhibitors, without active cardiovascular disease or history of myocardial infarction within the prior six months, and were not on concurrent CYP3A4 inhibitors or inducers.

III. The NTRK gene fusion mutation was confirmed using a validated laboratory testing method. Testing methods for NTRK gene fusion include NGS, RT-PCR, FISH, or Immunohistochemistry (ICH). The use of ICH may lead to a false positive result. ICH uses the presence of a surrogate marker (TRK proteins) to establish the likelihood of a NTRK gene fusion. The FISH method
requires the visual assessment of an experienced pathologist of several tests and is considered more subjective than NGS or RT-PCR.

IV. The trials were single-arm, open-label studies that included 55 patients with solid tumors. The tumor types that had represented AND reported a measurable Overall Response Rate (ORR) were the following:

- Salivary gland cancer
- Soft tissue sarcoma (STS)
- Infantile fibrosarcoma (IFS)
- Gastrointestinal Stromal Tumor (GIST)
- Non-small cell lung cancer (NSCLC)
- Colorectal cancer (CRC)
- Melanoma
- Thyroid carcinoma
- Colon cancer

V. Tumors that were evaluated in one or more subjects but did not show an ORR included cholangiocarcinoma, appendix, breast and pancreatic cancer.

VI. Adverse reactions were common with larotrectinib (Vitrakvi), and included fatigue, pyrexia, peripheral edema, CNS, gastrointestinal, respiratory, musculoskeletal, and laboratory disturbances (e.g., ASK, ALT). Adverse events leading to dose discontinuation, interruption or reduction occurred in 37% of subjects. The safety profile of larotrectinib (Vitrakvi) is likely not fully developed given the small number of subjects in the clinical trials and short trial duration. Additionally, due to rarity of the NTRK gene fusion mutation, post-marketing information is likely to remain limited.

VII. There are currently two available therapies for NTRK gene fusion positive mutations. Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek), currently there is no direct comparison data showing safety and/or efficacy differences between these therapies OR safety or efficacy of using them sequentially after progression. Additionally, caution should be exercised when making cross trial comparisons. At this time, entrectinib (Rozlytrek) provides a better value for general populations with NTRK gene fusion positive tumors given the sum of safety, efficacy, and cost information currently available.

VIII. It should also be noted that due to single-arm, open-label trial designs, as well as outcomes evaluated, no NTRK gene fusion therapies available have been shown to improve health outcomes to date.

IX. Entrectinib (Rozlytrek) is FDA-approved down to 12 years of age, but has been, and will continue to be, evaluated in younger populations. Larotrectinib (Vitrakvi) FDA-approval is nonspecific to pediatrics and adults.

Investigational or Not Medically Necessary Uses

I. Larotrectinib (Vitrakvi) does not have sufficient activity in those with resistance mutations. As of December 2019, known resistance mutations include: G595R, G623R, G696A, F617L.

II. Larotrectinib (Vitrakvi) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. Oncolytic indications as an adjunct therapy
B. Non-small cell lung cancer without NTRK fusion gene rearrangements
C. Solid tumors that do not harbor NTRK gene fusions
D. Leukemias or lymphomas

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

References


Policy Implementation/Update:

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

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<td>Policy updated to newest formatting. Initial approval duration changed to three months from six months given safety concerns and split-fill designation, quantity limit for solution now based on BSA, removal of designated test requirement, removed requirements for lab value monitoring, requirement for lack of CV comorbidities and CNS symptoms. Addition of monotherapy requirement, documentation of intolerance of contraindication to entrectinib (Rozlytrek) and requirement the member has not previously progressed on other NTRK therapies.</td>
<td>12/2019</td>
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lenalidomide (Revlimid®), pomalidomide (Pomalyst®), thalidomide (Thalomid®)

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

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<td>lenalidomide (Revlimid)</td>
<td>2.5 mg capsules</td>
<td>Follicular lymphoma; Marginal zone lymphoma; Multiple myeloma; Myelodysplastic syndromes</td>
<td>28 capsules/28 days</td>
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<td>5 mg capsules</td>
<td>Follicular lymphoma; Mantle cell lymphoma; Marginal zone lymphoma; Multiple myeloma</td>
<td>28 capsules/28 days</td>
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<tr>
<td></td>
<td>10 mg capsules</td>
<td>Multiple myeloma maintenance therapy following auto-HSCT; Myelodysplastic syndromes</td>
<td>28 capsules/28 days</td>
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<td>15 mg capsules</td>
<td>Multiple myeloma maintenance therapy following auto-HSCT; Myelodysplastic syndromes</td>
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<td></td>
<td>1 mg capsules</td>
<td>Multiple Myeloma</td>
<td>21 capsules/28 days</td>
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Initial Evaluation

I. Lenalidomide (Revlimid) may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; AND
   B. A diagnosis of multiple myeloma (MM) when the following is met:
      1. Medication will be used with dexamethasone as part of a doublet or triplet regimen; OR
      2. Medication will be used as monotherapy; OR
   C. A diagnosis of myelodysplastic syndrome (MDS) when the following are met:
      1. Member has lower risk disease (e.g. IPSS Low or Intermediate-1; IPSS-R Very Low, Low, Intermediate; WPSS Very Low, Low, Intermediate); AND
      2. Member has transfusion-dependent anemia (i.e. 2 or more units of red blood cells in the previous 8 weeks); AND
         i. MDS with del(5q) abnormality; OR
         ii. MDS without del(5q) abnormality; AND
            a. Serum erythropoietin levels are less than 500 mU/mL; AND
               i. Medication will be used in combination with an erythropoiesis-stimulating agent (ESA) (e.g. Procrit, Retacrit, or Aranesp) with or without granulocyte-colony stimulating factor (GCSF) (e.g., filgrastim, pegfilgrastim); AND
                  1. History of inadequate response to ESA with or without GCSF; OR
            b. Serum erythropoietin levels are greater than 500 mU/mL; AND
               i. History of failure, contraindication, or intolerance to immunosuppressive therapy (IST) (e.g. anti-thymocyte globulin ± cyclosporine A); OR
   D. A diagnosis of mantle cell lymphoma (MCL) when the following is met:

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<td>200 mg capsules</td>
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Washington State Rx Services is administered by

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

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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.
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 with del(5q) generally has a relatively good prognosis and is highly responsive to lenalidomide (Revlimid) therapy.
  i. A Phase 3 trial in 205 patients demonstrated superiority of lenalidomide (Revlimid) compared to placebo for achieving RBC transfusion-independence.
1. Patients with transfusion-dependent, lower risk MDS with del(5q) were treated with low dose lenalidomide (Revlimid) (10 mg), lower dose lenalidomide (Revlimid) (5 mg), and placebo.
2. The rates of transfusion-independence for greater than 26 weeks were 57%, 37%, and 2% respectively for low dose lenalidomide (Revlimid), lower dose lenalidomide (Revlimid), and placebo.
3. The risk of transformation to acute myeloid leukemia (AML) was not significantly different between lenalidomide (Revlimid) and placebo.
   ii. Additionally, a Phase 2 trial in anemic transfusion-dependent patients with del(5q) also reported similar hematologic responses in two-thirds of the 148 patients with del(5q).

   The safety and efficacy of lenalidomide (Revlimid) for lower-risk MDS without del(5q) was evaluated in a Phase 3 trial in 239 patients with transfusion-dependent MDS.
   i. Patients receiving lenalidomide (Revlimid) compared to placebo had a higher rate of transfusion-independence (26.9% vs 2.5%; p< 0.001). Transfusion reduction of four or more units of packed RBCs was seen in 22% of lenalidomide (Revlimid)-treated patients while no reduction was seen in the placebo group.
   ii. Incidence of treatment-related mortality was 2.5% in both groups, but the incidence of myelosuppression was higher in the lenalidomide-treated group. Furthermore, when comparing lenalidomide (Revlimid) to placebo, the incidence of grade 3 or 4 neutropenia was 61.9% vs 12.7%, respectively, and the rate of thrombocytopenia was 35.6% vs 3.8%, respectively.

III. Mantle cell lymphoma (MCL):
   • Lenalidomide (Revlimid) is approved for the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.
   • The safety and efficacy of single-agent lenalidomide (Revlimid) for relapsed or refractory MCL was evaluated in a Phase 2, open-label trial in 134 patients with prior bortezomib therapy. The ORR was 28% and a median duration of response (DoR) was 16.6 months.
   • An additional Phase 2 trial included 254 patients with relapsed MCL who were not candidates for intensive therapy were randomized to receive single-agent lenalidomide (Revlimid) or single-agent of the investigator’s choice (e.g. rituximab, gemcitabine, fludarabine, chlorambucil, cytarabine) and were allowed to receive lenalidomide (Revlimid) at the time of progression. After a median follow-up of 15.9 months, PFS was 8.7 months for lenalidomide (Revlimid) verses 5.2 months for the control arm.
   • The NCCN B-Cell Lymphomas guideline suggests the use of lenalidomide (Revlimid) outside of the relapsed/refractory setting, including as initial treatment or in the second-line setting. However, there is limited evidence to support use outside of the relapsed/refractory setting. A small Phase 2 study evaluated the use of lenalidomide (Revlimid) plus rituximab as initial therapy for patients with MCL. The ORR in the...
intention-to-treat population (n = 38) was 87% and 92% in the population that could be evaluated (n = 36).

IV. Previously treated follicular lymphoma (FL)/marginal zone lymphoma (MZL):

- The efficacy of lenalidomide (Revlimid) with rituximab in patients with relapsed or refractory follicular and marginal zone lymphoma was evaluated in the AUGMENT (NCT01938001) and MAGNIFY (NCT01996865) trials.
- AUGMENT was a randomized, double-blind, multicenter trial (n=358) in patients with relapsed or refractory follicular or marginal zone lymphoma who received lenalidomide (Revlimid) and rituximab or rituximab and placebo for a maximum of 12 cycles or until unacceptable toxicity.
  i. Efficacy results in the follicular and marginal zone lymphoma population reported a PFS of 39.4 months in the lenalidomide (Revlimid) and rituximab arm versus 14.1 months in the rituximab plus placebo arm.
- MAGNIFY is an open-label, multicenter trial (n=232) in which patients with relapsed or refractory follicular, marginal zone, or mantle cell lymphoma received 12 induction cycles of lenalidomide (Revlimid) and rituximab.
  i. Overall response by investigator assessment was 59% (104/177) [95% CI: 51, 66] for patients with follicular lymphoma. Median DoR was not reached within a median follow-up time of 7.9 months [95% CI: 4.6, 9.2]. With an overall response of 51% (23/45) [95% CI: 36, 66] for patients with marginal zone lymphoma and median DoR not reached within a median follow-up time of 11.5 months [95% CI: 8.0, 18.9].

V. Erythema nodosum leprosum (ENL)

- Erythema nodosum leprosum (ENL) is a serious immunological complication of leprosy, causing inflammation of skin, nerves, other organs, and general malaise. There is limited high-quality, prospective data supporting the use of thalidomide (Thalomid) for ENL. Data are mainly derived from small randomized trials or retrospective studies conducted by the U.S. Public Health Service. These data consistently report generally successful treatment of the cutaneous manifestations of moderate to severe ENL.
- Thalidomide (Thalomid) is not indicated as monotherapy for ENL treatment in the presence of moderate to severe neuritis. Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering should be maintained on the minimum dose necessary to control the reaction. Tapering off the medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.
- Dosing with thalidomide (Thalomid) in ENL should usually continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks.
- In patients with moderate to severe neuritis associated with a severe erythema nodosum leprosum reaction, corticosteroids may be started concomitantly with thalidomide (Thalomid). Steroid usage can be tapered and discontinued when the neuritis has improved.
Investigational or Not Medically Necessary Uses

I. Kaposi sarcoma
   A. A preliminary study of thalidomide (Thalomid) has shown some activity in patients with AIDS-related KS; however, further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.
   B. Pomalidomide (Pomalyst) was studied in one ongoing, open-label, single center, single arm, Phase 1/2 trial with 28 patients with KS. There were 18 HIV-positive patients and 10 HIV-negative patients included in the trial. The HIV-positive patients continued on HAART. The primary efficacy outcome was ORR. The ORR was 71% (95% CI 51, 87) for all patients with 12 HIV-positive patients and 8 HIV-negative patients having a response. The duration of response was 12.5 months (95% CI 6.5, 24.9) for HIV-positive patients and 10.5 months (95% CI 3.9, 24.2) for HIV-negative patients. NCCN guidelines recommend pomalidomide (Pomalyst) as the preferred subsequent systemic therapy for relapsed/refractory therapy after first-line systemic options liposomal doxorubicin or paclitaxel; however, this is based on preliminary evidence from an early-phase, single center, open-label trial. Further evaluation in larger, well-controlled studies are needed to support the use of pomalidomide (Pomalyst) in the setting of KS.

II. Behçet syndrome
   A. The efficacy of thalidomide monotherapy for mucocutaneous manifestations of Behçet syndrome was evaluated in 96 patients compared to placebo. Only a minority of thalidomide (Thalomid)-treated patients responded to treatment, and some symptoms worsened. Furthermore, 7% of thalidomide-treated patients developed peripheral neuropathy.
   B. The use of thalidomide (Thalomid) for Behçet syndrome has fallen out of favor due to lack of proven efficacy and significant risk of neuropathy and teratogenicity.

III. Chronic lymphocytic leukemia (CLL)
   A. Lenalidomide (Revlimid) was studied in patients with previously treated CLL in a randomized, double-blind, placebo-controlled, Phase 3 trial (CONTINUUM). Patients included in the trial had been treated with two lines of therapy with at least a partial response after second-line therapy, had received a purine analogue, bendamustine, anti-CD20 antibody, chlorambucil, or alemtuzumab as first-line or second-line treatment; and had an Eastern Cooperative Oncology Group performance score of 0–2. Co-primary endpoints were PFS and OS; the primary endpoint was later changed to OS after the data cutoff for analysis. With a median follow-up of 31.5 months, there was no significant difference in OS between the lenalidomide (Revlimid) and the placebo groups (median 70.4 months, 95% CI 57.5–not estimable [NE] vs NE, 95% CI 62.8–NE; hazard ratio [HR] 0.96, 95% CI 0.63–1.48; p=0.86).

IV. Diffuse large B-cell lymphoma (DLBCL)
   A. NCCN guidelines list lenalidomide (Revlimid) maintenance for patients 60-80 years of age as a Category 2B recommendation. This is based off the results of an open-label, single-arm, Phase 2 trial in 48 adults with de novo DLBCL. Further evaluation in higher quality trials is needed to support its use.
B. In the relapsed setting, lenalidomide (Revlimid) was studied in small, Phase 2, open-label trials consisting of low-quality evidence. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.

V. Multiple myeloma, as part of quadruple (“quad”) regimen
   A. Although triplet regimens remain the standard of care for MM, there is growing interest in quad regimens which may include the addition of monoclonal antibodies [e.g. daratumumab (Darzalex), elotuzumab (Empliciti)] to standard triplet backbone regimens. The current evidence available to support this use is limited to case series or small trials. Larger studies evaluating the safety and efficacy of these regimens are underway.

VI. Non-Hodgkin’s lymphoma (NHL)
   A. Lenalidomide (Revlimid) was evaluated in patients with relapsed or refractory aggressive NHL, in an open-label, Phase 2 trial (n=49). Treatment with lenalidomide (Revlimid) led to an ORR of 35% and a median PFS of 4 months. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.

VII. Myelofibrosis
   A. Lenalidomide (Revlimid) was evaluated in a small, open-label, Phase 2 trial in combination with prednisone that reported a treatment response in 10 of 42 subjects, with 37 patients reporting a grade 3 or 4 toxicity. In an analysis of three consecutive Phase 2 trials of patients with myelofibrosis (n=125), single agent lenalidomide (Revlimid) and lenalidomide (Revlimid) plus prednisone produced higher response rates than thalidomide (Thalomid), though not statistically significant (p=0.06). Further studies are warranted. An additional trial by Daver et al. that evaluated lenalidomide (Revlimid) in combination with ruxolitinib (Jakafi) was terminated early due to failure to meet the predetermined efficacy rules for treatment success.

B. Pomalidomide (Pomalyst) has been evaluated as a treatment option for MF-associated anemia. Results from two small randomized studies produced conflicting results.

C. Enrollment in a clinical trial should be considered for all patients with myelofibrosis-associated anemia.

VIII. POEMS syndrome
   A. Regimens used as systemic therapy for POEMS syndrome with widespread osteosclerotic lesions or bone marrow involvement are modelled after those used in other conditions, such as MM. There are limited data to guide choice in therapy.

   B. Case reports have demonstrated clinical improvement after treatment with lenalidomide (Revlimid) with or without dexamethasone. Two small, uncontrolled studies reported responses in over 70% with 60 to 75% progression free at three years.

   C. Thalidomide (Thalomid) has also shown activity but is associated with a less favorable side effect profile.

   D. Larger, well-controlled trials are needed to confirm the safety and efficacy of these agents for POEMS syndrome.

IX. Systemic light chain amyloidosis (AL)
   A. There is insufficient evidence to support the use of lenalidomide (Revlimid) or pomalidomide (Pomalyst) for the management of AL. Both medications are listed in NCCN guidelines among several other treatment options; however, the optimal treatment of the...
underlying plasma cell disorder has not been identified. Treatment of AL should be in the context of a clinical trial when possible.

References

25. Freedman AS. Treatment of relapsed or refractory mantle cell lymphoma. In: UpToDate, Lister A (Ed), UpToDate, Waltham, MA. (Accessed on February 05, 2020).

Policy Implementation/Update:

<table>
<thead>
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<tr>
<td>Addition of new indication for Kaposi Sarcoma for Pomalyst as experimental and investigational</td>
<td>06/2020</td>
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<td>- 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</td>
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<td>- Added CLL to the not medically necessary section</td>
<td>04/2020</td>
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<td>- Added the following experimental/investigational indications:</td>
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<td>- As part of a quadruple regimen for MM</td>
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<tr>
<td>- Systemic light chain amyloidosis</td>
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<td>- POEMS</td>
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<td>- Behçet syndrome</td>
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<td>Added pomalidomide (Pomalyst) and thalidomide (Thalomid) agents to policy; removed black box warnings and precautions readily available in compendia; removed laboratory criteria.</td>
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<td>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.</td>
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<td>Excluded package insert/monitoring question and removed renewal question regarding regular hematological laboratory tests, extended initial approval from 3 months to 6 months.</td>
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**Ietermovir (Prevymis™)**

**UMP POLICY**

**Policy Type: PA/SP**

**Pharmacy Coverage Policy: UMP130**

**Description**

Ietermovir (Prevymis) is an orally administered antiviral agent that inhibits cytomegalovirus (CMV) deoxyribonucleic acid (DNA) terminase complex which helps prevent CMV infection in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

**Length of Authorization**

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

**Quantity limits**

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<td>Ietermovir (Prevymis)</td>
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**Initial Evaluation**

I. Ietermovir (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 ietermovir (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. Treatment with valacyclovir (Valtrex), or ganciclovir (Cytobene) has been ineffective, contraindicated, or not tolerated; **AND**
   H. If the request is for ietermovir (Prevymis) 240 mg, it will be used in combination with cyclosporine.

II. Ietermovir (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

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

I. 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).

II. Guidelines for HSCT recommend valacyclovir (Valtrex), ganciclovir (Cytobene), foscavir (Foscarnet), or letermovir (Prevymis) for CMV prophylaxis. The guidelines state that foscavir (Foscarnet) and letermovir (Prevymis) have a more favorable side effect profile; however, do not recommend preference of one agent over another in regards to efficacy.

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)].

Investigational or Not Medically Necessary Uses

I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the following indications below:
   A. Prevention of CMV infection or disease in all other settings EXCEPT HSCT
   B. Treatment for CMV infection or disease

References


Policy Implementation/Update:

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<th>November 2019</th>
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</thead>
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</table>
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP044

Description
Levodopa (Inbria) 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

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<tr>
<th>Dosage Form</th>
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<td>42 mg capsules</td>
<td>Parkinson’s Disease</td>
<td>120 capsules/30 days</td>
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<td></td>
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<td>300 capsules/30 days</td>
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Initial Evaluation

I. Levodopa (Inbria) 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); 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 4 times a day for a minimum of 2 weeks prior to starting levodopa (Inbria); 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 (Inbria) 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 (Inbria); AND
6. Treatment with 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**
   iii. 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 previously received treatment with levodopa (Inbrija); **AND**
II. Continues to meet criteria identified in section I of the Initial Evaluation; **AND**
III. Documentation that member has a reduction in wearing off period from baseline; **AND**
IV. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. Moderate to severe Parkinson’s disease symptoms were defined in the pivotal SPAMSTM-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 SPAMSTM-PD trial
IV. Due to the safety concerns, patients with chronic respiratory disease are excluded from the SPAMSTM-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

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

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

October 01, 2020

Policy Implementation/Update:

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

Pharmacy Coverage Policy: UMP131

Description
Lomitapide (Juxtapid) is a microsomal triglyceride transfer protein inhibitor used to reduce low density lipoprotein-cholesterol (LDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

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

Quantity Limits

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<th>Indication</th>
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<tr>
<td>Lomitapide (Juxtapid)</td>
<td>5 mg capsules</td>
<td>Homozygous familial hypercholesterolemia (HoFH)</td>
<td>30 capsules /30 days</td>
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<td>10 mg capsules</td>
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<td>20 mg capsules</td>
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<td>60 mg capsules</td>
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Initial Evaluation

I. Lomitapide (Juxtapid) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a cardiologist, endocrinologist, or lipid specialist; **AND**
   C. Member has a diagnosis of **homozygous familial hypercholesterolemia (HoFH)** as confirmed by one of the following:
      1. Genetic confirmation of two mutant alleles at the LDLR, Apo-B, PCSK9, or ARH adaptor protein 1/LDLRAP1 gene locus; **OR**
      2. Untreated LDL-C >500 mg/dL; **OR**
      3. Treated LDL-C ≥ 300 mg/dL with one of the following:
         i. Cutaneous or tendon xanthoma before ten years of age; **OR**
         ii. History of heterozygous familial hypercholesterolemia (HeFH) in both parents; **AND**
   D. Member will be on concurrent treatment with a high dose statin **plus** another lipid lowering therapy (e.g. ezetimibe, fibrate, nicotinic acid, LDL-apheresis) unless all are contraindicated, or not tolerated; **AND**
   E. Treatment with a PCSK-9 inhibitor [e.g. alirocumab (Praluent), evolocumab (Repatha)] has been ineffective, contraindicated, or not tolerated; **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

4. Rosenson, RS. Familial hypercholesterolemia in adults: Overview. In; UpToDate. Saperia, GM (Ed), UpToDate, Waltham, MA, 2019
5. Rosenson, RS. Treatment of drug-resistant hypercholesterolemia. In: UpToDate, Saperia, GM (Ed), UpToDate, Waltham, MA, 2019

Policy Implementation/Update:

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<tr>
<td>Last Reviewed</td>
<td>11/2015, 12/2019</td>
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Action and Summary of Changes

- 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
mecasermin (Increlex®)
UMP POLICY

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

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
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<tr>
<td>mecasermin (Increlex)</td>
<td>40 mg/4 mL multiple dose vial</td>
<td>Severe primary insulin-like growth factor (IGF-1) deficiency; Growth hormone (GH) gene deletion with neutralizing antibodies to GH</td>
<td>7.2 mg/kg/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation
I. Mecasermin (Increlex) may be considered medically necessary when the following criteria below are met:
   A. Member is a between 2-18 years of age; AND
   B. Medication is prescribed by, or in consultation with, a pediatric endocrinologist or a pediatric nephrologist; AND
   C. Member has evidence of non-closure of the epiphyseal plate confirmed by radiograph; AND
   D. A diagnosis of one of the following:
      1. Severe primary insulin-like growth factor (IGF-1) deficiency
         i. Member meets ALL of the following:
            a. Height standard deviation score ≤ -3.0; AND
            b. Basal IGF-1 standard deviation score ≤ -3.0; AND
            c. Normal or elevated growth hormone (GH) level, [serum growth hormone level of ≥ 10 ngm/mL to at least two stimuli (insulin, levodopa, arginine, clonidine, or glucagon)]; OR
      2. Growth hormone (GH) gene deletion
         i. Member has developed neutralizing antibodies to GH; AND
         ii. Member has normal thyroid function (TSH in the range of 0.5-6 uIU/mL); AND
iii. Member is not malnourished (BMI < 18 kg/m²); AND
iv. Member does not have active or suspected neoplasia (e.g. cancer)

II. Mecasermin (Increlex) is considered investigational when used for all other conditions, including but not limited to:
   A. Secondary forms of IGF-1 deficiency such as:
      1. GH deficiency
      2. Malnutrition
      3. Hypothyroidism
      4. Chronic treatment with pharmacologic doses of anti-inflammatory steroids

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through the health plan; AND
II. Member has shown a response in the first 6 months of the IGF-1 therapy (e.g. increase in height, increase in height velocity); AND
III. Member has evidence of non-closure of the epiphyseal plate, confirmed by radiograph

Supporting Evidence

I. Mecasermin (Increlex) is for the long-term treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency (primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Severe primary IGFD is defined by:
   • Height standard deviation score ≤ -3.0
   • Basal IGF-1 standard deviation score ≤ -3.0
   • Normal or elevated GH

II. Insulin-like growth factor (IGF-1) is the principal hormonal mediator of statural growth. Under normal circumstances, growth hormone (GH) binds to its receptor in the liver and other tissues, and stimulates the synthesis/secretion of IGF-1.
   • In target tissues, the type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signaling, which stimulates multiple processes leading to statural growth.
   • The metabolic actions of IGF-1 are, in part, directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues.

III. Severe primary IGF-1 deficiency includes members with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient; therefore, they cannot be expected to respond adequately to exogenous GH treatment.

IV. Mecasermin (Increlex) is not a substitute to growth hormone (GH) for approved GH indication.

V. Mecasermin (Increlex) is not indicated for use after epiphyseal closure.

Investigational Use

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
I. Mecasermin (Increlex) is not intended for use in members with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

References


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<td>12/2008, 11/2019</td>
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<tr>
<td>Criteria updated to new policy format. Specific changes include: removal of bone age requirement (If male, bone age is less than 16 years of age; or if female, bone age is less than 14 years of age) and update on child 2 years of age or older.</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP134

Description
Mechlorethamine (Valchlor) is a topical nitrogen analog of sulfur mustard and is a biologic alkylating agent.

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

Quantity limits

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

Initial Evaluation

I. Mechlorethamine (Valchlor) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**  
   B. Medication is prescribed by, or in consultation with an oncologist or dermatologist; **AND**  
   C. Will not be used in combination with bexarotene (Targretin); **AND**  
   D. A diagnosis of **cutaneous T-cell lymphoma** when the following are met:  
      1. The disease is stage IA or IB (i.e., limited, localized); **AND**  
      2. The member is relapsed, refractory, or intolerant to at least one other skin-directed therapy (e.g., corticosteroids, phototherapy, imiquimod, topical retinoids, carmustine, local radiation).

II. Mechlorethamine (Valchlor) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Contact dermatitis  
   B. Non-Hodgkin lymphoma  
   C. Lichen planopilaris
Renewal Evaluation

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

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

III. Medication is prescribed by, or in consultation with, an oncologist or dermatologist; AND

IV. Member has exhibited response to therapy such as improvement in CAILS score, decrease in affected surface area, or decrease in plaque/scale elevation or severity.

Supporting Evidence

I. Mechlorethamine (Valchlor) gel was assessed in a randomized, observer-blinded, active-controlled (versus compounded mechlorethamine ointment), non-inferiority clinical trial of subjects with stage IA, IB, and II A mycosis fungoides-type cutaneous T-cell lymphoma. Subjects had received at least one prior skin-directed therapy, including the following: topical corticosteroids, phototherapy, bexarotene (Targretin) gel, topical nitrogen mustard. The median number of prior therapies was two. Mechlorethamine (Valchlor) was applied topically on a daily basis for 12 months. Subjects were evaluated for a response on a monthly basis for the first six months and then every two months for the last six months using the Composite Assessment of Index Lesion Severity (CAILS) score. This score is obtained by adding the severity score of each of the following categories for up to five index lesions: erythema, scaling, plaque elevation, and surface area. Response was defined by a 50% or greater reduction in baseline score. A complete response was defined as achieving a score of 0. Subjects were also evaluated using the Severity Weighted Assessment Tool (SWAT). The SWAT score is derived by measuring each involved area as a percentage of total body surface area (% BSA) and multiplying it by a severity weighting factor. Response was defined as a 50% or greater reduction in baseline SWAT score. Sixty percent of subjects achieved a response in CAILS score versus 48% with the comparator arm. For the SWAT score, 50% in the mechlorethamine (Valchlor) arm met criteria for response versus 46% of the comparator arm. Mechlorethamine (Valchlor) statistical non-inferiority was met.

II. The mean average daily use in the trial was 1-2 tubes per month. The cost of one tube of mechlorethamine (Valchlor) is $4,000-$5,000 per month; thus for a quantity exception to be considered, clinical review of body surface area affected, application amount, frequency, adherence, etc. is warranted.

Investigational or Not Medically Necessary Uses

I. Mechlorethamine (Valchlor) has not been sufficiently evaluated for safety and/or efficacy in the following settings:
   A. Contact dermatitis
   B. Non-Hodgkin lymphoma
   C. Lichen planopilaris
References


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<td>Prior authorization criteria transitioned to policy format. Criteria updated to allow for oncologist prescribing. Renewal criteria changed to require specialist prescriber and specified parameters for improvement.</td>
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Policy Type: PA/SP  

Pharmacy Coverage Policy: UMP046

**Description**

Mepolizumab (Nucala) is a monoclonal antibody (IgG1 Kappa) that antagonizes interleukin-5 (IL-5) for the indication of severe eosinophilic asthma (SEA) and eosinophilic granulomatosis with polyangiitis (EGPA).

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

**Quantity limits**

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<td>granulomatosis with polyangiitis</td>
<td>3 syringes/28 days</td>
<td>206952</td>
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<td>100 mg/mL syringe</td>
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<td>3 autoinjectors/28 days</td>
<td>206951</td>
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**Initial Evaluation**

I. Mepolizumab (Nucala) may be considered medically necessary when the following criteria below are met:
   A. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, omalizumab, reslizumab, etc.); AND
   B. A diagnosis of one of the following:
      1. **Severe Eosinophilic Asthma (SEA); AND**
         i. Member must be six years of age or older; AND
         ii. The member has severe asthma as defined by one of the following:
            a. Symptoms throughout the day
            b. Nighttime awakenings, often 7x/week
            c. SABA 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. The 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. Must be used for add-on maintenance treatment in members regularly receiving BOTH of the following:

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
a. Medium to high-dose inhaled corticosteroids; **AND**
b. An additional controller medication (e.g., long-acting beta agonist, leukotriene modifiers, etc.); **AND**
v. 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 above); **OR**

2. **Eosinophilic Granulomatosis with Polyangiitis (EGPA); AND**
   i. The member must be 18 years of age or older; **AND**
   ii. Member has a confirmed diagnosis of EGPA (aka Churg-Strauss Syndrome) as defined by ALL of the following:
      a. History or presence of asthma; **AND**
      b. Blood eosinophil level 10% or an absolute eosinophil count >1000 cells/mm3; **AND**
      c. TWO or more of the following criteria:
         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.).

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)

**Renewal Evaluation**

*Washington State Rx Services is administered by Moda Health*

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

*October 01, 2020*
I. Absence of unacceptable toxicity from the drug. (Examples of unacceptable toxicity include the following: parasitic (helminth) infection, herpes zoster infection, severe hypersensitivity reactions, etc.); **AND**

II. Treatment has resulted in clinical benefit for the following indications:

- **Severe Eosinophilic Asthma**
  
  i. Improvement in asthma symptoms or asthma exacerbations as evidenced by decrease in one or more of the following:

   1. Use of systemic corticosteroids
   2. Two-fold or greater decrease in inhaled corticosteroid use for at least 3 days
   3. Hospitalizations
   4. ER Visits
   5. Unscheduled visits to healthcare provider; **OR**

  ii. Improvement from baseline in forced expiratory volume in 1 second (FEV₁); **OR**

- **Eosinophilic Granulomatosis with Polyangiitis**

  i. Disease response as indicated by improvement in signs and symptoms compared to baseline 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

**Supporting Evidence**

I. Mepolizumab (Nucala) is indicated as an add-on maintenance treatment for members 6 years and older with a diagnosis of severe eosinophilic asthma (SEA), and indicated to treat adult members with eosinophilic granulomatosis with polyangiitis. 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.

II. The FDA approval of mepolizumab (Nucala) in the setting of severe eosinophilic asthma were evaluated in 3 randomized, placebo controlled multicenter trials of 24 to 52 weeks in duration. The primary outcome was the rate of exacerbation, and it was reduced by 47% (95% confidence interval [CI], 28 to 60) among members receiving intravenous mepolizumab and by 53% (95% CI, 36 to 65) among those receiving subcutaneous mepolizumab, as compared with those receiving placebo (P<0.001 for both comparisons). The members enrolled in this trial were 12 to 82 years of age.

III. 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.

Investigational or Not Medically Necessary Uses

I. Non-severe, non-eosinophilic phenotype asthma
   A. 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.

II. GPA (Wegener’s granulomatosis) with polyangiitis and MPA (microscopic polyangiitis)
   A. 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).

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>June 2019</th>
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</thead>
<tbody>
<tr>
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<td>August 2019</td>
</tr>
<tr>
<td>Last Updated</td>
<td>October 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>06/2019, 08/2019, 10/2019</td>
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<table>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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 &gt; 10% per ACR classification.</td>
<td>10/2019</td>
</tr>
<tr>
<td>New Policy</td>
<td>06/2019</td>
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</table>
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

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

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 Generalized Lipodystrophy** when the following are met:
      1. Provider attests that the fasting leptin concentration at baseline is below the normal range; AND
      2. Member has a diagnosis of type 2 diabetes mellitus (T2DM) or insulin resistance; AND
      3. Member has a persistent hemoglobin A1c (HbA1c) > 7% despite dietary intervention and medication management (e.g., metformin) for T2DM; AND
      4. Member has a diagnosis of hypertriglyceridemia; AND
      5. Member has persistent triglyceride levels > 250 mg/dL despite dietary intervention and medication management for hypertriglyceridemia (e.g., fibrates, omega-3 fatty acids); AND
      6. Member does not have any hematologic abnormalities (e.g., leukopenia, neutropenia, bone marrow abnormalities, lymphadenopathy).

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

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.

October 01, 2020
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, hypertriglyceridermia)

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 hypertriglyceridermia, fibrates and/or long-chain omega-3 fatty acids should be used for hypertriglyceridermia.
V. As part of the metreleptin (Myalept) Risk Evaluation and Mitigation Strategy (REMS) program, provider will need to evaluate members with acquired generalized lipodystrophy for significant hematologic abnormalities due to the reported risk of T-cell lymphoma in that population.

Investigational or Not Medically Necessary Uses

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

October 01, 2020
I. There is limited evidence to suggest the safety and efficacy of metreleptin (Myalept) outside of the FDA-approved indications of congenital or acquired generalized lipodystrophy. Additionally, the following indications listed below were denoted to have a “limitation of use” in the metreleptin (Myalept) package insert.

   A. Partial lipodystrophy
   B. Liver disease (e.g., nonalcoholic steatohepatitis [NASH])
   C. Human Immunodeficiency Virus (HIV) – related lipodystrophy
   D. Metabolic disease (e.g., T2DM, hypertriglyceridemia)

References


Policy Implementation/Update:

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<th>Date Created</th>
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<tr>
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<tr>
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<td>October 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>10/2019</td>
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<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
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<tbody>
<tr>
<td>Criteria transitioned into policy with the following updates: addition of supporting evidence, addition of investigational section along with supporting evidence, inserted lab values for type 2 diabetes and hypertriglyceridemia, added sample language to the renewal section, and assess for stability parameters upon renewal.</td>
<td>10/2019</td>
</tr>
</tbody>
</table>
midostaurin (Rydapt®)
UMP POLICY

Policy Type: PA/SP
Pharmacy Coverage Policy: UMP094

Description
Midostaurin (Rydapt) is an orally administered tyrosine kinase inhibitor (TKI) targeting FLT3 and KIT D816V receptors to induce cell apoptosis.

Length of Authorization
- Initial: Six months
- Renewal:
  i. AML: Cannot be renewed
  ii. Systemic mast cell disease: 12 months

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>midostaurin (Rydapt)</td>
<td>25 mg capsule</td>
<td>Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with cytarabine/daunorubicin induction and cytarabine consolidation</td>
<td>56 capsules/28 days</td>
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<tr>
<td></td>
<td></td>
<td>Systemic mast cell disease: aggressive systemic mastocytosis, systemic mastocytosis with hematological neoplasm, mast cell leukemia</td>
<td>224 capsules/28 days</td>
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Initial Evaluation
I. Midostaurin (Rydapt) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, an oncologist; AND
   C. A diagnosis of one of the following:
      1. Acute myeloid leukemia (AML); AND
         i. The member has FLT3 mutation-positive AML; AND
         ii. Will be used in combination with standard cytarabine and daunorubicin induction AND cytarabine consolidate therapy; AND
         iii. Will not be used with any other oncolytic therapy outside of cytarabine and daunorubicin; AND
         iv. The member has received no prior therapy for AML; OR
2. **Systemic mast cell disease; AND**
   i. Systemic mast cell disease is characterized by one of the following:
      aggressive systemic mastocytosis (ASM), systemic mastocytosis with
      associated hematological neoplasm (SM-AHN), or mast cell leukemia
      (MCL); **AND**
   ii. Midostaurin (Rydapt) will not be used in combination with any other
      oncolytic medication.

II. **Midostaurin (Rydapt) is considered investigational when used for all other conditions, including**
    but not limited to:
    A. Pediatric leukemia
    B. Rectal cancer
    C. Acute myeloid leukemia in absence of FLT3 mutation

**Renewal Evaluation**

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

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

III. Midostaurin (Rydapt) is prescribed by, or in consultation with an oncologist; **AND**
    A. For **acute myeloid leukemia**:
       a. No renewal, one 6-month (initial) approval per lifetime.
    B. For **systemic mast cell disease**;
       a. Midostaurin (Rydapt) will not be used in combination with any other oncolytic
          medication; **AND**
       b. Clinical documentation of response to treatment, such as stabilization or
          improvement of disease, and absence of unacceptable toxicity from the medication.

**Supporting Evidence**

I. Midostaurin (Rydapt) was evaluated in three trials. Trial 1: in combination with chemotherapy in
   a randomized, double-blind, placebo-controlled trial in adults with FLT3-mutated AML. Subjects
   received 50 mg twice daily on days 8-21 for up to two cycles, followed by up to 12 months of
   midostaurin (Rydapt) therapy. Although evaluated for up to one year of therapy, the FDA-
   approval for midostaurin (Rydapt) indicates combination therapy with cytarabine and
daunorubicin for two cycles of induction and four cycles of consolidation - for a complete total
   of six 28-day cycles. The primary outcome was overall survival (OS) which was statistically in
   favor of midostaurin (Rydapt) [HR 0.77; 95% CI 0.63-0.95, p=0.016]; however, OS data plateaued
   before reaching the median. Median survival could not be reliably estimated.

II. Midostaurin (Rydapt) has not been sufficiently evaluated for safety and/or efficacy in
    combination with any other oncolytic medication outside of cytarabine and daunorubicin in the
    setting of AML.
III. In Trial 2, midostaurin (Rydapt) was evaluated in a single-arm, open-label trial in ASM, SM-AHN, and MCL, collectively referred to as advanced SM. The trial included 116 adult subjects that had relapsed or progressed on or after 0-2 prior therapies. The primary outcome was complete remission (CR) plus incomplete remission (ICR) by six cycles via the Valent criteria for ASM and SM-AHN, with twenty-one percent of subjects meeting the primary endpoint (16-38%, depending on the specific type of SM). The median duration of CR+ICR was not reached at time of evaluation, and the median time to CR+ICR was 0.5 months.

IV. Trial 3 was a single-arm, open-label trial of 26 subjects with advanced SM. By Valent criteria, 10 achieved a response by two cycles that was sustained for at least eight weeks.

V. Midostaurin (Rydapt) is available in 25 mg capsules to be given as 50 mg twice daily on days 8-21 of each 28-day cycle for a total of six cycles in AML or, given as 100 mg twice daily continuously for SM.

Investigational or Not Medically Necessary Uses

I. The safety and efficacy of midostaurin (Rydapt) has not been sufficiently established in the following settings:
   A. Pediatric leukemia
   B. Rectal cancer
   C. Acute myeloid leukemia in absence of FLT3 mutation

References


Policy Implementation/Update:

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<th>Date Created</th>
<th>July 2017</th>
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<tr>
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<td>August 2017</td>
</tr>
<tr>
<td>Last Updated</td>
<td>November 2019</td>
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<table>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior authorization criteria transitioned to policy. Age requirement added. Clarification of appropriate line of therapy required for approval. Renewal allowance removed for AML and extended to six months for SM.</td>
<td>11/2019</td>
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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP095

Description
Mifepristone (Korlym) is a cortisol receptor blocker indicated for hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing’s syndrome.

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

Quantity limits

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

Initial Evaluation

I. Mifepristone (Korlym) may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
   C. A diagnosis of **hyperglycemia secondary to hypercortisolism in members with endogenous Cushing’s syndrome** when the following are met:
      1. Member has a diagnosis of type 2 diabetes **OR** glucose intolerance; **AND**
      2. Baseline hemoglobin A1c (HbA1c) has been provided in this request; **AND**
      3. Member has had an inadequate response to pituitary surgery or is not a candidate for surgery; **AND**
      4. Treatment with **TWO** of the following has been ineffective, not tolerated, or all are contraindicated:
         i. Ketoconazole; **OR**
         ii. Cabergoline (Dostinex); **OR**
         iii. Metyrapone (Metopirone); **OR**
         iv. Mitotane (Lysodren)

II. Mifepristone (Korlym) is considered not medically necessary when criteria above are not met and/or when used for:
   A. Hypertension associated with Cushing’s syndrome
   B. Termination of pregnancy
   C. Induction of labor
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 hypercortisolism despite first-line intervention via surgical treatment and radiotherapy. Per label, the reasons for medical treatment was failed surgery, recurrence of disease, and a poor medical candidate for surgery. The study was split into two cohorts, diabetes and hypertension. A. The primary efficacy analysis for the diabetes cohort was an analysis of responders (patient who had a ≥25% reduction from baseline in glucose AUC). The primary efficacy analysis was conducted in the modified intent-to-treat population (n=25); 15 of 25 patients (60%) were treatment responders (95% CI: 39%, 78%).
   B. As for the hypertension cohort, there were no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21).
   C. Participants in the study showed varying degrees of improvement in Cushing’s syndrome manifestations such as cushingoid appearance, acne, hirsutism, striae, psychiatric symptoms, and excess total body weight.
II. According to the Endocrine Society Clinical Practice Guideline, first line treatment is transsphenoidal surgery (TSS) regardless of the cause. Although surgical treatment is optimal, medical therapy is often required when surgery is delayed, contraindicated, or unsuccessful. Medical therapy options within guidelines consist of steroidogenesis inhibitors (i.e. ketoconazole, metyrapone, mitotane, etomidate), pituitary-directed treatments (i.e. cabergoline, pasireotide), and glucocorticoid antagonists (i.e. mifepristone). Guidelines do not prefer one medical therapy over another; however, guidelines do recommend glucocorticoid antagonists (i.e. mifepristone) in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after TSS.
Investigational or Not Medically Necessary Uses

I. Hypertension associated with Cushing’s syndrome
   A. In the clinical trial, the hypertension cohort demonstrated no changes in mean systolic and diastolic blood pressures at the end of the trial relative to baseline in the modified intent-to-treat population (n=21).

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

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

IV. Type 2 diabetes related hyperglycemia
   A. Safety and efficacy has only been established for hyperglycemia secondary to hypercortisolism in members with endogenous Cushing’s syndrome; therefore, hyperglycemia due to type 2 diabetes alone is considered experimental and investigational.

References


Policy Implementation/Update:

<table>
<thead>
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<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed criteria regarding previous therapy to require treatment with two agents to have been ineffective, not tolerated, or contraindicated</td>
<td>08/2020</td>
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<tr>
<td>Updated renewal language to reflect new standard language</td>
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<tr>
<td>Updated supporting evidence</td>
<td></td>
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<tr>
<td>Transitioned criteria to policy with the following updates: defined surgery in the policy, removed pregnancy question, addition of supporting evidence, and addition of investigational diagnoses along with supporting evidence.</td>
<td>10/2019</td>
</tr>
<tr>
<td>Criteria created</td>
<td>09/2012</td>
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Policy Type: PA/SP | Pharmacy Coverage Policy: UMP096

Description
Migalastat (Galafold) is a pharmacologic chaperone that binds to and stabilizes specific mutant forms of alfa-galactosidase, thereby facilitating proper trafficking of the enzyme to lysosomes and increasing enzyme activity.

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

Quantity limits

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

Initial Evaluation
I. Migalastat (Galafold) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with an endocrinologist or a specialist in genetics; **AND**
   C. Medication will not be used in combination with Enzyme Replacement Therapy (ERT); **AND**
   D. A diagnosis of **Fabry disease** when the following are met:
      1. Documentation of a confirmed diagnosis with mutation of alpha-galactosidase A (alpha-Gal A) gene; **AND**
      2. Documentation that member has a mutation in the gene encoding galactosidase alpha gene (GLA) resulting in a mutant protein that would respond to migalastat (Galafold) (i.e. member has an **amenable** GLA variant); **AND**
      3. Documentation of the member’s baseline value of GL-3 inclusions per kidney interstitial capillary; **AND**
      4. Member does not have an eGFR <30 mL/minute/1.73 m2 OR ESRD requiring dialysis; **AND**
      5. Member is ERT-naïve and is not a candidate for ERT (due to contraindication, etc.); **OR**
      6. Member is ERT-experienced and not able to continue ERT therapy

Renewal Evaluation

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

October 01, 2020
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](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

Washington State Rx Services is administered by Moda Health

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

October 01, 2020
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.


Policy Implementation/Update:

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

**Policy Type:** 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

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</table>

**Initial Evaluation**

I. A quantity exception may be considered medically necessary when the following criteria below are met:
   
   A. Member has tried and failed prophylactic therapy with at least one agent listed in EACH of the three groups (these specific agents required). Please note, if a group is contraindicated, a trial and failure of three remaining agent is required:
      
      1. Group 1: propranolol, metoprolol, atenolol, timolol, nadolol

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*October 01, 2020*
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), ubrogepant (Ubrelvy), and rimegepant (Nurtec ODT) 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 rimegepant (Nurtec ODT) 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. The FDA maximum monthly dose for rimegepant (Nurtec ODT) is 15
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

IV. Lasmiditan (Reyvow) has warnings for MOH in the prescribing information. The label indicates treatment of more than four migraine days per month 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), ubrogepant (Ubrelvy), and rimegepant (Nurtec ODT) have not been FDA-approved, or sufficiently studied for safety and efficacy for migraine prophylaxis.

References

Policy Implementation/Update:

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<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
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<td>Corrected quantity limit for Nurtec to reflect manufacturer guidance and allowance of 8/30 or 16/30</td>
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<td>New FDA-approved migraine therapies added to policy: lasmiditan (Reyvow), ubrogepant (Ubrely),</td>
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<td>Prior authorization criteria transitioned to policy format. Addition of requirement to rule out</td>
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miltefeosine (Impavido®)
UMP POLICY

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

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<td>Cutaneous leishmaniasis</td>
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<td></td>
<td>Mucosal leishmaniasis</td>
<td>≥ 45 kg: 84 capsules/28 days</td>
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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](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**

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](https://www.cdc.gov/parasites/leishmaniasis/health_professionals/index.html#dx).
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<td>August 2016</td>
</tr>
<tr>
<td>Last Updated</td>
<td>October 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>4/2016, 10/2019</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitioned criteria into policy with the following additions:</td>
<td>10/2019</td>
</tr>
<tr>
<td>supporting evidence, investigational section and CDC diagnostic</td>
<td></td>
</tr>
<tr>
<td>recommendations.</td>
<td></td>
</tr>
</tbody>
</table>
### Multiple Sclerosis

#### UMP POLICY

**Policy Type:** PA/SP  
**Pharmacy Coverage Policy:** UMP047

**Description**
Medications included in this policy are subcutaneous and oral disease modifying therapies for the treatment of multiple sclerosis.

**Length of Authorization**

**Cladribine (Mavenclad) only**
- Initial: 12 months
- Renewal: Two months, maximum of one renewal per lifetime

**All other agents**
- Initial: Six months
- Renewal: 12 months

**Quantity limits**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>cladribine (Mavenclad)</td>
<td>10 mg tablets (box of 4 tablets)</td>
<td>Relapsing forms of multiple sclerosis (MS)</td>
<td>1 box (4 tablets)/26 days*</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets (box of 5 tablets)</td>
<td></td>
<td>1 box (5 tablets)/26 days*</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets (box of 6 tablets)</td>
<td></td>
<td>1 box (6 tablets)/26 days*</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets (box of 7 tablets)</td>
<td></td>
<td>1 box (7 tablets)/26 days*</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets (box of 8 tablets)</td>
<td></td>
<td>1 box (8 tablets)/26 days*</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets (box of 9 tablets)</td>
<td></td>
<td>1 box (9 tablets)/26 days*</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets (box of 10 tablets)</td>
<td></td>
<td>1 box (10 tablets)/26 days*</td>
</tr>
<tr>
<td>daclizumab (Zinbryta)</td>
<td>150mg/mL single-dose PFS</td>
<td></td>
<td>1 syringe/28 days</td>
</tr>
<tr>
<td>dimethyl fumarate (Tecfidera)</td>
<td>30 day starter pack</td>
<td></td>
<td>1 starter pack/30 days (60 capsules/30 days)</td>
</tr>
<tr>
<td></td>
<td>120 mg capsule</td>
<td></td>
<td>60 capsule/30 days</td>
</tr>
<tr>
<td></td>
<td>240 mg capsule</td>
<td></td>
<td>60 capsule/30 days</td>
</tr>
<tr>
<td>diroximel fumarate (Vumerity)</td>
<td>231 mg capsule</td>
<td></td>
<td>120 capsule/30 days</td>
</tr>
<tr>
<td>fingolimod (Gilenya)</td>
<td>0.25 mg capsule</td>
<td></td>
<td>30 capsules/30 days</td>
</tr>
<tr>
<td></td>
<td>0.5 mg capsule</td>
<td></td>
<td>30 capsules/30 days</td>
</tr>
</tbody>
</table>

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

October 01, 2020
<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage/Description</th>
<th>PFS/30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>glatiramer acetate (Copaxone, Glatopa, glatiramer acetate)</td>
<td>20 mg/mL single dose PFS</td>
<td>30 syringes per/30 days</td>
</tr>
<tr>
<td>glatiramer acetate (Copaxone, Glatopa, glatiramer acetate)</td>
<td>40 mg/mL single dose PFS</td>
<td>12 syringes/28 days</td>
</tr>
<tr>
<td>interferon beta-1a (Avonex)</td>
<td>30 mcg/0.5mL PFS</td>
<td>4 syringes (1 kit)/28 days</td>
</tr>
<tr>
<td>interferon beta-1a (Avonex)</td>
<td>30 mcg/0.5mL pen</td>
<td>4 pens/28 days</td>
</tr>
<tr>
<td>interferon beta-1a (Plegridy)</td>
<td>Starter Pack – (Pen Injector or PFS)</td>
<td>1 starter pack/28 days</td>
</tr>
<tr>
<td>interferon beta-1a (Plegridy)</td>
<td>125 mcg/0.5mL (Pen Injector or PFS)</td>
<td>2 pens (or PFS)/28 days</td>
</tr>
<tr>
<td>interferon beta-1a (Rebif)</td>
<td>22 mcg/0.5mL (Auto-injector or PFS)</td>
<td>12 syringes/28 days</td>
</tr>
<tr>
<td>interferon beta-1a (Rebif)</td>
<td>44 mcg/0.5mL (Auto-injector or PFS)</td>
<td>12 syringes/28 days</td>
</tr>
<tr>
<td>interferon beta-1a (Rebif)</td>
<td>Titration Pack (PFS or Solution)</td>
<td>1 pack (12 syringes)/28 days</td>
</tr>
<tr>
<td>interferon beta-1b (Betaseron)</td>
<td>0.3 mg powder for reconstitution</td>
<td>14 syringes/28 days</td>
</tr>
<tr>
<td>interferon beta-1b (Extavia)</td>
<td>0.3 mg powder for reconstitution</td>
<td>15 syringes/30 days</td>
</tr>
<tr>
<td>ozanimod (Zeposia)</td>
<td>0.23 mg capsules</td>
<td>4 tablets/4 days</td>
</tr>
<tr>
<td>ozanimod (Zeposia)</td>
<td>0.46 mg capsules</td>
<td>3 tablets/3 days</td>
</tr>
<tr>
<td>ozanimod (Zeposia)</td>
<td>0.92 mg capsules</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>siponimod (Mayzent)</td>
<td>0.25 mg starter pack</td>
<td>12 tablets/5 days</td>
</tr>
<tr>
<td>siponimod (Mayzent)</td>
<td>0.25 mg tablets</td>
<td>112 tablets/28 days</td>
</tr>
<tr>
<td>siponimod (Mayzent)</td>
<td>2 mg tablets</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>teriflunomide (Aubagio)</td>
<td>7 mg tablets</td>
<td>28 tablets/28 days</td>
</tr>
<tr>
<td>teriflunomide (Aubagio)</td>
<td>14 mg tablets</td>
<td>28 tablets/28 days</td>
</tr>
</tbody>
</table>

*Maximum of 2 boxes/331 days

PFS: Prefilled Syringe

**Initial Evaluation**

**Interferon beta-1a (Avonex), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), glatiramer acetate (Glatopa), and glatiramer acetate (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.

1. Cladribine (Mavenclad), daclizumab (Zinbryta), diroximel fumarate (Vumerity), interferon beta-1a (Plegridy), interferon beta-1a (Rebif), interferon beta-1b (Betaseron), ozanimod (Zeposia),
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 two of the following have been ineffective, contraindicated, or not tolerated: interferon beta-1a (Avonex), dimethyl fumarate (Tecfidera), fingolimod (Gilenya), glatiramer acetate (Glatopa), glatiramer acetate (glatiramer acetate)

II. Glatiramer acetate (Copaxone) may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(D) above are met; AND
B. Documentation of treatment with Glatopa or generic glatiramer acetate has been ineffective, contraindicated, or not tolerated

III. Siponimod (Mayzent) may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(E) above are met; AND
B. CYP2C9 genotype has been confirmed; AND
C. Member does not have a CYP2C9*3/*3 genotype

IV. Interferon beta-1b (Extavia) may be considered medically necessary when the following criteria below are met:
A. Criteria I(A)-I(E) above are met; AND
B. Documentation of treatment with interferon beta-1b (Betaseron) has been ineffective, contraindicated, or not tolerated

V. Medications listed above are considered investigational when used for all other conditions, including but not limited to:
A. Primary Progressive MS (PPMS)
Renewal Evaluation

I. 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 a branded Copaxone product, documentation of treatment with Glatopa or glatiramer acetate has been ineffective, contraindicated, or not tolerated; **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. Tools used in diagnosis of MS:

### MS with a relapsing-remitting course
- Based upon two separate areas of damage (dissemination in space) in the CNS that have occurred at different points in time (dissemination in time). Unless contraindicated, MRI should be obtained.

<table>
<thead>
<tr>
<th>Dissemination in time (Development/appearance of new CNS lesions over time)</th>
<th>Dissemination in space (Development of lesions in distinct anatomical locations within the CNS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2 clinical attacks; OR</td>
<td>≥ 2 lesions; OR</td>
</tr>
<tr>
<td>1 clinical attack AND one of the following:</td>
<td>1 lesion AND one of the following:</td>
</tr>
<tr>
<td>o MRI indicating simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI compared to baseline scan</td>
<td>o Clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location</td>
</tr>
<tr>
<td>o CSF-specific oligoclonal bands</td>
<td>o MRI indicating ≥ 1 T2-hyperintense lesions characteristic of MS in ≥ 2 of 4 areas of the CNS (periventricular, cortical or juxtacortical, infratentorial, or spinal cord)</td>
</tr>
</tbody>
</table>

### 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.

Washington State Rx Services is administered by moda health

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October 01, 2020
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Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated to include ozanimod (Zeposia) as a non-preferred product</td>
<td>04/2020</td>
</tr>
<tr>
<td>Updated fingolimod (Gilenya) as a preferred product effective 4/1/2020 per WA PDL update</td>
<td>03/2020</td>
</tr>
<tr>
<td>Updated to add non-preferred Vumerity</td>
<td>11/2019</td>
</tr>
<tr>
<td>Updated to include box around preferred agents not requiring prior authorization</td>
<td>10/2019</td>
</tr>
<tr>
<td>Updated to new policy format. Added newly approved drugs Mayzent and Mavenclad. Added question requiring diagnosis confirmed and documented by laboratory report (e.g., MRI).</td>
<td>08/2019</td>
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<tr>
<td>Policy created from criteria</td>
<td>11/2017</td>
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</tbody>
</table>

References

1. daclizumab (Zinbryta) [Prescribing Information]. Biogen Inc. Cambridge, MA. May 2016
2. teriflunomide (Aubagio) [Prescribing Information]. Sanofi. Cambridge, MA. January 2016
4. Interferon beta-1a (Rebif) [Prescribing Information]. Serono, Inc. September 2005
6. Interferon beta-1b (Betaseron) [Prescribing Information]. Berlex Laboratories. Revised October 2006
7. Interferon beta-1b (Extavia) [Prescribing Information]. Bayer Health Care Pharmaceuticals Inc. Whippany, NJ. Revised November 2017
8. glatiramer acetate (Copaxone) [Prescribing Information]. Teva Pharmaceuticals, Inc., Revised February 2004
11. fingolimod (Gilenya) [Prescribing Information]. East Hanover, NJ: Novartis Corp. Revised August 2015
12. dimethyl fumarate (Tecfidera) [Prescribing Information]. Biogen Idec Inc. Cambridge, MA. January 2013
neratinib (Nerlynx®)
UMP POLICY

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>neratinib (Nerlynx)</td>
<td>40 mg tablets</td>
<td>Breast cancer, early stage, HER2-positive, following trastuzumab</td>
<td>180 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast cancer, advanced or metastatic HER2-positive</td>
<td></td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Neratinib (Nerlynx) may be considered medically necessary when the following criteria are met:
   A. Member is a female 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, an oncologist; AND
   C. Neratinib (Nerlynx) will not be used in combination with another oncology therapy unless outlined below (e.g. in combination with capecitabine in metastatic disease); AND
   D. The member has not previously progressed on, or after, treatment with another tyrosine kinase inhibitor (e.g., lapatinib [Tykerb], tucatinib [Tukysa]); AND
   E. A diagnosis of one of the following:
      1. Early stage (I-III) breast cancer; AND
         i. Documentation is provided showing the disease is HER2-positive AND hormone receptor (HR)-positive; AND
         ii. The member has received adjuvant trastuzumab-based therapy (e.g., Herceptin, Trazimera, Kanjinti, etc.) within the past 12 months; OR
      2. Advanced or metastatic breast cancer; AND
         i. Documentation is provided showing the disease is HER2-positive; AND
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

II. 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-positive breast cancer and had received 2 or more prior anti-HER2 regimens [e.g., trastuzumab (Herceptin), pertuzumab (Perjeta), trastuzumab emtansine (Kadcyla; TDM-1)] in the metastatic setting. Median progression free survival (PFS) was 5.6 months with neratinib (Nerlynx) plus capecitabine and 5.5 months with lapatinib plus capecitabine (HR, 0.76; 95% CI, 0.63 to 0.93; P=0.0059). Overall survival was 21.0 months with the neratinib (Nerlynx) arm and 18.7 months with the lapatinib arm; however, the between group difference was not statistically significant (HR, 0.88; 95% CI, 0.72 to 1.07; P=0.2086).

V. Patients in the NALA trial were excluded if they were previously treated with capecitabine, neratinib, lapatinib, or any other HER2 directed tyrosine kinase inhibitor. At this time, there is a lack of scientific evaluation for safety and efficacy of neratinib (Nerlynx) following progression on, or after, another tyrosine kinase inhibitor.

VI. In the NALA trial, 59% of patients were hormone receptor positive (HR+) and 41% were hormone receptor negative (HR-). Thus, coverage of neratinib (Nerlynx) is available regardless of hormone receptor status.

VII. ER testing should be used to determine if a patient is a candidate for endocrine therapies. Per NCCN guidelines, women with Stage IV or recurrent disease characterized by tumors that are HR-positive, HER2-positive tumors have the option of receiving HER2-directed therapy as a component of their treatment plan. Options include, treatment with a HER2-targeted therapy plus chemotherapy or endocrine therapy alone or in combination with HER2-targeted therapy. Endocrine therapy alone or in combination with HER2-targeted therapy is a less toxic approach compared with HER2-targeted therapy combined with chemotherapy. Premenopausal women treated with HER2-targeted therapy and endocrine therapy should receive ovarian suppression or ablation.
Investigational or Not Medically Necessary Uses

I. In the early stage breast cancer pivotal trial, ExteNET, subgroup analyses showed non statistically significant results for neratinib (Nerlynx) in the following populations:
   A. Breast cancer in members that have not received trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.) in the past 12 months
   B. Breast cancer that is not HR-positive
   C. Breast cancer in combination with trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.)

II. Neratinib (Nerlynx) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. Triple negative breast cancer
   B. Breast cancer that is HER-2 negative
   C. Non-small cell lung cancer
   D. Colorectal cancer
   E. Head and neck cancer
   F. Ovarian, endometrial, uterine cancer
   G. Bladder or rectal cancer
   H. Breast cancer for greater than one year
   I. Solid tumors, other than breast cancer

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

References


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of new indication for advanced or metastatic breast cancer. Addition of split fill management.</td>
<td>07/2020</td>
</tr>
<tr>
<td>Criteria transitioned to policy, with updates to newest format: inclusion of specialty provider, clarification on concurrent therapies, age requirement.</td>
<td>10/2019</td>
</tr>
<tr>
<td>Criteria created</td>
<td>09/2017</td>
</tr>
</tbody>
</table>
null
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 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


Policy Implementation/Update:

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<tr>
<td>Date Effective</td>
<td>August 2010</td>
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<tr>
<td>Last Updated</td>
<td>December 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>03/2012, 07/2012, 08/2012, 01/2013, 05/2018, 12/2019</td>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
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<tr>
<td>Prior authorization criteria transitioned to policy format. Expanded renewal duration from 6 months to 12 months for all indications. Required agent be used as monotherapy and not in combination with other oncologics.</td>
<td>12/2019</td>
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<tr>
<td>Added new indication in pediatric patients one year of age or older with Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase (Ph+ CML-CP). Allowed for approval in the second line CML setting after being treated with a TKI (other than imatinib). For GIST off-label use, added a requirement to try/fail regorafenib as well as the existing agents (imatinib and sunitinib).</td>
<td>05/2018</td>
</tr>
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</table>
nintedanib (Ofev®); pirfenidone (Esbriet®)
UMP POLICY

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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>nintedanib</td>
<td>100 mg capsules</td>
<td>Idiopathic pulmonary fibrosis (IPF); Systemic sclerosis-associated interstitial lung disease (SSc-ILD); Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype</td>
<td>60 capsules/30 days</td>
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<tr>
<td>Ofev</td>
<td>150 mg capsules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pirfenidone</td>
<td>267 mg capsules or tablets</td>
<td>Idiopathic Pulmonary Fibrosis (IPF)</td>
<td>207 capsules or tablets/30 days</td>
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<tr>
<td>Esbriet</td>
<td>801 mg tablets</td>
<td></td>
<td>90 tablets/30 days</td>
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</table>

Initial Evaluation

I. Nintedanib (Ofev) and pirfenidone (Esbriet) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, a pulmonologist; **AND**
   C. Nintedanib (Ofev) and pirfenidone (Esbriet) will not be used in combination with each other; **AND**
   D. Provider attests the member is currently abstaining from any form of smoking; **AND**

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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.

October 01, 2020
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:

<table>
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<tr>
<th>End Points</th>
<th>INPULSIS-1</th>
<th>INPULSIS-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted absolute mean change from baseline in FVC (mL)</td>
<td>Nintedanib (N=307)</td>
<td>-95.1</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=204)</td>
<td>-205.0</td>
</tr>
<tr>
<td></td>
<td>95% CI; p value</td>
<td>(71.3, 148.6; P&lt;0.001)</td>
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<tr>
<td>Adjusted absolute mean change from baseline in FVC (% predicted)</td>
<td>Nintedanib (N=307)</td>
<td>-2.8%</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=204)</td>
<td>-6.0%</td>
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<tr>
<td></td>
<td>95% CI; p value</td>
<td>(2.1, 4.3; P&lt;0.001)</td>
</tr>
</tbody>
</table>
V. The presence of SSc-ILD is defined by the identification of fibrotic features on HRCT scan. Surgical lung biopsy is seldom performed in SSc patients, unless the HRCT pattern is atypical, there is suspicion of a different diagnosis, or there is a complication such as cancer.

VI. Pulmonary function tests (PFT) in patients with SSc-ILD demonstrate a restrictive pattern, with FVC and diffusion capacity of the lung for carbon monoxide (DLCO). DLCO is a measure of the conductance of gas transfer from inspired gas to the red blood cells. A low DLCO combined with reduced lung volumes suggests interstitial lung disease (ILD).

VII. For systemic sclerosis-associated interstitial lung disease (SSc-ILD), nintedanib (Ofev) was studied in a Phase 3, randomized, double-blind, placebo-controlled trial (N=576) (SENSCIS trial). Patients received either nintedanib (Ofev) 150 mg twice daily (N=228) or placebo (N=288) for at least 52 weeks.

- The primary outcome: The adjusted annual rate of change in FVC (in mL): -52.4 mL per year in the nintedanib (Ofev) group and -93.3 mL per year in the placebo group over week 52 (absolute difference of 40.9 mL, 95% CI: 2.9, 79.0; p=0.04).

VIII. Safety and efficacy of nintedanib (Ofev) have not been established in pediatric patients.

IX. The safety and efficacy of pirfenidone (Esbriet) was studied in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in patients (40 to 80 years of age) with idiopathic pulmonary fibrosis (IPF) and a %FVC of at least 50%.

A. Study One: 52-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=278) versus placebo (n=277). The primary efficacy outcome for the change in %FVC at week 52 demonstrated a statistically significant treatment effect with pirfenidone (Esbriet) when compared to placebo.

B. Study Two: 72-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=174) or pirfenidone (Esbriet) 1197 mg/day (n=87) to placebo (n=174). The primary efficacy outcome for the change in %FVC at week 72 demonstrated a statistically significant treatment effect with pirfenidone (Esbriet) when compared to placebo.

C. Study Three: 72-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=171) to placebo (n=173). In this study, there was no statistically significant difference at week 72 for the change in %FVC from baseline when compared to placebo.

X. The exact etiology of IPF is not known, but the associated risk factors include cigarette smoking, viral infection, environmental pollutants, chronic aspiration, genetic predisposition, and drugs.

XI. According to the American Thoracic Society guidelines, the diagnosis of IPF requires:

A. Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).

B. The presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy.

C. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.
XII. The clinical efficacy of nitendanib (Ofev) has been studied in patients with chronic fibrosing ILDs with a progressive phenotype in a randomized, double-blind, placebo-controlled phase 3 trial (Study 5). A total of 663 patients were randomized in a 1:1 ratio to receive either nitendanib (Ofev) 150 mg twice daily or matching placebo for at least 52 weeks. Randomization was stratified based on high resolution computed tomography (HRCT) fibrotic pattern.

A. The primary endpoint was the annual rate of decline in FVC (in mL) over 52 weeks. There was a statistically significant reduction by 107 mL in patients receiving OFEV compared to patients receiving placebo.

XIII. High-resolution computed tomography (HRCT) of the chest is mandatory in order to assess if ILD is present and, if so, to begin the differential diagnosis.

XIV. Progression of fibrosing ILDs is reflected in an increase in fibrosis evident on a computed tomography scan, a decline in FVC and gas exchange (DLCO), worsening of symptoms and exercise capacity (6MWD), and deterioration in health-related quality of life.

A. There is no standardized definition of PF-ILD that clinicians and researchers have agreed upon. Several criteria have been used to define progression in patients with IPF, with most of these based on an absolute or relative decline in FVC and diffusing capacity of the lung for DLCO of greater than or equal to 5–10% or greater than or equal to 10–15%, a decline in 6MWD > 50 m, or worsening dyspnea and quality of life scores. FVC is a reliable, valid, and responsive measure of clinical status in patients, and a decline of 2-6%, although small, represents a clinically important difference. FVC is used as a surrogate marker of disease severity and progression. DLCO is considered a standard predictor of survival. The distance walked in the 6MWT is used in a variety of pulmonary diseases and is predictive of mortality.

Investigational or Not Medically Necessary Uses

I. There is currently no evidence to suggest safety and/or efficacy with nitendanib (Ofev) or pirfenidone (Esbriet), when used for the treatment of bronchiolitis obliterans syndrome (BOS), lymphangioleiomyomatosis (LAM), non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), 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).

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References


**Policy Implementation/Update:**

<table>
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<th>Action and Summary of Changes</th>
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<tbody>
<tr>
<td>Added nintedanib (Ofev) to the Moda Split Fill program</td>
<td></td>
</tr>
<tr>
<td>Added criteria for nintedanib (Ofev) new indication Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype [request is for nintedanib (Ofev) and member has greater than 10% fibrotic features confirmed by a high resolution computed tomographic (HRCT) scan and clinical signs of progression (eg. decline in %FVC with worsening of respiratory symptoms, or increasing extent of fibrotic changes on chest imaging)].</td>
<td>06/2020</td>
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<tr>
<td>Added criteria for baseline assessment [eg. forced vital capacity (%FVC) or carbon monoxide diffusing capacity (DLCO) or six minute walking distance (6MWD)]</td>
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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.

Policy created                                                                                       | 10/2014 |

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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.
niraparib (Zejula®)
UMP POLICY

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

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<tr>
<td>niraparib (Zejula)</td>
<td>100 mg capsules</td>
<td>Treatment for: advanced ovarian, fallopian tube, or primary peritoneal cancer</td>
<td>90 capsules/30 days</td>
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<tr>
<td></td>
<td></td>
<td>Maintenance for: recurrent or advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer</td>
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</tr>
</tbody>
</table>

Initial Evaluation

I. Niraparib (Zejula) may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; AND
   B. Medication is prescribed by, or in consultation with, an oncologist; AND
   C. Niraparib (Zejula) will be used as monotherapy; AND
   D. Member has not progressed on prior PARP inhibitor (e.g. olaparib [Lynparza], rucaparib [Rubraca]) therapy; AND
   E. Provider is requesting niraparib (Zejula) for Treatment (and not maintenance therapy); AND
   1. Member has a diagnosis of advanced (stage III or IV) ovarian, fallopian tube, or primary peritoneal cancer; AND
      i. Member has been treated with three or more prior lines of chemotherapy (e.g. cisplatin, carboplatin, paclitaxel, doxorubicin, bevacizumab, gemcitabine); AND
      a. Member has homologous recombination deficiency (HRD) positive tumor (i.e., tBRCAm); OR
b. Member without BRCA mutations and progressed at least six months after their last dose of platinum-based chemotherapy regimen (e.g. cisplatin, oxaliplatin, carboplatin); OR  

F. Provider is requesting niraparib (Zejula) for **Maintenance** therapy; **AND**  
   1. Member is in complete or partial response to their last platinum-based chemotherapy regimen (i.e., platinum-sensitive) (e.g. cisplatin, oxaliplatin, carboplatin); **AND**  
   2. Provider attests that member’s epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based chemotherapy regimen (e.g. cisplatin, oxaliplatin, carboplatin); **AND**  
   3. A diagnosis of one of the following:  
      i. **Advanced** (stage III or IV) ovarian, fallopian tube, or primary peritoneal cancer; **AND**  
         a. Member has completed at least one prior platinum-based chemotherapy regimen (e.g. cisplatin, oxaliplatin, carboplatin); **AND**  
         b. The member has **not** received bevacizumab (Avastin) in prior treatment; **AND**  
         c. Niraparib (Zejula) will **not** be used in combination with bevacizumab (Avastin); **OR**  
      ii. **Recurrent** epithelial ovarian, fallopian tube, or primary peritoneal cancer; **AND**  
         a. Member has experienced disease progression on or after at least two or more prior platinum-based chemotherapy regimens (e.g., cisplatin, carboplatin, oxaliplatin)

II. Niraparib (Zejula) is considered **investigational** when used for all other conditions, including but not limited to:  
   A. Used in combination with other chemotherapy or targeted therapy regimen.  
   B. Breast Cancer  
   C. Prostate Cancer  
   D. Lung Cancer  
   E. Advance Solid Tumors  
   F. Melanoma  
   G. Pancreatic cancer  
   H. Gastroesophageal cancer
Renewal Evaluation

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

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

III. Medication is prescribed by, or in consultation with, an oncologist; AND

IV. Member has exhibited a response to therapy such as stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

I. The safety and efficacy of niraparib (Zejula) in the setting of maintenance therapy for recurrent ovarian cancer was studied in a double-blind, placebo-controlled trial in adult patients with platinum-sensitive recurrent epithelial, ovarian fallopian tube, or primary peritoneal cancer. The patients were randomized 2:1 niraparib (Zejula) 300 mg orally daily or matched placebo within eight weeks of the last platinum-based chemotherapy regimen. The trial demonstrated a statistically significant improvement in progression free survival (PFS) for patients randomized to niraparib (Zejula) as compared with placebo in the gBRCAmut cohort and the non-gBRCAmut cohort.
   A. gBRCAmut Cohort: PFS in the niraparib (Zejula) arm was 21 and 5.5 in the placebo arm with a HR of 0.26 and 95% CI (0.17, 0.41).
   B. Non-gBRCAmut Cohort: PFS in the niraparib (Zejula) arm was 9.3 and 3.9 in the placebo arm with a HR of 0.45 and 95% CI (0.34, 0.61).

II. Therapy in the maintenance setting was initiated within eight weeks after completion of the last dose of platinum-based chemotherapy. Therefore, the inclusion of this as criteria (see above) is that treatment is started within a reasonable timeframe consistent with a maintenance treatment plan (i.e. as close to eight weeks as possible) while still recognizing that scheduling or other factors may impact the ability of a patient to start exactly within these first eight weeks.

III. The safety of niraparib (Zejula) for the treatment of advanced ovarian cancer after three or more chemotherapies was studied in a single arm trial with the investigator assessment of objective response rate (ORR) as the efficacy outcome measure. That trial included 98 patients with advanced ovarian cancer positive for homologous recombination deficiency (HRD) tumors, also known as BRCAmut positive tumors. Those patients were required to have been treated with three or more prior lines of chemotherapy, and those with history of PARP inhibitors were excluded. Additionally, patients without BRCA mutations must have progressed at least six months after their last dose of platinum-based chemotherapy regimen.
   IV. HRD (BRCAmut) positive ORR was 24% with 95% CI (16, 34) without BRCAmut, ORR was 20% with 95% CI (8, 37). Efficacy and safety of niraparib (Zejula) was assessed in a phase three, double-blind, randomized (PRIMA) clinical trial in patients with newly diagnosed advanced (stage III or IV) ovarian cancer. Seven hundred and thirty-three patients, who were in complete or partial response to first-line platinum-based chemotherapy, were randomized 2:1 to niraparib (Zejula) or matched placebo. Patients with and without homologous recombination deficiency (HRD, e.g. gBRCAm) were included. At the end of treatment period, niraparib (Zejula) treatment...
arm showed a statistically significant improvement in median progression free survival (PFS) as compared to placebo arm.

A. Homologous recombination deficiency (HRD; e.g. gBRCAm) cohort: median PFS was 21.9 months in niraparib (Zejula) arm and 10.4 months in placebo arm (hazard ratio 0.43; 95% CI, 0.31 to 0.59; P<0.001)

B. Overall population (without HRD; gBRCAm) cohort: median PFS was 13.8 months in niraparib (Zejula) arm and 8.2 months in placebo arm (HR 0.62; 95% CI, 0.5 to 0.76; p<0.001).

None of the treated patients had a history of taking bevacizumab (Avastin). Therefore, efficacy and safety of niraparib (Zejula) after first-line therapy with bevacizumab (Avastin), or in combination with, bevacizumab (Avastin) is not supported.

V. During PRIMA trial, serious adverse events occurred in 98.8% (N=478) patients in the treatment arm with 70.5% being grade ≥ 3. These numbers were 91.8% (N=224) and 46%, respectively in the placebo arm. Serious adverse events led to 79.5% dose interruption rates, 70.9% dose reduction rates, and 12% treatment discontinuation in the treatment group vs. 18%, 8.2%, and 2.5%, respectively, in the placebo group.

VI. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy to support the use of a subsequent PARP inhibitor following progression of disease on another PARP inhibitor.

Investigational or Not Medically Necessary Uses

I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the use of niraparib (Zejula) in the following settings listed below:
   A. Used in combination with other chemotherapy or targeted therapy regimen.
   B. Breast Cancer
   C. Prostate Cancer
   D. Lung Cancer
   E. Advance Solid Tumors
   F. Melanoma
   G. Pancreatic cancer
   H. Gastroesophageal cancer

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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of new indication and supporting evidence for first-line maintenance therapy in women with advanced ovarian cancer; Updated policy format to categorize recommendation for niraparib (Zejula) based treatment OR maintenance therapy; added split fill management</td>
<td>09/2020</td>
</tr>
<tr>
<td>Criteria transition into policy with the following updates made: addition of supporting evidence and investigation section, broke out the different indications (treatment versus maintenance therapy) due to the newly approved indication for late-line treatment in women with recurrent ovarian cancer, included mutation status for the treatment of recurrent ovarian cancer, included criterion around prior PARP inhibitor use, increase initial approval duration from three months to six months to be consistent with other payers, included age criterion per label, and removed the 8 weeks criterion around most recent platinum-based therapy in the setting of maintenance therapy in recurrent ovarian cancer; in place of the 8 weeks criterion, provider attestation and documentation is required instead.</td>
<td>11/2019</td>
</tr>
<tr>
<td>Criteria created</td>
<td>08/2017</td>
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</tbody>
</table>
nitisinone (Nityr™; Orfadin®)

UMP POLICY

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP140

Description
Nitisinone (Nityr; Orfadin) competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase (4HPPD), an enzyme present early in the tyrosine degradation pathway, thereby preventing the accumulation of toxic metabolites.

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

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>nitisinone</td>
<td>2 mg capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitisinone</td>
<td>2 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg tablet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitisinone</td>
<td>2 mg capsule</td>
<td>Hereditary tyrosinemia type 1</td>
<td>2 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>5 mg capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 mg capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 mg/mL suspension</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Nitisinone (Nityr; Orfadin) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a provider who specializes in the treatment of genetic or metabolic disorders; AND
   B. A diagnosis of hereditary tyrosinemia type 1 (HT-1) when the following are met:
      1. Elevated succinylacetone (SA); AND
      2. Documentation of baseline plasma tyrosine level; AND
      3. Treatment will be used in conjunction with a diet restricted in tyrosine and phenylalanine

II. Nitisinone (Nityr; Orfadin) is considered investigational when used for all other conditions, including but not limited to:
   A. Alkaptonuria

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

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

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

III. Member has exhibited improvement or stability of disease symptoms (e.g. biochemical and/or clinical response).

Supporting Evidence

I. In patients with HT-1, tyrosine metabolism is interrupted due to a lack of the enzyme (fumarylacetoacetate hydrolase) needed in the last step of tyrosine degradation. Toxic metabolites of tyrosine, succinylacetoacetate (SAA) and succinylacetone (SA), accumulate and cause liver and kidney toxicity. Nitisinone (Nityr; Orfadin) competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase (4HPPD), an enzyme present early in the tyrosine degradation pathway, thereby preventing the build-up of the toxic metabolites SAA and SA.

II. Nitisinone (Nityr; Orfadin) must be used in conjunction with a diet restricted in tyrosine and phenylalanine to prevent further increased tyrosine levels. Dose is titrated as needed based on biochemical and/or clinical response. If the biochemical response is satisfactory, the dosage should be adjusted only according to body weight gain. Dose should not be adjusted according to tyrosine concentration.

III. Nitisinone (Nityr; Orfadin) should be started as early as possible (i.e. immediately after diagnosis of HT1 by blood or urine measurement of SA).

IV. If the biochemical parameters (except plasma SA) have not normalized within one month of starting therapy, the dose should be increased to 1.5 mg/kg/day. The dose of nitisinone should be adjusted to completely suppress excretion of SA; however, it may take as long as three months for complete suppression of SA to occur. A dose of 2 mg/kg/day may be needed, especially in infants; although, this dose should be considered maximal. Monitoring of the nitisinone blood levels is recommended for dose adjustment and also to check adherence.

Investigational or Not Medically Necessary Uses

I. Nitisinone (Nityr; Orfadin) has not been sufficiently evaluated in the following settings. Limited evidence is available; however, safety and efficacy have not been established for:
   A. Alkaptonuria

References

Policy Implementation/Update:

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

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

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>obeticholic acid</td>
<td>5 mg tablets</td>
<td>Primary Biliary Cholangitis (PBC)</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial Evaluation
I. Obeticholic acid (Ocaliva) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, a gastroenterologist or hepatologist; AND
   B. A diagnosis of **Primary Biliary Cholangitis (PBC)** [i.e. primary biliary cirrhosis]; AND
      1. Diagnosis confirmed by **TWO** of the following:
         i. Alkalaine phosphate (e.g. ALP) level at least 1.5 times the upper limit of normal
         ii. Positive antimitochondrial antibodies (AMA) test
         iii. Histopathologic evidence (i.e. nonsuppurative cholangitis and destruction of small or medium-sized bile ducts); AND
      2. Treatment with ursodeoxycholic acid (e.g. Urso, Ursodiol) has been ineffective, contraindicated, or not tolerated; AND
         i. Inadequate response is defined as an alkaline phosphate level greater than 1.67 times the upper limit of normal after one year of treatment with ursodeoxycholic acid; AND
      3. Member has compensated liver disease (Child-Pugh A).

II. Obeticholic acid (Ocaliva) is considered **investigational** when used for all other conditions, including but not limited to:
   A. Non-alcoholic steatohepatitis (NASH)
   B. Non-alcoholic fatty liver disease (NAFLD)

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

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.
         o 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

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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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added supporting evidence for the investigational use in NASH</td>
<td>07/2020</td>
</tr>
<tr>
<td>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.</td>
<td>12/2019</td>
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<tr>
<td>Policy created</td>
<td>06/2016</td>
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</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>octreotide acetate (generic, Sandostatin)</td>
<td>50 mcg/mL ampule, vial, syringe</td>
<td>Acromegaly</td>
<td>90 ampules, vials, syringes/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastatic carcinoid tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vasoactive intestinal peptide tumor (VIPoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mcg/mL ampule, vial, syringe</td>
<td>Acromegaly</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastatic carcinoid tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vasoactive intestinal peptide tumor (VIPoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>500 mcg/mL ampule, vial, syringe</td>
<td>Acromegaly</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastatic carcinoid tumor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vasoactive intestinal peptide tumor (VIPoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1000mcg/5mL (200 mcg/mL) vial</td>
<td>Acromegaly</td>
<td>9 vials/30 days</td>
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<tr>
<td></td>
<td></td>
<td>Metastatic carcinoid tumor</td>
<td>23 vials/30 days</td>
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<tr>
<td></td>
<td></td>
<td>Vasoactive intestinal peptide tumor (VIPoma)</td>
<td>14 vials/30 days</td>
</tr>
<tr>
<td></td>
<td>5000mcg/5mL (1000 mcg/mL) vial</td>
<td>Acromegaly</td>
<td>2 vials/30 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastatic carcinoid tumor</td>
<td>5 vials/30 days</td>
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<tr>
<td></td>
<td></td>
<td>Vasoactive intestinal peptide tumor (VIPoma)</td>
<td>3 vials/30 days</td>
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<tr>
<td>octreotide acetate (Bynfezia Pen)</td>
<td>7000mcg/2.8mL (2500 mcg/mL) prefilled injection pen</td>
<td>Acromegaly</td>
<td>2 pens/30 days</td>
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<td></td>
<td>Metastatic carcinoid tumor</td>
<td>4 pens/30 days</td>
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<tr>
<td></td>
<td></td>
<td>Vasoactive intestinal peptide tumor (VIPoma)</td>
<td>2 pens/30 days</td>
</tr>
<tr>
<td>octreotide acetate (Mycapssa)</td>
<td>20 mg capsule</td>
<td>Acromegaly</td>
<td>112 capsules/28 days</td>
</tr>
</tbody>
</table>

Provider Administered Agents*

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

<table>
<thead>
<tr>
<th>Octreotide Acetate</th>
<th>10 mg vial</th>
<th>20 mg vial</th>
<th>30 mg vial</th>
<th>Acromegaly; Metastatic Carcinoid Tumor; Vasoactive Intestinal Peptide Tumor (VIPomas)</th>
<th>N/A</th>
</tr>
</thead>
</table>

*Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit.

**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**.
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.

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.
References

2. Melmed, S. Treatment of acromegaly. In: UpToDate. Martin, KA (Ed), UpToDate, Waltham, MA, 2019

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>9/2020</td>
</tr>
<tr>
<td>Transitioned to policy format and updated the following:</td>
<td>12/2019</td>
</tr>
<tr>
<td>• Added age requirement of 18 years or older</td>
<td></td>
</tr>
<tr>
<td>• For octreotide (Sandostatin), added requirement for inadequate response to generic octreotide, unless not tolerated or contraindicated</td>
<td></td>
</tr>
<tr>
<td>• Removed octreotide (Sandostatin LAR) from the policy as it is excluded from coverage under the pharmacy benefit</td>
<td></td>
</tr>
<tr>
<td>Previous review</td>
<td>10/2017</td>
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<tr>
<td>Criteria created</td>
<td>10/2016</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>olaparib</td>
<td>100 mg, 150 mg tablets</td>
<td>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); Ovarian cancer, recurrent (maintenance therapy); Pancreatic cancer, first-line therapy for gBRCA-mutated, metastatic adenocarcinoma</td>
<td>120 tablets/30 days</td>
</tr>
</tbody>
</table>

Please note: quantity exceptions of either strength are not allowed.

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; 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. Documented diagnosis of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer; AND

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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. Documented diagnosis of advanced (stage ≥III) epithelial ovarian, fallopian tube, or primary peritoneal cancer; AND

iii. Has not received bevacizumab in prior treatment; 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 an 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. Documented 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. Documented 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 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. Documented 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 attest that the disease has not progressed while on the first-line platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin).

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. Use after disease progression on or after prior PARP inhibitor therapy

E. 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 Stage I, IIA, IIB, or IIC) and patients with prior bevacuzimab 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
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

IV. In the pivotal trial for breast cancer with metastatic, HER2-negative and gBRCAm; eligible patients had received neoadjuvant or adjuvant treatment 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. Patients had received no more than two previous chemotherapy regimens for metastatic disease. More than two therapies in other settings (e.g., neoadjuvant, adjuvant) do not apply to this criterion.
- Eligible patients 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; the primary end point was 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, the treatment with olaparib (Lynparza) in the setting of metastatic gBRCAm pancreatic 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
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. Use in combination with other anti-cancer agents
   A. Olaparib has not been studied in combination with other anti-cancer agents for the treatment of ovarian or breast cancer. The evidence for safety in efficacy is limited to monotherapy. Use in combination with other anti-cancer agents is considered investigational.

References

### Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>02/2020</td>
</tr>
<tr>
<td>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.</td>
<td>12/2019</td>
</tr>
<tr>
<td>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.</td>
<td>03/2019</td>
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<tr>
<td>Criteria update: Added coverage criteria for ovarian cancer maintenance and metastatic breast cancer</td>
<td>02/2018</td>
</tr>
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</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>omacetaxine mepesuccinate (Synribo)</td>
<td>3.5 mg vial</td>
<td>Chronic or accelerated phase CML</td>
<td>Initial: 28 vials/28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 14 vials/28 days</td>
</tr>
</tbody>
</table>

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 performed 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

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### Policy Implementation/Update:

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

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

Pharmacy Coverage Policy: UMP175

Description
Omalizumab (Xolair®) is a 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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omalizumab (Xolair)</td>
<td>75 mg/0.5mL prefilled syringe</td>
<td>Allergic asthma</td>
<td>2 syringe per 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic mastocytosis</td>
<td>2 syringe per 28 days</td>
</tr>
<tr>
<td></td>
<td>150 mg/mL prefilled syringe</td>
<td>Allergic asthma</td>
<td>4 syringes per 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic idiopathic urticaria (CIU)</td>
<td>2 syringes per 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic mastocytosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg vial</td>
<td>Allergic asthma</td>
<td>6 vials per 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic idiopathic urticaria (CIU)</td>
<td>2 vials per 28 day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic mastocytosis</td>
<td></td>
</tr>
</tbody>
</table>

* Quantity limit can vary by IgE level and body weight. Higher allowances will be determined at point of request.

Initial Evaluation

I. **Omalizumab (Xolair)** may be considered medically necessary when the following criteria below are met:
   A. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, mepolizumab, reslizumab, etc.); AND
   B. A diagnosis of one of the following:
      1. Moderate to severe persistent allergic asthma; AND
      i. Member must be at least 6 years of age; AND
      ii. Member has a positive skin test or in vitro reactivity to a perennial aeroallergen; AND
      iii. Member must weigh between 20 kg (44 lbs.) and 150 kg (330 lbs.); AND
iv. Member has a serum total IgE level, measured before the start of treatment, of either:
   a. ≥ 30 IU/mL and ≤ 700 IU/mL in members age ≥ 12 years; OR
   b. ≥ 30 IU/mL and ≤ 1300 IU/mL in members age 6 to <12 years; AND
v. Member has documented ongoing symptoms of moderate-to-severe asthma* with a minimum (3) month trial on previous combination therapy including medium- or high-dose inhaled corticosteroids PLUS another controller medication (e.g., long-acting beta-2 agonist, leukotriene receptor antagonist, theophylline, etc.); OR

2. Chronic idiopathic urticaria (CIU); AND
   i. Member must be at least 12 years of age; AND
   ii. The 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 one, or more, month trial on previous therapy of a second-generation H1-antihistamine product**; AND
   vi. Member had an inadequate response to a one, or more, 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-antihistamine (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

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; 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:
   i. **Moderate to severe persistent allergic asthma**; AND
      1. Member must weigh between 20 kg (44 lbs.) and 150 kg (330 lbs.); AND
      2. Treatment has resulted in clinical improvement as documented by **one** or more of the following:
         a. Decreased utilization of rescue medications (e.g. albuterol); OR
         b. Decreased frequency of exacerbations (defined as worsening of asthma that requires increase in inhaled corticosteroid dose or treatment with systemic corticosteroids); OR
         c. Improvement in lung function (increase in percent predicted FEV1 or PEF) from pre- treatment baseline; OR
         d. Reduction in reported symptoms (e.g., decrease in asthma symptom score), as evidenced by decreases in frequency or magnitude of **one** or more of the following symptoms:
            i. Asthma attacks
            ii. Chest tightness or heaviness
            iii. Coughing or clearing throat
            iv. Difficulty taking deep breath or difficulty breathing out
            v. Shortness of breath
            vi. Sleep disturbance, night wakening, or symptoms upon awakening
            vii. Tiredness
            viii. Wheezing/heavy breathing/fighting for air; AND
   ii. **Chronic idiopathic Urticaria (CIU)**; AND
      1. Treatment with Xolair (omalizumab) has resulted in clinical improvement
as documented by improvement from baseline using objective clinical evaluation tools such as the 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. Disease response as indicated by improvement in signs and symptoms compared to baseline or a decreased frequency of exacerbations

### 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. Treatment for moderate to severe asthma has been studied in patients six years of age and older.

III. In clinical trials, patient’s disease was confirmed with a diagnosis of asthma for more than one year and a positive skin prick test demonstrating allergy to at least one perennial aeroallergen.

IV. Patients with baseline IgE between 30 and 700 IU/mL and body weight not more than 150kg were studied. Patients with IgE levels less than 30 IU/mL or greater than 700 IU/mL or weight greater than 150kg have not been studied and efficacy has not been demonstrated in a randomized controlled clinical trial.

V. Patients in clinical trials demonstrated lack of stability of asthma condition on inhaled or oral corticosteroids and controller inhalers.

VI. Use of omalizumab (Xolair) for the treatment of chronic idiopathic urticaria has not been studied in patients under 12 years of age.

VII. Clinical trials required a UAS17 score of greater than or equal to 16 with weekly reassessments to objectively measure treatment benefit.

VIII. Patients in the clinical trials demonstrated elevated disease severity scores despite ongoing treatment with standard of care H1 antihistamines for at least 2 weeks.

IX. 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.
X. Asthma severity classifications:

*Components of severity for classifying asthma as moderate may include any of the following (not all inclusive):

- Daily symptoms
- Nighttime awakenings > 1x/week but not nightly
- SABA use for symptom control occurs daily
- Some limitation to normal activities
- Lung function (percent predicted FEV1) >60%, but <80%
- Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to mild asthma

*Components of severity for classifying asthma as severe may include any of the following (not all inclusive):

- Symptoms throughout the day
- Nighttime awakenings, often 7x/week
- SABA use for symptom control occurs several times daily
- Extremely limited in normal activities
- Lung function (percent predicted FEV1) <60%
- Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma

XI. Abbreviated list of H1 antihistamine products:

**H1 Antihistamine Products (not all inclusive)**

- fexofenadine
- loratadine
- desloratadine
- cetirizine
- levocetirizine
- clemastine
- diphenhydramine
- chlorpheniramine
- hydroxyzine
- cyproheptadine
- brompheniramine
- tripolidine
- 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Asthma</td>
<td>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.</td>
</tr>
<tr>
<td>Chronic idiopathic urticaria</td>
<td>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.</td>
</tr>
<tr>
<td>All other indications</td>
<td>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.</td>
</tr>
</tbody>
</table>

II. Table 2: Weight based dosing every 4 weeks in members ≥ 12 years

<table>
<thead>
<tr>
<th>Omalizumab Doses Administered Every 4 Weeks (mg) in members ≥ 12 years</th>
<th>Pre-treatment serum IgE (IU/mL)</th>
<th>Body weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 to 60</td>
<td>&gt; 60 to 70</td>
</tr>
<tr>
<td>≥ 30 to 100</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>&gt; 100 to 200</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>&gt; 200 to 300</td>
<td>300</td>
<td>See the following table.</td>
</tr>
</tbody>
</table>

Washington State Rx Services is administered by Moda Health

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
III. Table 3: Weight based dosing every 2 weeks in members ≥ 12 years

<table>
<thead>
<tr>
<th>Pre-treatment serum IgE (IU/mL)</th>
<th>Body weight (kg)</th>
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<tbody>
<tr>
<td></td>
<td>30 to 60</td>
</tr>
<tr>
<td>&gt; 100 to 200</td>
<td>See previous table.</td>
</tr>
<tr>
<td>&gt; 200 to 300</td>
<td>See previous table.</td>
</tr>
<tr>
<td>&gt; 300 to 400</td>
<td>225</td>
</tr>
<tr>
<td>&gt; 400 to 500</td>
<td>300</td>
</tr>
<tr>
<td>&gt; 500 to 600</td>
<td>300</td>
</tr>
<tr>
<td>&gt; 600 to 700</td>
<td>375</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Pre-treatment IgE (IU/mL)</th>
<th>Dosing Freq. (weeks)</th>
<th>Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20-25</td>
<td>&gt;25-30</td>
</tr>
<tr>
<td>30-100</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>&gt;100-200</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>&gt;200-300</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>&gt;300-400</td>
<td>225</td>
<td>225</td>
</tr>
<tr>
<td>&gt;400-500</td>
<td>225</td>
<td>300</td>
</tr>
<tr>
<td>&gt;500-600</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>&gt;600-700</td>
<td>300</td>
<td>225</td>
</tr>
<tr>
<td>&gt;700-900</td>
<td>225</td>
<td>225</td>
</tr>
<tr>
<td>&gt;900-1100</td>
<td>225</td>
<td>300</td>
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<tr>
<td>&gt;1100-1200</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>&gt;1200-1300</td>
<td>300</td>
<td>375</td>
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Do Not Dose
References


Policy Implementation/Update:

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<tr>
<td>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.</td>
<td>02/2020</td>
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Previous reviews

- 02/2019
- 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
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Policy Type: PA

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnipod Dash Pod</td>
<td>5 pack Pod</td>
<td>Diabetes Mellitus</td>
<td>10 pods/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. 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 inability to self-inject insulin (e.g. unable to draw insulin from a vial or handle insulin pen)
         iv. Documentation of member inability to self-adjust insulin dose (e.g sliding scale dosing); AND
         v. Documentation of member ability to self-test glucose at least 4 times daily while on insulin

II. Omnipod Dash is considered not medically necessary 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 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 Dash insulin delivery system is not medically necessary for Type II Diabetes Mellitus in members that are not dependent on insulin.

References


Policy Implementation/Update:

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Opioid-Induced Constipation Agents

UMP POLICY

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

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<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>methylnaltrexone bromide</td>
<td>150 mg tablets</td>
<td>Treatment of opioid-induced constipation in adults with chronic non-cancer pain</td>
<td>90 tablets/30 days</td>
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<tr>
<td>bromide (Relistor)</td>
<td>12 mg vial/syringe</td>
<td>Treatment of opioid-induced constipation with advanced illness or pain caused by active cancer requiring opioid dosage escalation</td>
<td>30 single use vials or syringes/30 days</td>
</tr>
<tr>
<td></td>
<td>8 mg vial/syringe</td>
<td></td>
<td>30 single use vials or syringes/30 days</td>
</tr>
<tr>
<td>naldemedine (Symproic)</td>
<td>0.2 mg tablets</td>
<td>Treatment of opioid-induced constipation in adults with chronic non-cancer pain</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td>naloxegol (Movantik)</td>
<td>12.5 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>25 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
</tr>
</tbody>
</table>

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 lubiprostone (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). Methylaltrexone 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 methylaltrexone 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitioned criteria to policy: removed required trial and failure of lubiprostone (Amitiza) for all agents</td>
<td>11/2019</td>
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</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>osilodrostat (Isturisa)</td>
<td>1 mg tablets</td>
<td>Cushing’s disease</td>
<td>180 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>5 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 mg tablets</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 **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 (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.
   o 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.
   o 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%).
   o The key secondary endpoint was the proportion of patients with mUCFsULN 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.

Policy Implementation/Update:

<table>
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<tr>
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Washington State Rx Services is administered by modahealth

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.

October 01, 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

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<tbody>
<tr>
<td>ospemifene</td>
<td>60 mg tablets</td>
<td>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</td>
<td>30 tablets/30 days</td>
<td>178807</td>
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</tbody>
</table>

Initial Evaluation

I. Ospemifene (Osphena) may be considered medically necessary when the following criteria below are met:
   A. A diagnosis of moderate to severe vaginal dryness; AND
      1. Member is being treated for vaginal dryness as a symptom of vulvar and vaginal atrophy, due to menopause; AND
      2. Treatment with the following has been ineffective, contraindicated, or not tolerated:
         i. One systemic hormone replacement therapy (e.g., estradiol oral tablets, estradiol patch, estradiol injection); AND
         ii. One vaginal hormone replacement therapy (e.g., Estring, generic estradiol cream)

II. Ospemifene (Osphena) is an excluded medication when the following criteria below are met:
   A. A diagnosis of moderate to severe dyspareunia (difficult or painful sexual intercourse) as a symptom of vulvar and vaginal atrophy, due to menopause

Renewal Evaluation

I. 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

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

Policy Implementation/Update:

<table>
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<th>Date Created</th>
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<tr>
<td>Last Updated</td>
<td>September 2019</td>
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<td>Last Reviewed</td>
<td>03/2019, 09/2019</td>
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</tr>
</thead>
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<tr>
<td>Updated policy to remove coverage in the setting of dyspareunia as this is an excluded benefit.</td>
<td>09/2019</td>
</tr>
<tr>
<td>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.</td>
<td>03/2019</td>
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</table>
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP050

Description
Palbociclib (Ibrance®) is an orally administered CDK4/6 kinase inhibitor that reduces cellular proliferation of estrogen receptor-positive breast cancer.

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

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>palbociclib</td>
<td>75 mg</td>
<td>Breast cancer, advanced or metastatic, Her2-negative, hormone receptor-positive, in combination with fulvestrant following endocrine therapy</td>
<td>21 capsules or tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>capsules/tablets*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg</td>
<td>Breast cancer, advanced or metastatic, HER2-negative, hormone receptor-positive in men or postmenopausal women as initiation therapy in combination with an aromatase inhibitor</td>
<td>21 capsules or tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>capsules/tablets*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>125 mg</td>
<td>Breast cancer, advanced or metastatic, Her2-negative, hormone receptor-positive in men or postmenopausal women as initiation therapy in combination with an aromatase inhibitor</td>
<td>21 capsules or tablets/28 days</td>
</tr>
<tr>
<td></td>
<td>capsules/tablets*</td>
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*Please note: Beginning April 1st, 2020 the capsule formulation will no longer be available as the tablet formulation will be taking its place.

Initial Evaluation
I. Palbociclib (Ibrance®) 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; AND
   C. The medication will not be used in combination with other CDK4/6 inhibitors (e.g., ribociclib [Kisqali], abemaciclib [Verzenio]); AND
   D. The member has not previously progressed on or after treatment with another CDK4/6 inhibitor (e.g., ribociclib [Kisqali], abemaciclib [Verzenio]); AND
   E. A diagnosis of breast cancer when the following are met:
      1. The member has a diagnosis of hormone receptor-positive (HR+) and HER2-negative (HER2-) disease; AND
2. Disease is advanced (stage III) or metastatic (stage IV); **AND**
3. The medication is being prescribed for one of the following settings; 
   i. Initial endocrine based therapy for a man or postmenopausal woman 
      (natural or pharmacotherapy-induced); **AND**
      a. Palbociclib (Ibrance) will be administered in combination with an 
         aromatase inhibitor (e.g., letrozole [Femara], anastrozole 
         [Arimidex], exemestane [Aromasin]); **AND**
      b. If the member is male, a GnRH analog (e.g., goserelin [Zoladex], 
         leuprolide [Lupron]); will be administered along with an aromatase 
         inhibitor concurrently; **OR**
   ii. Following progression after endocrine therapy in a man or woman 
      (regardless of menopausal status); **AND**
      a. Palbociclib (Ibrance) will be administered in combination with 
         fulvestrant (Faslodex)

II. Palbociclib (Ibrance) is 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. Pancreatic neuroendocrine tumors (pNET)
   C. Ovarian cancer
   D. Central nervous system cancers (e.g., glioma, astrocytoma, head and neck, etc.)
   E. Colorectal cancer
   F. Urothelial cancer
   G. Leukemias and lymphomas
   H. Non-small-cell lung cancer
   I. Liposarcoma

**Renewal Evaluation**
   I. Member is 18 years of age or older; **AND**
   II. The medication is prescribed by, or in consultation with, an oncologist; **AND**
   III. Palbociclib (Ibrance) is not used in combination with other CDK4/6 inhibitors (e.g., ribociclib 
        [Kisqali], abemaciclib [Verzenio]); **AND**
   IV. Documentation is provided indicating disease response with palbociclib (Ibrance) as defined by 
       stabilization of disease or decrease in size of tumor or tumor spread; **AND**
   V. Absence of unacceptable toxicity from the medication

**Supporting Evidence**
   I. Clinical trials for the approval of palbociclib (Ibrance) evaluated adults with breast cancer of the 
      following characteristics: HR+, HER2-, advanced (stage III) or metastatic (stage IV). Two settings 
      were evaluated; Initial endocrine based therapy in combination with an aromatase inhibitor and 
      in combination with fulvestrant after progression on initial endocrine therapy. Initial FDA- 
      approvals were indicated for women only.
II. 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, 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 has been associated with inferior outcomes; likely due to inadequate estradiol suppression.

III. There is lack of scientific evidence from randomized controlled trials supporting the safety and/or efficacy for increased dosing or frequency. 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.

IV. 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. Either is considered acceptable status for aforementioned criteria.

V. There is lack of scientific evaluation for safety and efficacy of palbociclib (Ibrance) used concurrently, or following progression on or after, with another CDK 4/6 inhibitor. As of April 2019, 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.

VI. Known serious toxicities of palbociclib (Ibrance) include, but are not limited to, the following: neutropenia, embryo-fetal toxicity, thromboembolism, and hepatotoxicity. Common adverse events include, but are not limited to, the following: diarrhea, nausea, fatigue, abdominal pain, anemia, leukopenia, anorexia, vomiting, headache, dysgeusia, alopecia, thrombocytopenia, stomatitis, constipation, increase in liver enzymes, cough, pruritus, dizziness, increase creatinine levels, arthralgia, peripheral edema, respiratory infections, rash.

Investigational or Not Medically Necessary Uses

I. Palbociclib (Ibrance) has not been FDA-approved, or sufficiently studied for safety and efficacy, for the conditions or settings listed below:
   A. In combination with, or following progression on, another CDK4/6 inhibitor (e.g., ribociclib [Kisqali], abemaciclib [Verzenio])
   B. Pancreatic neuroendocrine tumors (pNET)
   C. Ovarian cancer
   D. Central nervous system cancers (e.g., glioma, astrocytoma, head and neck, etc.)
   E. Colorectal cancer
   F. Urothelial cancer
   G. Leukemias and lymphomas
   H. Non-small-cell lung cancer
I. Liposarcoma. Palbociclib (Ibrance) was evaluated in a phase II, nonrandomized, open-label, without comparator clinical trial that assessed the surrogate endpoint of progression-free survival. The quality of this evidence is considered very low, and clinical
value of this medication in liposarcoma, specifically dedifferentiated liposarcomas (WD/DDLS), is unknown at this time.

References


Policy Implementation/Update:

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<tr>
<th>Date Created</th>
<th>February 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>March, 2016</td>
</tr>
<tr>
<td>Last Updated</td>
<td>May 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>02/2016, 05/2019</td>
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<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated QL box to inform about transition to tablets</td>
<td>03/2020</td>
</tr>
<tr>
<td>Criteria update with new indication and FDA-approval of breast cancer in men. Criteria updated to avoid combination use or use after progression on another CDK4/6 inhibitor. Age criteria added. Approval durations increased.</td>
<td>05/2019</td>
</tr>
<tr>
<td>Criteria updated based on NCCN guidelines and PALOMA3 trial to allow treatment after disease progression on prior endocrine therapy.</td>
<td>01/2016</td>
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</table>

Washington State Rx Services is administered by moda HEALTH

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

October 01, 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

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
</thead>
<tbody>
<tr>
<td>palivizumab (Synagis)</td>
<td>100 mg/1mL</td>
<td>Respiratory syncytial virus (RSV) prophylaxis</td>
<td>15 mg/kg (1 dose) per 28 days</td>
<td>095334</td>
</tr>
<tr>
<td></td>
<td>50 mg/0.5mL</td>
<td></td>
<td></td>
<td>095335</td>
</tr>
</tbody>
</table>

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 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 age; OR
      2. Preterm Infants WITH Chronic Lung Disease; AND
         i. Member was born before 32 weeks, 0 days; AND
         ii. Member required 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 Chronic 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 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 has previous 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 not medically necessary 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. CDC utilized the past year’s surveillance season data to predict the timing of the next year’s outbreak; this information is updated annually.

II. 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.

III. 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 its high cost is associated with minimal benefit. 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.

IV. 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.
V. The indications and criteria associated are directly from the guidance provided by AAP 2014 RSV guidance.

Investigational or Not Medically Necessary Uses

I. The above listed diagnoses under the section of not medically necessary were called out in the APP 2014 RSV Guidance as not medically necessary for immunoprophylaxis with palivizumab (Synagis).

II. Treatment of RSV
   A. Safety and efficacy has not been established for the use of palicizumab (Synagis) for the treatment of RSV.

References

3. American Academy of Pediatrics: Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. Available at: https://pediatrics.aappublications.org/content/134/2/415

Policy Implementation/Update:

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<th>September 2008</th>
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<tr>
<td>Date Effective</td>
<td>October 2008</td>
</tr>
<tr>
<td>Last Updated</td>
<td>August 2012</td>
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<tr>
<td>Last Reviewed</td>
<td>12/2008, 07/2012, 05/2013, 09/2019</td>
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<tr>
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<th>Date</th>
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<tbody>
<tr>
<td>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.</td>
<td>09/2019</td>
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</tbody>
</table>
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

October 01, 2020
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>Parathyroid hormone (Natpara)</td>
<td>25 mcg/dose cartridge</td>
<td>Adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism</td>
<td>2 cartridges/28 days</td>
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<td>50 mcg/dose cartridge</td>
<td></td>
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<tr>
<td></td>
<td>75 mcg/dose cartridge</td>
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<tr>
<td></td>
<td>100 mcg/dose cartridge</td>
<td></td>
<td>2 cartridges/28 days</td>
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</tbody>
</table>

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

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.

October 01, 2020
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


Policy Implementation/Update:

<table>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria updated to new policy format.</td>
<td>11/2019</td>
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</table>
Parathyroid Hormones:
teriparatide (Forteo®), abaloparatide (Tymlos®)

UMP POLICY

Policy Type: PA/SP

Description
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, with a maximum of 26 fills total)

Quantity limits

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>teriparatide (Forteo)</td>
<td>250 mcg/mL</td>
<td>Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men</td>
<td>1 syringe/28 days</td>
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<td></td>
<td>Post-Menopausal Osteoporosis in Women</td>
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<tr>
<td></td>
<td></td>
<td>Glucocorticoid-induced Osteoporosis</td>
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<tr>
<td>abaloparatide (Tymlos)</td>
<td>2000 mcg/mL</td>
<td>Post-Menopausal Osteoporosis in Women</td>
<td>1 syringe/30 days</td>
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Initial Evaluation

I. Abaloparatide (Tymlos) 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. Use not 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: bisphosphonates (e.g., alendronate, ibandronate, zoledronic acid injection), raloxifene, or calcitonin (Fortical) has been ineffective, not tolerated, or ALL are contraindicated; AND

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

October 01, 2020
F. For teriparatide (Forteo):
   1. A diagnosis of one of the following:
      i. **Post-Menopausal Osteoporosis in Women**; **AND**
         a. Treatment with abaloparatide (Tymlos) has been ineffective, not tolerated or contraindicated; **OR**
      ii. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men**; **OR**
      iii. **Glucocorticoid-induced Osteoporosis**; **AND**
         a. Member is taking ≥ 5 mg prednisone or its equivalent daily with an anticipated duration of ≥ 3 months; **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), 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) 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) 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


Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
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<tr>
<td>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</td>
<td>04/2020</td>
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<tr>
<td>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</td>
<td>02/2020</td>
</tr>
<tr>
<td>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.</td>
<td>12/2019</td>
</tr>
<tr>
<td>Update criteria to include abaloparatide (Tymlos)</td>
<td>08/2017</td>
</tr>
<tr>
<td>Date effective</td>
<td>03/2016</td>
</tr>
<tr>
<td>Policy created</td>
<td>09/2005</td>
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</table>
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**

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>pasireotide diaspartate (Signifor)</td>
<td>0.3 mg/mL ampule</td>
<td>Cushing’s disease</td>
<td>60 ampules/30 days</td>
</tr>
<tr>
<td></td>
<td>0.6 mg/mL ampule</td>
<td></td>
<td>60 ampules/30 days</td>
</tr>
<tr>
<td></td>
<td>0.9 mg/mL ampule</td>
<td></td>
<td>60 ampules/30 days</td>
</tr>
</tbody>
</table>

*Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit.

**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

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>08/2020</td>
</tr>
<tr>
<td>Removal of UFC 24-hour urinary free cortisol level (UFC). Addition of age requirement and addition of previous trial of ketoconazole, metyrapone, or mitotane.</td>
<td>12/2019</td>
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<td>Criteria created</td>
<td>07/2013</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>peanut allergen powder-dnfp (Palforzia)</td>
<td>0.5 mg – 6 mg capsule sprinkle</td>
<td>Peanut allergy</td>
<td>13 capsule sprinkles/1 day</td>
</tr>
<tr>
<td></td>
<td>3 mg daily dose capsule sprinkle</td>
<td></td>
<td>45 capsule sprinkles/15 days</td>
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<td></td>
<td>6 mg daily dose capsule sprinkle</td>
<td></td>
<td>90 capsule sprinkles/15 days</td>
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<td>12 mg daily dose capsule sprinkle</td>
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<td>240 mg daily dose capsule sprinkle</td>
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<td>300 mg titration powder pack</td>
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<td>15 capsule sprinkles/15 days</td>
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<td></td>
<td>300 mg maintenance capsule sprinkle powder pack</td>
<td></td>
<td>30 capsule sprinkles/30 days</td>
</tr>
</tbody>
</table>

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 (> 0.35 kUA/L) or positive skin test (mean wheal diameter ≥ 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


Policy Implementation/Update:

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<th>Date</th>
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<tbody>
<tr>
<td>Policy created</td>
<td>05/2020</td>
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</table>
pegfilgrastim (Neulasta®, Neulasta Onpro®, Fulphila™; Udenyca™; Ziextenzo®)
UMP POLICY

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

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

Initial Evaluation

I. Products may be considered medically necessary when the following criteria below are met:

<table>
<thead>
<tr>
<th>Udenyca AND Neulasta/Neulasta Onpro are the preferred long-acting G-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients must have failed, or have a contraindication or intolerance to, Udenyca and one Neulasta product prior to consideration of any other long-acting G-CSF</td>
</tr>
</tbody>
</table>

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/mm^3) 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 <50 mL/min); OR
   k. Liver dysfunction (elevated bilirubin >2.0 mg/dL); OR
   l. Chronic immunosuppression in the post-transplant setting including organ transplant

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

Investigational or Not Medically Necessary Uses

I. N/A

References

10. 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

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.
Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc.” To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2018. Moda Health Plan, Inc. Medical Necessity Criteria Page 4/6


Policy Implementation/Update:

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<tr>
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<th>February 2018</th>
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<tr>
<td>Last Updated</td>
<td>December 2019</td>
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<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated policy to allow for 28 days supply</td>
<td>02/2020</td>
</tr>
<tr>
<td>Added Ziextenzo, biosimilar to Neulasta; update quantity limits to allow for 30 days supply</td>
<td>12/2019</td>
</tr>
<tr>
<td>Added Udenyca, biosimilar to Neulasta</td>
<td>01/2019</td>
</tr>
<tr>
<td>Added Nivestym, biosimilar to Neulasta</td>
<td>10/2018</td>
</tr>
<tr>
<td>Added Fulphila, biosimilar to Neulasta</td>
<td>07/2018</td>
</tr>
<tr>
<td>Neulasta, Neulasta Onpro preferred GCSF</td>
<td>12/2018</td>
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<tr>
<td>Added Udenyca, biosimilar to Neulasta</td>
<td>01/2019</td>
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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

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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>peginterferon-alfa 2b (Sylatron)</td>
<td>200 mcg subcutaneous powder for solution</td>
<td>Adjuvant treatment of melanoma with microscopic or gross nodal involvement</td>
<td>4 vials/ 28 days</td>
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<td>300 mcg subcutaneous powder for solution</td>
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</tr>
<tr>
<td></td>
<td>600 mcg subcutaneous powder for solution</td>
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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. Peginterferon-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 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


Policy Implementation/Update:

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>pegvaliase (Palynziq)</td>
<td>2.5 mg/0.5 mL</td>
<td>Phenylketonuria (PKU)</td>
<td>60 syringes/30 days</td>
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<td>10 mg/0.5 mL</td>
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<tr>
<td></td>
<td>20 mg/1 mL</td>
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<td></td>
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<tr>
<td>sapropterin dihydrochloride (Kuvan)</td>
<td>100 mg tablets</td>
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<td>20 mg/kg/day</td>
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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**

Washington State Rx Services is administered by moda health

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

October 01, 2020
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 BH₄ 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.

References

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**Action and Summary of Changes**

- 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

**Date**

| 12/2019 |
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

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<td>Acromegaly</td>
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<td>15 mg vial</td>
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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 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 (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

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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.*

October 01, 2020
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


Policy Implementation/Update:

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<th>Date</th>
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<tr>
<td>Addition of confirmed diagnosis requirements (elevated IGF-1 or GH level). Added requirement of reduced or normalized IGF-1 levels at renewal. Updated initial approval duration from 12 months to 6 months.</td>
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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

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<th>Product Name</th>
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<td>Previously treated, unresectable, locally advanced or metastatic cholangiocarcinoma in adults with FGFR2 fusions or rearrangements</td>
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<td>4.5 mg tablet</td>
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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.

References


Washington State Rx Services is administered by Moda Health

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

October 01, 2020

**Policy Implementation/Update:**

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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**

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**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 **not** 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


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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

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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

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

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>July 2016</th>
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<tr>
<td>Date Effective</td>
<td>August 2016</td>
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<tr>
<td>Last Updated</td>
<td>September 2019</td>
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<td>September 2019</td>
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Action and Summary of Changes

| Date
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<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Transition from criteria to policy: Included requirements to attempt dose reduction in parkinson’s medications, and specified what members must try and fail.</td>
</tr>
</tbody>
</table>
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

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
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<tbody>
<tr>
<td>pretomanid</td>
<td>200 mg tablet</td>
<td>Pulmonary tuberculosis that is extensively drug resistant (XDR), treatment tolerant, or nonresponsive multidrug-resistant (MDR)</td>
<td>30 tablets/30 days</td>
<td>TBD</td>
</tr>
</tbody>
</table>

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-aminosalicylic 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 investigational when used for all other conditions, including but not limited to:
   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

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October 01, 2020
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 bedaquiline and linezolid was assessed.

<table>
<thead>
<tr>
<th>Definition of TB Types</th>
</tr>
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<tbody>
<tr>
<td>Drug-resistant TB</td>
</tr>
<tr>
<td>Multidrug-resistant TB (MDR-TB)</td>
</tr>
<tr>
<td>Extensively drug-resistant TB (XDR-TB)</td>
</tr>
<tr>
<td>Totally drug-resistant TB (TDR-TB)</td>
</tr>
</tbody>
</table>

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 fluoroquinolone 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

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
6. Clinicaltrial.gov

Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>September 2019</th>
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<tr>
<td>Date Effective</td>
<td>November 2019</td>
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Action and Summary of Changes

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<th>Date</th>
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</table>
Policy Type: Step Pharmacy Coverage Policy: UMP054

Description
Prucalopride (Motegrity™) is an orally administered 5-HT₄ 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 (ETα and ETβ) 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 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:
  1. Ambrisentan (generic, Letairis), bosentan (generic, Tracleer), and macitentan (Opsumit):
     Three months
  2. Riociguat (Adempas), iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram), and selexipag (Uptravi):
     12 months
- Renewal: 12 months

Quantity limits

<table>
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<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
<td>ambrisentan (Letairis)</td>
<td>5 mg tablets</td>
<td>Pulmonary arterial hypertension (PAH)</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>generic ambrisentan</td>
<td>5 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>10 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bosentan (Tracleer)</td>
<td>32 mg tablet for oral suspension</td>
<td></td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>62.5 mg film-coated tablet</td>
<td></td>
<td>60 tablets/30 days</td>
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<td></td>
<td>125 mg film-coated tablet</td>
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<td>generic bosentan</td>
<td>32 mg tablet for oral suspension</td>
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<td>62.5 mg film-coated tablet</td>
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<td>125 mg film-coated tablet</td>
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<tr>
<td>macitentan (Opsumit)</td>
<td>10 mg tablet</td>
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<td>30 tablets/30 days</td>
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</table>
### 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), 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); **OR**

B. Medication is prescribed by, or in consultation with, cardiologist or pulmonologist; **AND**

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<table>
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<tr>
<th><strong>Medication</strong></th>
<th><strong>Strengths</strong></th>
<th><strong>Quantity</strong></th>
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<tr>
<td>riociguat (Adempas)</td>
<td>0.5 mg tablets, 1 mg tablets, 1.5 mg tablets, 2 mg tablets, 2.5 mg tablets</td>
<td>Chronic thromboembolic pulmonary hypertension (CTEPH); Pulmonary arterial hypertension (PAH)</td>
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<tr>
<td>iloprost (Ventavis)</td>
<td>10 mcg/mL inhalation solution ampule, 20 mcg/mL inhalation solution ampule</td>
<td>Pulmonary arterial hypertension (PAH)</td>
</tr>
<tr>
<td>treprostinil (Tyvaso)</td>
<td>1.74 mg/2.9 mL inhalation solution ampule</td>
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</tr>
<tr>
<td>treprostinil (Orenitram)</td>
<td>0.125 mg, 0.25 mg, 1 mg, 2.5 mg, 5 mg</td>
<td>Pulmonary arterial hypertension (PAH)</td>
</tr>
<tr>
<td>selexipag (Uptravi)</td>
<td>200 mcg, 400 mcg, 600 mcg, 800 mcg, 1000 mcg, 1200 mcg, 1400 mcg, 1600 mcg</td>
<td></td>
</tr>
</tbody>
</table>

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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 three months 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 three months of therapy, contraindicated, or not tolerated; AND
    c. The request is for **generic ambrisentan, generic bosentan, macitentan (Opsumit), or riociguat (Adempas)**; OR
   d. The request is for **brand ambrisentan (Letairis)**; AND
      i. Generic ambrisentan has been ineffective, contraindicated, or not tolerated; OR
   e. The request is for **brand bosentan (Tracleer)**; AND
      i. Generic bosentan has been ineffective, contraindicated, or not tolerated; OR
   f. The request is for **iloprost (Ventavis) inhalation solution or treprostinil (Tyvaso) inhalation solution**; OR
   g. The request is for **treprostinil (Orenitram) or selexipag (Uptravi)**; AND
      i. Treatment with endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)] has been ineffective, contraindicated, or not tolerated; OR

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)**.

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:

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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.*

*October 01, 2020*
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. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) 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) and idiopathic pulmonary fibrosis (IPF)
      • Group IV - Chronic thrombotic and/or embolic disease
      • Group V – Sarcoidosis

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 [include if anticipate these will occur for the product in the policy]

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. 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.

II. 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.

III. PAH and Chronic Thromboembolic Pulmonary Hypertension (CTEPH) are progressive and life-threatening diseases. The medication as well as the disease state need to be managed by a specialist.

IV. 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.

V. 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.

VI. 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) prostanooids, 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.

VII. 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.

VIII. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram), 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.

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. 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%).

XIII. 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.

XIV. 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.

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/cm², 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/cm² (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).

IV. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi)
A. Pulmonary hypertension (PH) WHO Groups II-V
   • Left heart disease, including congestive heart failure (CHF)
   • Lung diseases, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF)
   • Chronic thrombotic and/or embolic disease
   • Sarcoidosis
B. 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.

References

1. Ambrisentan (Letairis®) [Prescribing Information]. Gilead Sciences, Inc., Foster City, CA. 04/23/2019
5. Iloprost (Ventavis®) [Prescribing Information]. South San Francisco, CA; Actelion Pharmaceuticals US, Inc. 10/16/2017
6. Treprostinil (Tyvaso®) [Prescribing Information]. Research Triangle Park, NC: United Therapeutics Corp. 10/19/2017
7. Treprostinil (Orenitram®) [Prescribing Information]. Research Triangle Park, NC: United Therapeutics Corp. 01/24/2017
8. Selexipag (Uptravi®) [Prescribing Information]. South San Francisco, CA; Actelion Pharmaceuticals US, Inc. 09/04/2019
12. CHEST website https://foundation.chestnet.org/patient-education-resources/pah/
16. Galie, Nazzareno MD; Olschewski, Horst MD; Oudiz, Ronald J. MD; Torres, Fernando MD. Ambrisentan for the Treatment of Pulmonary Arterial Hypertension: Results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) Study 1 and 2. Circulation. 117(23), 10 June 2008. DOI: 10.1161/CIRCULATIONAHA.107.742510 PMID: 18506008
17. K Ahmadi-Simab; P Lamprecht; B Hellmisch. Treatment of pulmonary arterial hypertension (PAH) with oral endothelin-receptor antagonist bosentan in systemic sclerosis: BREATHE-1 trial and clinical experience. 63(6). 495-497. DOI: 10.1007/s00393-004-0594-3 PMID: 15605216
18. N. Channick MD; Marion Delcroix MD; Hossein-Ardeshir Ghofrani MD; Elke Hunsche PhD. Effect of Macitentan on Hospitalizations: Results from the SERAPHIN Trial. January 2015. 3(1). 1-8. https://doi.org/10.1016/j.jchf.2014.07.013
Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated renewal section with standard renewal language</td>
<td>03/2020</td>
</tr>
<tr>
<td>Added chronic thromboembolic pulmonary hypertension (CTEPH) as an investigational indication to bosentan (generic, Tracleer), ambrisentan (generic, Letairis), macitentan (Opsumit) and selexipag (Uptravi)</td>
<td>03/2020</td>
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<tr>
<td>Updated the criteria into policy format</td>
<td>12/2019</td>
</tr>
<tr>
<td>Added acute vasoreactivity test criteria to apply to all agents</td>
<td>12/2019</td>
</tr>
<tr>
<td>Added age limit to reflect clinical trial data</td>
<td>12/2019</td>
</tr>
<tr>
<td>Combined criteria for bosentan (generic, Tracleer), ambrisentan (generic, Letairis) &amp; macitentan (Opsumit) with riociguat (Adempas) criteria and iloprost (Ventavis), treprostinil (Tyvaso and Orenitram), selexipag (Uptravi)</td>
<td>12/2019</td>
</tr>
<tr>
<td>Quantity limit change iloprost (Ventavis) and bosentan (Letairis) to reflect the dosing in the package insert</td>
<td>12/2019</td>
</tr>
<tr>
<td>Treprostinil (Orenitram) 5mg dosage form added</td>
<td>12/2019</td>
</tr>
<tr>
<td>Added criteria because generic bosentan and generic ambrisentan became available we are driving patients to a more cost effective option</td>
<td>12/2019</td>
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</table>

Washington State Rx Services is administered by Moda Health

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

| Updated formatting.          | 03/17/2016 |
| 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. | Prior to 3/17/2016 (no date available) |
| Removed questions regarding contraindications, warnings/precautions. | 03/14/2016 |
| Updated header, footer and formatting [riociguat (Adempas)] | 03/14/2016 |
| Reviewed | 03/14/2016 |

Policy created and effective [iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi)]

Policy created [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]

Previously reviewed [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]

Criteria for ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit) created

Prior to 3/17/2016 (no date available)
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
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</table>
| 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.

References

1. Obizur® [Prescribing Information]. Lexington, MA: Baxalta; September 2017

Policy Implementation/Update:

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Action and Summary of Changes

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<tr>
<td>New policy created for Obizur</td>
<td>08/2019</td>
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</table>
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**

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<tbody>
<tr>
<td>regorafenib (Stivarga)</td>
<td>40 mg tablets</td>
<td>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</td>
<td>84 tablets/28 days</td>
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**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

References


7. Grothy A., Sobrero AF., Siena S., et al. Results of a phase III randomized, double-blind, placebo-controlled, multicenter trial (CORRECT) or regorafenib plus best supportive care versus placebo in patients with metastatic colorectal cancer who have progressed after standard therapies.


Policy Implementation/Update:

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<tr>
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<tr>
<td>Last Updated</td>
<td>November 2019</td>
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<td>Last Reviewed</td>
<td>01/2013, 02/2013, 04/2014, 09/2014, 11/2019</td>
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<tr>
<td>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.</td>
<td>11/2019</td>
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**Policy Type: PA/SP**

**Pharmacy Coverage Policy: UMP078**

**Description**

Ribociclib (Kisqali) is an orally administered small molecule cyclin-dependent kinase (CDK) 4/6 inhibitor.

**Length of Authorization**

- Initial: Six months
- Renewal: 12 months

**Quantity limits**

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<td>ribociclib (Kisqali)</td>
<td>200 mg tablet dose pack</td>
<td>Breast cancer, HR-positive, HER2-negative, advanced or metastatic, for initial endocrine therapy in combination with fulvestrant</td>
<td>21 tablets/28 days</td>
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<td></td>
<td>400 mg tablet dose pack</td>
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<td></td>
<td>600 mg tablet dose pack</td>
<td>Breast cancer, HR-positive, HER2-negative, advanced or metastatic, for progression following endocrine therapy in combination with fulvestrant</td>
<td>63 tablets/28 days</td>
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<td>ribociclib/letrozole (Kisqali/Femara)</td>
<td>200 mg and 2.5 mg tablet dose pack</td>
<td>Breast cancer, HR-positive, HER2-negative, advanced or metastatic, for initial endocrine therapy in combination with fulvestrant</td>
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<td>400 and 2.5 mg tablet dose pack</td>
<td>Breast cancer, HR-positive, HER2-negative, advanced or metastatic, for initial endocrine therapy in combination with fulvestrant</td>
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<td>600 and 2.5 mg tablet dose pack</td>
<td>Breast cancer, HR-positive, HER2-negative, advanced or metastatic, for initial endocrine therapy in combination with fulvestrant</td>
<td>91 tablets/28 days</td>
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**Initial Evaluation**

I. Ribociclib (Kisqali) 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**

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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.

October 01, 2020
C. Ribociclib (Kisqali) will not be used in combination with any other oncolytic medication, with the exception of an aromatase inhibitor (e.g., anastrozole, letrozole) or fulvestrant; **AND**

D. The member has not previously progressed on or after treatment with another CDK4/6 inhibitor (e.g., abemaciclib [Verzenio], palbociclib [Ibrance]); **AND**

E. A diagnosis of *breast cancer* when the following are met:
   1. The member has hormone receptor-positive (HR+), and HER2-negative (HER2-) disease; **AND**
   2. The member is female; **AND**
   3. The disease is advanced (stage III) or metastatic (stage IV); **AND**
   4. The member is postmenopausal (natural or pharmacotherapy induced [e.g., GnRH therapy used concomitantly [e.g., Lupron]]); **AND**
   5. The medication is prescribed for one of the following settings:
      i. Initial endocrine therapy in combination with an aromatase inhibitor or fulvestrant; **OR**
      ii. For progression following endocrine therapy in combination with fulvestrant.

II. Ribociclib (Kisqali) is 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., abemaciclib [Verzenio], palbociclib [Ibrance])
   B. For the treatment of breast cancer in males
   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 carcinoma

**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. Ribociclib (Kisqali) will not be used in combination with any other oncolytic medication with the exception of an aromatase inhibitor (e.g., anastrozole, letrozole) or fulvestrant; **AND**

V. Documentation is provided indicating response to therapy, as defined by one of the following: stabilization of disease, decrease in the size of the tumor, or tumor spread.

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

**October 01, 2020**
Supporting Evidence

I. Ribociclib (Kisqali) was evaluated in adult, female subjects with HR-positive, HER2-negative, advanced or metastatic breast cancer. Please note, palbociclib (Ibrance) 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 naive for their disease. The outcomes were progression-free survival (PFS) and overall response rate (ORR), which were found to be statistically significant in favor of ribociclib (Kisqali) plus letrozole.
   - MONALEESA-7: Kisqali in Combination with an Aromatase Inhibitor. Randomized, double-blind, placebo-controlled trial of pre-perimenopausal subjects evaluating ribociclib (Kisqali) plus an aromatase inhibitor or tamoxifen with goserelin versus an aromatase inhibitor or tamoxifen and goserelin. The outcomes included PFS and ORR, which were statistically significant in favor of ribociclib (Kisqali).
     i. Overall survival data was reported in June 2019, and showed a hazard ratio (HR) of 0.712 (0.535-0.948; p=0.00973).
   - MONALEESA-3: Randomized, double-blind, placebo-controlled study of ribociclib (Kisqali) in combination with fulvestrant for treatment of postmenopausal women who had received no or only one line or 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).

II. 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.

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

Investigational or Not Medically Necessary Uses

I. Ribociclib (Kisqali) has not been FDA-approved, or sufficiently studied for safety and efficacy, for the conditions or settings listed below:
   A. In combination with, or following progression on or after, another CDK4/6 inhibitor (e.g., palbociclib [Ibrance], abemaciclib [Verzenio])
   B. Breast cancer in males — consider palbociclib (Ibrance) as an alternative
   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

References

Policy Implementation/Update:

| Date Created | April 2017 |
| Date Effective | May 2017 |
| Last Updated | October 2019 |
| Last Reviewed | 08/2018, 09/2018, 10/2019 |

<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria transitioned to policy, criteria updated to include age, specialist, limit concurrent therapy, with renewal criteria to align with current practice.</td>
<td>10/2019</td>
</tr>
<tr>
<td>Quantity limit and product availability updated with Kisqali-Femara dose pack.</td>
<td>09/2018</td>
</tr>
<tr>
<td>Criteria updated: New indications added: pre/perimenopausal setting in combination with aromatase inhibitor, as well as postmenopausal setting in combination with fulvestrant as first or second line endocrine therapy. Initial approval updated from three to six months. Addition of question assessing if previous CDK4/6 inhibitor has been used.</td>
<td>08/2018</td>
</tr>
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</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
<th>DDID</th>
</tr>
</thead>
<tbody>
<tr>
<td>rifaximin (Xifaxan)</td>
<td>550 mg</td>
<td>Treatment of irritable bowel syndrome with diarrhea (IBS-D).</td>
<td>42 tablets/14 days</td>
<td>150969, 152498</td>
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<tr>
<td></td>
<td>tablets</td>
<td>Hepatic encephalopathy recurrence.</td>
<td>60 tablets/30 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200 mg</td>
<td>Travelers’ diarrhea caused by noninvasive strains of Escherichia coli</td>
<td>9 tablets/3 days</td>
<td>088395, 088393</td>
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</tbody>
</table>

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

d. 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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October 01, 2020
Policy Implementation/Update:

<table>
<thead>
<tr>
<th>Date Created</th>
<th>August 2015</th>
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<tr>
<td>Date Effective</td>
<td>August 2015</td>
</tr>
<tr>
<td>Last Updated</td>
<td>July 2019</td>
</tr>
<tr>
<td>Last Reviewed</td>
<td>08/2015; 04/2019, 07/2019</td>
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<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>07/2019</td>
</tr>
<tr>
<td>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.</td>
<td>04/2019</td>
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</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roflumilast (Daliresp)</td>
<td>250 mcg tablet</td>
<td>Severe chronic obstructive pulmonary disease (COPD) with chronic bronchitis and a history of exacerbation</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>500 mcg tablet</td>
<td></td>
<td>30 tablets/30 days</td>
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</table>

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; FEV₁ < 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 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; **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\textsubscript{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


Policy Implementation/Update:

<table>
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<tr>
<th>Date Created</th>
<th>April 2018</th>
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<tbody>
<tr>
<td>Date Effective</td>
<td>April 2018</td>
</tr>
<tr>
<td>Last Updated</td>
<td>November 2019</td>
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<td>Last Reviewed</td>
<td>11/2019</td>
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Action and Summary of Changes

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<th>Date</th>
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<tbody>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Criteria created</td>
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</table>
Policy Type: PA/SP

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>rucaparib</td>
<td>200 mg tablets</td>
<td>Maintenance for: recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer;</td>
<td>60 tablets/30 days</td>
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<tr>
<td></td>
<td>250 mg tablets</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>300 mg tablets</td>
<td>Treatment for: advanced ovarian, fallopian tube, or primary peritoneal cancer</td>
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</tbody>
</table>

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 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 a 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. Prostate Cancer
   D. Solid Tumors

References


Policy Implementation/Update:

<table>
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<tr>
<th>Date Created</th>
<th>December 2016</th>
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<tr>
<td>Date Effective</td>
<td>February 2017</td>
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<tr>
<td>Last Updated</td>
<td>December 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>12/2016, 05/2018, 12/2019</td>
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October 01, 2020
<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criteria transition into policy with the following updates made: addition of supporting evidence and investigation section, broke out the different indications (treatment versus maintenance therapy), included mutation status for the treatment of recurrent ovarian cancer, included criterion around prior PARP inhibitor use, increase initial approval duration from three months to six months to be consistent with other payers, included age criterion per label, and removed the 8 weeks criterion around most recent platinum-based therapy in the setting of maintenance therapy in recurrent ovarian cancer; in place of the 8 weeks criterion, provider attestation and documentation is required instead.</td>
<td>12/2019</td>
</tr>
</tbody>
</table>
Policy Type: PA/SP  
Pharmacy Coverage Policy: UMP057

Split Fill Management*

Description
Ruxolitinib (Jakafi) is an orally administered Janus associated kinase (JAK) inhibitor. JAK signaling mediates the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function.

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

Quantity limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indications</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>ruxolitinib</td>
<td>5 mg tablets</td>
<td>Intermediate or high-risk myelofibrosis</td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td>(Jakafi)</td>
<td>10 mg tablets</td>
<td>Polycythemia vera</td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>15 mg tablets</td>
<td></td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>20 mg tablets</td>
<td>Acute Graft Versus-Host disease</td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>25 mg tablets</td>
<td></td>
<td>60 tablets/30 days</td>
</tr>
</tbody>
</table>

Initial Evaluation

I. Ruxolitinib (Jakafi) may be considered medically necessary when the following criteria below are met:
   A. Medication is prescribed by, or in consultation with, an oncologist or endocrinologist; AND
   B. Member does not have an active infection, including clinically important localized infections; AND
   C. 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; AND
         i. Treatment with hydroxyurea has been ineffective, contraindicated, or not tolerated; OR
      2. Polycythemia vera; AND
         i. Treatment with hydroxyurea has been ineffective, contraindicated, or not tolerated; OR
      3. Acute Graft Versus-Host Disease (GVHD); AND
         i. Member is 12 years of age or older; AND
         ii. Documentation that member has Grades 2 to 4 GVHD; AND...
iii. Member is steroid refractory

II. Ruxolitinib (Jakafi) is considered investigational when used for all other conditions, including but not limited to:
   A. Low risk myelofibrosis
   B. Acute leukemia

Renewal Evaluation

I. The member has an absence of unacceptable toxicity from the medication; AND

II. A diagnosis of one of the following:
   A. Intermediate- to high-risk myelofibrosis (MF); AND
      1. Documentation of reduction in spleen volume; AND
      2. Documentation of improvement in symptoms; OR
   B. Polycythemia vera; AND
      1. Documentation of reduction in spleen volume; AND
      2. Does not require phlebotomy
   C. Acute Graft Versus-Host Disease (GVHD); AND
      1. Member has responded to therapy with ruxolitinib (Jakafi) (e.g. decreased GVHD symptoms)

Supporting Evidence

I. Length of authorization for initial approval has been extended to six months due to the clinical trial design, efficacy was not evaluated until 24 weeks.

II. Serious bacterial, mycobacterial (including tuberculosis), fungal, or viral infections have occurred. Active serious infections should be resolved prior to treatment initiation. Continual monitoring for infections (including signs/symptoms of active tuberculosis and herpes zoster) should be performed while on treatment with ruxolitinib (Jakafi).

III. 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; meanwhile, 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. In both studies, a significantly larger proportion of participants in the ruxolitinib (Jakafi) arm (Study 1 = 41.9%, Study 2 = 28.5%) achieved a 35% or greater reduction in spleen volume from baseline compared to placebo (Study 1 = 0.7% and Study 2 = 0%).

• Available therapies for intermediate- to high-risk MF include: hydroxyurea, busulfan, 6-mercaptopurine, anagrelide, thalidomide, lenalidomide, interferon, corticosteroids, androgens, erythropoiesis stimulating agents, or growth factors. Although there are many “available therapies” for intermediate- to high-risk MF, the most robust evidence – and the majority of patients in the clinical trials – were previously on hydroxyurea.
IV. 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 (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.

- The inclusion criteria in this trial was that participants must have had a resistance or intolerance to hydroxyurea.

V. The FDA approval of ruxolitinib (Jakafi) in the setting of acute graft versus host disease (GVHD) was based on the results of an open-label, single-arm, multicenter study in participants with steroid-refractory acute GVHD Grades 2 to 4. The primary efficacy of ruxolitinib (Jakafi) was based on 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.

Investigational or Not Medically Necessary Uses

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

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

References


Policy Implementation/Update:

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<tr>
<th>Date Created</th>
<th>February 2012</th>
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<td>Date Effective</td>
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<td>Last Updated</td>
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<td>Date</td>
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<tr>
<td>Criteria update: added acute graft versus host disease to renewal evaluation section with renewal criterion to assess for response.</td>
<td>01/2020</td>
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<tr>
<td>Transitioned Jakafi criteria into policy. Added newly FDA approved indication of acute graft versus host disease, the route to approval is per label. Remove diagnostic questions for intermediate to high-risk myelofibrosis since provider is a specialist that will be diagnosing members. Remove the following assessment: CYP3A4 inhibitor drug-drug interactions, creatinine clearance and platelet count as the providers will already be assessing for treatment appropriateness. For the diagnosis of polycythemia vera, the requirement of trial and failure of hydroxyurea has been added as that is standard of practice.</td>
<td>07/2019</td>
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Select Insulin Products
UMP POLICY

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

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<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<td>insulin aspart (Novolog)</td>
<td>U100 vial</td>
<td>Diabetes mellitus, type I and II</td>
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<td></td>
<td>U100 Flexpen</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>U100 PenFill (cartridge)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin aspart</td>
<td>U100 vial</td>
<td></td>
<td>60 mL per 30 days</td>
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<tr>
<td></td>
<td>U100 Flexpen</td>
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<td></td>
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<tr>
<td></td>
<td>U100 PenFill (cartridge)</td>
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<tr>
<td>insulin aspart (Novolog Mix 70/30)</td>
<td>U100 vial</td>
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<td></td>
<td>U10 Flexpen</td>
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<tr>
<td>insulin aspart Mix 70/30</td>
<td>U100 vial</td>
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<tr>
<td></td>
<td>U100 Flexpen</td>
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<td></td>
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<tr>
<td>insulin regular (Novolin R)</td>
<td>U100 vial</td>
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<td>60 mL per 30 days</td>
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<tr>
<td></td>
<td>U100 ReliOn</td>
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<tr>
<td>insulin isophane; NPH (Novolin N)</td>
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<td>U100 ReliOn</td>
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<td></td>
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<td></td>
<td>60 mL per 30 days</td>
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<td></td>
<td>U100 Flexpen</td>
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<td></td>
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<tr>
<td></td>
<td>U100 Flexpen ReliOn</td>
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<tr>
<td></td>
<td>U100 ReliOn</td>
<td></td>
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<tr>
<td>insulin aspart (Fiasp)</td>
<td>U100 vial</td>
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<td>60 mL per 30 days</td>
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<td></td>
<td>U100 FlexTouch</td>
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<tr>
<td>insulin human powder (Afrezza)</td>
<td>4 unit powder</td>
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<td>1530 units per 30 days</td>
</tr>
<tr>
<td></td>
<td>4 &amp; 8 unit powder</td>
<td></td>
<td>630 units per 30 days</td>
</tr>
<tr>
<td></td>
<td>60 x 4 unit &amp; 30 x 8 unit powder</td>
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<td>630 units per 30 days</td>
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<td></td>
<td>30 x 4 unit &amp; 60 x 8 unit powder</td>
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<td>1170 units per 30 days</td>
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<td></td>
<td>60 x 8 unit &amp; 30 x 12 unit powder</td>
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<td>900 units per 30 days</td>
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<td></td>
<td>90 x 4 unit &amp; 90 x 8 unit powder</td>
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<td>4, 8 &amp;</td>
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<td>720 units per 30 days</td>
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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

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<th>Insulin Type</th>
<th>12 unit powder</th>
<th>8 unit powder</th>
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<th>540 units per 30 days</th>
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<td>insulin glulisine (Apidra)</td>
<td>U100 vial</td>
<td>U100 SoloStar</td>
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<tr>
<td>insulin lispro (Humalog)</td>
<td>U100 vial</td>
<td>U100 Junior KwikPen</td>
<td>U100 KwikPen</td>
<td>U200 KwikPen</td>
<td>U100 Pen</td>
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<td>Insulin lispro</td>
<td>U100 vial</td>
<td>U100 Pen</td>
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<td>insulin lispro (Admelog)</td>
<td>U100 vial</td>
<td>U100 SoloStar</td>
<td></td>
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<tr>
<td>insulin lispro (Humalog mix 50/50)</td>
<td>U100 vial</td>
<td>U100 KwikPen</td>
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<td>insulin lispro (Humalog mix 75/25)</td>
<td>U100 vial</td>
<td>U100 KwikPen</td>
<td>U100 Pen</td>
<td>60 mL per 30 days</td>
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<tr>
<td>insulin isophane/regular (Humulin 70/30)</td>
<td>U100 vial</td>
<td>U100 KwikPen</td>
<td>U100 Pen</td>
<td>60 mL per 30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>insulin isophane/regular (Humulin 50/50)</td>
<td>U100 vial</td>
<td>U100 Pen</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(insulin isophane; NPH) Humulin N</td>
<td>U100 vial</td>
<td>U100 Kwikpen</td>
<td></td>
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<tr>
<td>insulin regular (Humulin R)</td>
<td>U100 vial</td>
<td>U-500 vial</td>
<td></td>
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</tr>
</tbody>
</table>

**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, 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. Documentation of concentrated dosing required
   4. Documentation of 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, and 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


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<td>July 2016</td>
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<td>January 2020</td>
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<td>Last Reviewed</td>
<td>06/2016, 09/2017, 01/2018, 06/2019, 01/2020</td>
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<table>
<thead>
<tr>
<th>Action and Summary of Changes</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addition of generic insulin aspart products and update to renewal policy</td>
<td>01/2020</td>
</tr>
<tr>
<td>Conversion to policy format; addition of generic insulin lispro</td>
<td>06/2019</td>
</tr>
<tr>
<td>Inserted Fiasp products; removed long acting insulins to which this policy does not apply</td>
<td>01/2018</td>
</tr>
<tr>
<td>Event Description</td>
<td>Date</td>
</tr>
<tr>
<td>-----------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Included questions to ensure members is injecting more than 200 units per day for U500 formulations</td>
<td>09/2017</td>
</tr>
<tr>
<td>Afrezza and Apidra added to policy</td>
<td>06/2016</td>
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<tr>
<td>Criteria developed</td>
<td>04/2016</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>testosterone undecanoate</td>
<td>158 mg tablets</td>
<td>Primary hypogonadism; hypogonadotropic hypogonadism</td>
<td>120 capsules/30 days</td>
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<tr>
<td>(Jatenzo)</td>
<td>198 mg tablets</td>
<td></td>
<td>120 capsules/30 days</td>
</tr>
<tr>
<td></td>
<td>237 mg capsules</td>
<td></td>
<td>60 capsules/30 days</td>
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<tr>
<td>testosterone undecanoate</td>
<td>750 mg/3 mL intramuscular solution</td>
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<td>3 mL/28 days</td>
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<td>(Aveed)</td>
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<td></td>
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<tr>
<td>testosterone (Striant)</td>
<td>30 mg buccal system</td>
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<td>60 buccal systems/30 days</td>
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<td>testosterone (Androderm)</td>
<td>2 mg/24 hour patch</td>
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<td>60 patches/30 days</td>
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<td>4 mg/24 hour patch</td>
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<td>30 patches/30 days</td>
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<td>testosterone 1% (AndroGel, Testim, Vogelxo)</td>
<td>25mg/2.5gm gel</td>
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<td>300 g/30 days</td>
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<td></td>
<td>50 mg/5gm gel</td>
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<td>300 g/30 days</td>
</tr>
<tr>
<td></td>
<td>1.25 g/actuation gel pump</td>
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<td>300 g/30 days</td>
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<tr>
<td>testosterone 1.62% (AndroGel, Vogelxo)</td>
<td>20.25 mg/1.25 gm gel packet</td>
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<td>40.5 mg/2.5gm gel packet</td>
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<td></td>
<td>20.25 mg/actuation gel pump</td>
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<td>150 g/30 days</td>
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<td>Testosterone Cypionate (Depot-testosterone)</td>
<td>100mg/mL intramuscular injection</td>
<td>8 mL/28 days</td>
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<tr>
<td>Testosterone Cypionate (Depot-testosterone)</td>
<td>200mg/mL intramuscular injection</td>
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<tr>
<td>Testosterone (Axiron)</td>
<td>30 mg actuation roll-on solution</td>
<td>110 mL/30 days</td>
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<td>Testosterone (Xyosted)</td>
<td>50 mg/0.5 mL subcutaneous solution autoinjector</td>
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<td>Testosterone Cypionate 2% (Fortesta)</td>
<td>10mg/actuation gel</td>
<td>120 g/30 days</td>
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<tr>
<td>Methyltestosterone (Methitest)</td>
<td>10 mg tablet or capsule</td>
<td>Men: 150 tablets/30 days Women: 600 tablets/30 days</td>
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</table>

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

iii. 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.
References


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Washington State Rx Services is administered by moda HEALTH

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

Pharmacy Coverage Policy: UMP086

Description
Selinexor (Xpovio) is an orally nuclear export inhibitor.

Length of Authorization
N/A

Quantity limits

<table>
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<tr>
<th>Product Name</th>
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<th>Indication</th>
<th>Quantity Limit</th>
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<tbody>
<tr>
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<td>Relapsed or refractory multiple myeloma</td>
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<td>100 mg tablet once weekly carton</td>
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<td>N/A</td>
<td>207238</td>
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<td></td>
<td>80 mg tablet once weekly carton</td>
<td></td>
<td>N/A</td>
<td>207236</td>
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<tr>
<td></td>
<td>60 mg tablet once weekly carton</td>
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Initial Evaluation
I. Selinexor (Xpovio) is considered investigational when used for all conditions, including but not limited to multiple myeloma.

Renewal Evaluation
N/A

Supporting Evidence
I. Selinexor (Xpovio) was evaluated in one, 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 relapsed, refractory, or intolerant to bortezomib, carfilzomib, lenalidomide and pomalidomide. Some patients were also refractory to daratumumab. 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. Selinexor (Xpovio) was approved via the accelerated approval pathway, and continued approval may be contingent upon verification and description of clinical benefit in confirmatory trials.

II. The safety profile is as follows: 60% of patients in the trial experiencing 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.
**Investigational or Not Medically Necessary Uses**

I. Multiple myeloma
   A. The quality of the current evidence for selinexor (Xpovio) 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 MM. The PFS and OS result have unknown value due to the single arm as well as the open-label design, and the medication has a significant safety profile. There is a lack of evidence indicated that selinexor (Xpovio) would provide a net health benefit for members. Additionally, treatment guidelines for MM specify use of a three drug regimen is preferred when available and appropriate (e.g., the member is not elderly or frail), and to utilize at least two new therapies compared to previous regimens if possible. Selinexor (Xpovio) has not been sufficiently studied in this space. Trials evaluating as a part of a triple regimen were underway as of August 2019, further clinical evaluation of safety and efficacy are needed to confirm a net health benefit and place in therapy for this medication.

**References**


**Policy Implementation/Update:**

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selpercatinib (Retevmo™)
UMP POLICY

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

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<td>selpercatinib (Retevmo)</td>
<td>40 mg capsules</td>
<td>RET Fusion-Positive Non-Small Cell Lung Cancer</td>
<td>180 capsules/30 days</td>
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<td>RET-Mutant Medullary Thyroid Cancer</td>
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<td>80 mg capsules</td>
<td>RET Fusion-Positive Thyroid Cancer, in those that are radioactive iodine refractory</td>
<td>120 capsules/30 days</td>
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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.

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<td>PFS (months)</td>
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<td>OS, 12 months (%)</td>
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<th>Clinical Efficacy in Treatment-Naïve Patients</th>
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<tr>
<td>Outcome</td>
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<td>ORR (n)</td>
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<td>PR (n)</td>
</tr>
<tr>
<td>PFS (months)</td>
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<tr>
<td>OS, 12 months (%)</td>
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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.

References


Washington State Rx Services is administered by moda health

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

October 01, 2020


**Policy Implementation/Update:**

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selumetinib (Koselugo™)

UMP POLICY

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

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<td>selumetinib</td>
<td>10 mg capsules</td>
<td>Neurofibromatosis type 1 (NF1)</td>
<td>120 capsules/30 days</td>
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<td>25 mg capsules</td>
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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**

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

References

4. National Cancer Institute (NCI). MEK 1/2 Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Adults With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas. ClinicalTrials.gov NCT02407405

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October 01, 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

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<td>20 mg tablets</td>
<td>Raynaud’s phenomena</td>
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<td>10 mg/mL</td>
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<td>30 tablets/30 days</td>
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Initial Evaluation

1. 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

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

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 contraindicated; 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 not medically necessary when criteria above are not met and/or when used for:
   A. Erectile dysfunction.

III. Medications listed in this policy are considered investigational when used for all other conditions, including but not limited to:
   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.

References

1. Oregon Insurance Division Bulletin INS 2014 – 1 Mental Health Parity
2. Diagnostic and Statistical Manual of Mental Disorder (DSM) Version IV-TR and V.


Policy Implementation/Update:

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Action and Summary of Changes

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<td>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.</td>
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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

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<td>Simvastatin (Zocor)</td>
<td>80 mg tablets</td>
<td>Prevention of cardiovascular events/cardiovascular disease and reduce the risk of atherosclerotic cardiovascular disease, homozygous familial hypercholesterolemia</td>
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Initial Evaluation
I. Simvastatin 80 mg (Zocor) may be considered medically necessary when the following criteria below are met:
   A. Member has been started and stabilized on this medication 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. 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.

II. 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).

References

Policy Implementation/Update:

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<tr>
<th>Date Created</th>
<th>January 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date Effective</td>
<td>April 2017</td>
</tr>
<tr>
<td>Last Updated</td>
<td>October 2019</td>
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<td>Last Reviewed</td>
<td>01/2017, 10/2019</td>
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<td>Criteria transitioned to policy with supporting evidence section added.</td>
<td>10/2019</td>
</tr>
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<td>New criteria</td>
<td>01/2017</td>
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</table>
sodium oxybate (Xyrem®)

UMP POLICY

Policy Type: PA/SP  Pharmacy Coverage Policy: UMP186

Description
Sodium oxybate (Xyrem) is an orally administered metabolite of the neurotransmitter GABA that acts as a central nervous system depressant with an unknown mechanism of action.

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

Quantity Limits

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<td>sodium oxybate (Xyrem)</td>
<td>500 mg/mL</td>
<td>Narcolepsy with cataplexy; Narcolepsy with excessive daytime sleepiness</td>
<td>540 mL/30 days</td>
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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 not 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 the following has been ineffective, contraindicated, or not tolerated:
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

a. A stimulant (e.g. methylphenidate, dextroamphetamine); AND
b. Modafinil (Provigil) or armodafinil (Nuvigil); AND
c. Solriamfetol (Sunosi); AND
iv. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving)

II. Sodium oxybate (Xyrem) is considered investigational when used for all other conditions, including but not limited to:
   A. 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. 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. Member will continue to not use sodium oxybate (Xyrem) 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.
II. The REMS program only allows certified prescribers and pharmacies to dispense sodium oxybate (Xyrem). 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. These patients 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) is 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) has 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 cost of sodium oxybate (Xyrem) is $18,000 per month at max dose, while solriamfetol (Sunosi) is $800 per month at max dose.

Investigational or Not Medically Necessary Uses

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

   A. Fibromyalgia

References

Policy Implementation/Update:

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<th>Date</th>
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<td>• Requirement to be prescribed by or in consultation with a sleep specialist, psychiatrist, or neurologist</td>
<td>05/2020</td>
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<tr>
<td>• Confirmation of diagnosis for narcolepsy</td>
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<tr>
<td>• Requirement for chronic narcolepsy defined as three-month history</td>
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<tr>
<td>• Requirement that member has functional impairment for activities of daily living</td>
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<tr>
<td>• Updated requirements for trial and failure to one stimulant, and modafinil or armodafinil, and Sunosi</td>
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<td>Policy created</td>
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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

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<th>Product Name</th>
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<th>Indication</th>
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<tr>
<td>solriamfetol</td>
<td>75 mg tablets</td>
<td>Excessive sleepiness associated with either OSA or narcolepsy</td>
<td>60 tablets/30 days</td>
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<tr>
<td>(Sunosi)</td>
<td>150 mg tablets</td>
<td></td>
<td>30 tablets/30 days</td>
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<tr>
<td>pitolisant</td>
<td>4.45 mg tablets</td>
<td>Excessive daytime sleepiness associated with narcolepsy</td>
<td>14 tablets/7 days</td>
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<tr>
<td>(Wakix)</td>
<td>17.8 mg tablets</td>
<td></td>
<td>60 tablets/30 days</td>
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</table>

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. A diagnosis of excessive daytime sleepiness; AND
   C. A diagnosis of one of the following:
      1. Narcolepsy; AND
         i. Treatment with the following has been ineffective, contraindicated, or not tolerated:
            a. Stimulant (e.g., methylphenidate, amphetamine, etc.); AND
            b. Modafinil or armodafinil; AND
            c. If the request is for pitolisant (Wakix): Treatment with solriamfetol (Sunosi) has been ineffective, contraindicated, or not tolerated; OR
      2. Obstructive sleep apnea (OSA); AND
         i. The request is for solriamfetol (Sunosi); AND
         ii. The member has current or prior use of a primary OSA therapy (e.g., CPAP, mandibular advancement device or surgical intervention); AND
         iii. Treatment with modafinil or armodafinil has been ineffective, contraindicated, or not tolerated

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
II. Solriamfetol (Sunosi) and pitolisant (Wakix) are considered investigational when used for all other conditions, including but not limited to:
   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., 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.

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.

**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

Policy Implementation/Update:

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<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Updated policy to require trial and failure of solriamfetol (Sunosi) prior to approval of pitolisant (Wakix) for narcolepsy.</td>
<td>06/2020</td>
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<td>Addition of pitolisant (Wakix) information for coverage including: experimental/investigational, coverage for narcolepsy, quantity limits, and evidence base.</td>
<td>09/2019</td>
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<tr>
<td>New policy for solriamfetol (Sunosi).</td>
<td>08/2019</td>
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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>sonidegib (Odomzo)</td>
<td>200 mg capsule</td>
<td>Basal cell carcinoma of the skin, locally advanced</td>
<td>30 capsules/30 days</td>
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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 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

**Policy Implementation/Update:**

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<th>Date Created</th>
<th>October 2015</th>
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<tr>
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<td>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.</td>
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**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**

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<tr>
<td>AlphaNine SD, coagulation factor IX (human)</td>
<td>500, 1000, 1500 IU</td>
<td>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</td>
<td>Control and prevention of bleeding episodes: Up to the number of doses requested every 28 days</td>
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<tr>
<td>BeneFIX, coagulation factor IX (recombinant)</td>
<td>250, 500, 1000, 2000, 3000 IU</td>
<td>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</td>
<td>Control and prevention of bleeding episodes and perioperative management: Up to the number of doses requested every 28 days</td>
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</tbody>
</table>
| Ixinity, coagulation factor IX (recombinant) | 250, 500, 1000 IU | Control and prevention of bleeding episodes*: Up to 100 IU/dL, doses every 12 to 24 hours on days two through 14 until healing is achieved Perioperative Management*:  
  - **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 | Perioperative Management: Up to the number of doses requested every 28 days |
<p>| MonoNine, coagulation | 500, 1000 IU | Control and prevention of bleeding episodes and perioperative management: | Control and prevention of bleeding episodes and perioperative management: |</p>
<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit‡</th>
</tr>
</thead>
</table>
| 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 T½ 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**: 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**: 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  
γ One unit 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

Washington State Rx Services is administered by moda

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

October 01, 2020
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**

5. Rixubis [package insert]. Westlake Village, CA; Baxalta US Inc.; May 2018
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Policy Type: PA/SP  
Pharmacy Coverage Policy: 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**

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
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</table>
| 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 |
<p>| Afstyla, antihemophilic factor | 250, 500, 1000, 1500, | <strong>On-demand Treatment:</strong> Up to 50 IU/kg every 8 to 24 hours until bleeding is resolved | <strong>On-demand Treatment:</strong> Up to the number of doses requested every 28 days |</p>
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<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit(^{\text{\textdagger}})</th>
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</table>
| (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, intrabdominal, 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\(^{\text{\textdagger\dagger}}\):** Up to 100 IU/dL; Repeat every 8 to 24 hours until the bleeding threat is resolved  
**Perioperative Management\(^{\text{\textdagger\dagger}}\):**  
- *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, intrabdominal, 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\(^{\text{\textdagger\dagger}}\):** Up to 100 IU/dL every 8 to 12 hours until bleeding threat is resolved  
**Perioperative Management\(^{\text{\textdagger\dagger}}\):** 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 |
<table>
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<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit(^\text{‡})</th>
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<tr>
<td>Kogenate FS, antihemophilic factor (recombinant), formulated with sucrose</td>
<td>250, 500, 1000, 2000, 3000 IU</td>
<td>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.</td>
<td>On-demand Treatment: Up to the number of doses requested every 28 days</td>
</tr>
<tr>
<td>Kovaltry, antihemophilic factor (recombinant)</td>
<td>250, 500, 1000, 2000, 3000 IU</td>
<td>on-demand Treatment: Up to 100 IU/dL every 8 to 24 hours until bleeding is resolved</td>
<td>On-demand Treatment: Up to the number of doses requested every 28 days</td>
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</tbody>
</table>

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<td>Perioperative Management ‡:</td>
<td>Perioperative Management: Up to the number of doses requested for 28 days</td>
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<tr>
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<td></td>
<td>• <em>Minor</em> (e.g. tooth extraction): Up to 60 IU/dL every 24 hours until healing is achieved</td>
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<td></td>
<td>• <em>Major</em> (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)</td>
<td></td>
</tr>
<tr>
<td>Novoeight, antihemophilic factor (recombinant)</td>
<td>250, 500, 1000, 2000, 3000 IU</td>
<td>On-demand Treatment ‡: Up to 100 IU/dL every 8 to 24 hours until resolution of bleed (approximately seven to ten days)</td>
<td>On-demand Treatment: Up to the number of doses requested every 28 days</td>
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<tr>
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<td>Routine Prophylaxis:</td>
<td>Routine Prophylaxis:</td>
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<tr>
<td></td>
<td></td>
<td>• ≥12 years: Up to 50 IU/kg three times per week or up to 40 IU/kg every other day</td>
<td>• ≥12 years: Up to 630 IU/kg every 28 days</td>
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<tr>
<td></td>
<td></td>
<td>• ≤ 12 years: Up to 60 IU/kg three times weekly or up to 50 IU/kg every other day</td>
<td>• ≤12 years: Up to 756 IU/kg every 28 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perioperative Management ‡:</td>
<td>Perioperative Management: Up to the number of doses requested for 28 days</td>
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<tr>
<td></td>
<td></td>
<td>• <em>Minor</em> (e.g. tooth extraction): Up to 60 IU/dL every 12 to 24 hours until bleeding is resolved</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>• <em>Major</em> (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)</td>
<td></td>
</tr>
<tr>
<td>Nuwiq, antihemophilic factor (recombinant)</td>
<td>250, 500, 1000, 2000, 2500, 3000, 4000 IU</td>
<td>On-demand Treatment ‡: Up to 100 IU/dL every 8 to 24 hours until bleeding risk is resolved</td>
<td>On-demand Treatment: Up to the number of doses requested every 28 days</td>
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</tbody>
</table>

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October 01, 2020
| Product Name | Dosage Form | Indication/ FDA Labeled Dosing | Quantity Limit

--- | --- | --- | ---
| **Recombinate**, antihemophilic factor (recombinant) | 250, 500, 1000, 1500, 2000 IU | **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**:  
- *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) |  |
| **On-demand Treatment**:  
- Up to 100 IU/dL every 8 to 24 hours until bleeding threat is resolved  
**Perioperative Management**:  
- *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 |  |
| **Xyntha**, antihemophilic factor (recombinant) | 250, 500, 1000, 2000 IU | **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 |  |
| **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

Washington State Rx Services is administered by Moda Health

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October 01, 2020
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


Policy Implementation/Update:

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</tr>
</thead>
<tbody>
<tr>
<td>New policy created for standard half-life factor products</td>
<td>08/2019</td>
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</table>
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

<table>
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<tr>
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<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
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<td>stiripentol (Diacomit)</td>
<td>250 mg capsules</td>
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<td>180 capsules/30 days</td>
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<td></td>
<td>500 mg capsules</td>
<td></td>
<td>180 capsules/30 days</td>
<td>179387</td>
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<tr>
<td></td>
<td>250 mg powder for oral suspension</td>
<td></td>
<td>180 packets/30 days</td>
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<td>500 mg powder for oral suspension</td>
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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 investigational when used for all other conditions, including but not limited to:
   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

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/

Policy Implementation/Update:

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Action and Summary of Changes

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October 01, 2020
sunitinib (Sutent®)
UMP POLICY

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

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<td>12.5 mg capsule</td>
<td>Gastrointestinal stromal tumor, after disease progression on or intolerance to imatinib;</td>
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<td>25 mg capsule</td>
<td>Neuroendocrine pancreatic tumor, locally advanced or metastatic;</td>
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<td>37.5 mg capsule</td>
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<td>50 mg capsule</td>
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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 **not** 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-α 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


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<td>01/2018, 11/2019</td>
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<td>01/2018</td>
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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

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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 **not medically necessary** when used for all other conditions, including but not limited to:

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October 01, 2020
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.

References

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


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October 01, 2020
These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

Policy Type: PA

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

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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 Type: PA/SP       Pharmacy Coverage Policy: UMP184

Split Fill Management*

**Description**
Tazemetostat (Tazverik) is an orally administered inhibitor of zeste homolog 2 enhancer.

**Length of Authorization**
- N/A

**Quantity Limits**

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**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 considered 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.

Investigational or Not Medically Necessary Uses

I. Tazemetostat (Tazverik) has not been sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. 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:
   B. Soft tissue sarcoma, including epithelioid sarcoma
   C. Non-Hodgkin lymphoma, including follicular lymphoma
   D. Other types of lymphoma, including but not limited to mediastinal, B-Cell, Mantle-Cell, Marginal Zone,
   E. Rhabdoid tumors
   F. Mesothelioma
   G. Kidney, bladder, urothelial cancers
   H. Hepatocellular carcinoma

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

October 01, 2020
* The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

References


Policy Implementation/Update:

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<tr>
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<td>05/2020</td>
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Teduglutide (Gattex®)

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

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<tr>
<td>teduglutide (Gattex)</td>
<td>5 mg vial kit (one vial)</td>
<td>Short Bowel Syndrome (SBS)</td>
<td>1 vial/1 day</td>
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<td>5 mg vial kit (30 vial)</td>
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<td>30 vials/30 days</td>
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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 investigational when used for all other conditions, including but not limited to:
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


Washington State Rx Services is administered by moda HEALTH

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

October 01, 2020
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<td>05/2013, 09/2013, 06/2019</td>
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Policy Type: PA

Pharmacy Coverage Policy: UMP087

Description
Tegaserod (Zelnorm) is an orally administered serotonin-4 (5-HT4) receptor agonist.

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

Quantity limits

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<tr>
<td>tegaserod (Zelnorm)</td>
<td>6 mg tablets</td>
<td>Irritable bowel syndrome with constipation</td>
<td>60 tablets/30 days</td>
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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 not medically necessary when criteria above are not met and/or when used for:
    A. Irritable bowel syndrome with constipation in males

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

6. Clinicaltrials.gov

Policy Implementation/Update:

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

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<th>Indication</th>
<th>Quantity Limit</th>
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<tr>
<td>telotristat ethyl (Xermelo)</td>
<td>250 mg tablets</td>
<td>Carcinoid Syndrome Diarrhea</td>
<td>84 tablets/28 days</td>
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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 investigational when used for all other conditions, including but not limited to:
   A. Carcinoid syndrome without diarrhea
   B. Biliary Tract Cancer
   C. Pancreatic Cancer

Renewal Evaluation

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


Policy Implementation/Update:

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Action and Summary of Changes

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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 O6 and N7 positions of guanine which leads to DNA double strand breaks and apoptosis.

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

Quantity Limits

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<td>temozolomide</td>
<td>5 mg capsules</td>
<td>All indications</td>
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<td>(Temodar)</td>
<td>20 mg capsules</td>
<td>All indications</td>
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<td>100 mg capsules</td>
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Provider Administered Agents*

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<td>(Temodar)</td>
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*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
**Policy Implementation/Update:**

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Policy Type: PA/SP  Pharmacy Coverage Policy: UMP170

Description
Tenapanor (Ibsrela) is an orally administered sodium/hydrogen exchange 3 inhibitor.

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

Quantity limits

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<td>50 mg tablets</td>
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Initial Evaluation

I. Tenapanor (Ibsrela) 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 gastroenterologist; AND
   C. A diagnosis of irritable bowel syndrome with constipation (IBS-C) when the following are met:
      1. The provider attests the member has less than three complete spontaneous bowel movements per week on average (defined as bowel movements without aid of laxatives that provide a sense of complete evacuation); AND
      2. The member experiences pain from the condition AND a pain score has been documented; AND
      3. The member has had an inadequate response to, intolerance of, or has a contraindication to the ALL of the following:
         i. Dietary and lifestyle 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: linaclootide (Linzess) OR plecanatide (Trulance).

II. Tenapanor (Ibsrela) is considered investigational when used for all other conditions, including but not limited to:
   A. Hyperphosphatemia
   B. Chronic kidney disease
   C. Irritable bowel syndrome with diarrhea

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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.
D. Mixed irritable bowel syndrome
E. Chronic idiopathich constipation
F. Opioid-induced constipation

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. The medication is prescribed by, or in consultation with, a gastroenterologist; AND
IV. Provider attests the member has exhibited improvement in disease symptoms as indicated by BOTH of the following:
   1. An increase of at least one complete spontaneous bowel movement per week; AND

Supporting Evidence

I. Tenapanor (Ibsrela) was evaluated in two double-blind, placebo-controlled, randomized trials in adult patients –T3MPO-2 and T3MPO-1. The majority of subjects were female, white, and all met Rome III criteria for IBS-C. This requires a pain score of at least three on a 0-10 scale, less than three complete spontaneous bowel movements (CSBMs) per week and less than five spontaneous bowel movements (SBMs) per week. Tenapanor (Ibsrela) has a Black Box Warning for serious dehydration in pediatric patients, and has not been evaluated in any pediatric population to date. It is contraindicated in those less than six years of age, and comes with a recommendation to avoid use in those less than 12 years of age. It should be avoided as animal studies showed cause of death to be dehydration in young juvenile rats.
   - The primary outcome was proportion of responders, defined as achieving both of the following for at least six of the first 12 weeks of the trials: an increase of at least one CSBM per week on average and a reduction of 30% in weekly average abdominal pain score compared to baseline.
   - T3MPO-2: 620 subjects were evaluated for 26 weeks of treatment. Responders active vs. placebo: 37% vs. 24% (CI 6-20%). Difference from placebo 13%.
   - T3MPO-1: 606 subjects were evaluated for 12 weeks and then were re-randomized to active drug or placebo for a 4-week withdrawal period. Responders active vs. placebo: 27% vs. 19% (CI: 2-15%). Difference from placebo 8%.

II. The quality of the evidence is considered low given the invalidated subjective endpoints used to determine efficacy and the short duration of therapy evaluated for safety and efficacy. Additionally, given the limited treatment effect and lack of place in therapy information, usability is uncertain at this time; thus, use of non pharmacologic agents and other established therapies are required prior to payment consideration.
Investigational or Not Medically Necessary Uses

I. Safety and efficacy have not yet been sufficiently established and/or clinical trials are currently underway for the following indications:
   A. Hyperphosphatemia
   B. Chronic kidney disease

References


Policy Implementation/Update:

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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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>tetrabenazine (Xenazine)</td>
<td>12.5 mg</td>
<td>Chorea associated with Huntington’s disease</td>
<td>60 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>Chorea associated with Huntington’s disease, genotyped extensive and intermediate metabolizers</td>
<td>120 tablets/30 days</td>
</tr>
<tr>
<td>generic tetrabenazine</td>
<td>12.5 mg</td>
<td>Chorea associated with Huntington’s disease</td>
<td>60 tablets/30 days</td>
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<td>25 mg</td>
<td></td>
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<tr>
<td></td>
<td>25 mg</td>
<td>Chorea associated with Huntington’s disease, genotyped extensive and intermediate metabolizers</td>
<td>120 tablets/30 days</td>
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<tr>
<td>deutetrabenazine (Austedo)</td>
<td>6 mg</td>
<td>Tardive dyskinesia in adults; Chorea associated with Huntington’s disease</td>
<td>30 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>9 mg</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>12 mg</td>
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<td></td>
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<tr>
<td>valbenazine (Ingrezza)</td>
<td>40 mg</td>
<td>Tardive Dyskinesia</td>
<td>30 capsules/30 days; 4-week Initiation Pack</td>
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<tr>
<td></td>
<td>80 mg</td>
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Initial Evaluation

I. Tetrabenazine (Xenazine), deutetetarbzenzine (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), deutetetarbzenzine (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 deutetetarbzenzine (Austedo) only:** Treatment with generic tetrabenazine has been ineffective, contraindicated or not tolerated; **AND**
         iv. **For Tetrabenazine (Xenazine) only:** Treatment with generic tetrabenazine and deutetetarbzenzine (Austedo) has been ineffective, contraindicated or not tolerated; **OR**
      2. **[For generic tetrabenazine, valbenazine (Ingrezza) and deutetetarbzenzine (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, benzotropine, 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 deutetetarbzenzine (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, benztrpine)] 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

1. Austedo [Prescribing Information]. Teva Pharmaceuticals USA, Inc.: North Wales, PA. April 2017
3. Ingrezza [Prescribing Information]. Neurocrine Pharmaceuticals; San Diego, CA. April 2017

Policy Implementation/Update:

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<td>December 2019</td>
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<tr>
<td>Last Reviewed</td>
<td>05/2017, 06/2017, 08/2019, 09/2017, 12/2019</td>
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Washington State Rx Services is administered by moda HEALTH

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

October 01, 2020
### Action and Summary of Changes

<table>
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<th>Date</th>
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<tbody>
<tr>
<td>Updated criteria to policy format and combined separate polices into one</td>
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<tr>
<td>Generic tetrabenazine added to tardive dyskinesia criteria</td>
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<tr>
<td>For deutetrabenazine (Austedo) only: Treatment with generic tetrabenazine and valbenazine (Ingrezza) has been ineffective, contraindicated or not tolerated</td>
<td>12/2019</td>
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<td>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</td>
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<tr>
<td>Added Tardive Dyskinesia indication for deutetrabenazine (Austedo™)</td>
<td>09/2017</td>
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<tr>
<td>Updated question 5 for valbenazine (Ingrezza™) based on P&amp;T recommendations</td>
<td>08/2017</td>
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tiopronin (Thiola®; Thiola EC®)  
UMP POLICY

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>tiopronin (Thiola)</td>
<td>100 mg tablet</td>
<td>Nephrolithiasis (cystine), prevention</td>
<td>450 tablets/30 days</td>
</tr>
<tr>
<td>tiopronin (Thiola EC)</td>
<td>100 mg delayed release tablet</td>
<td>Nephrolithiasis (cystine), prevention</td>
<td>450 tablets/30 days</td>
</tr>
<tr>
<td></td>
<td>300 mg delayed release tablet</td>
<td>Nephrolithiasis (cystine), prevention</td>
<td>150 tablets/30 days</td>
</tr>
</tbody>
</table>

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 not been responsive to all of the following:
         i. High fluid intake
         ii. Urinary alkalization
         iii. Diet modification (e.g. restriction of sodium and protein intake)

II. Tiopronin (Thiola; Thiola EC) 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 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**


**Policy Implementation/Update:**

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<th>Date Created</th>
<th>December 2019</th>
</tr>
</thead>
<tbody>
<tr>
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</table>
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

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<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>tobramycin (TOBI)</td>
<td>300 mg/5mL one single-use ampule</td>
<td>Cystic fibrosis with <em>Pseudomonas aeruginosa</em></td>
<td>56 single-dose ampules/28 days</td>
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<tr>
<td>generic tobramycin inhalation solution</td>
<td>300 mg/5mL one single-use ampule</td>
<td></td>
<td>56 single-dose ampules/28 days</td>
</tr>
<tr>
<td>tobramycin (KITABIS)</td>
<td>300 mg/5mL one single-use ampule</td>
<td></td>
<td>56 single-dose ampules/28 days</td>
</tr>
<tr>
<td>tobramycin (Bethkis)</td>
<td>300 mg/4 mL one single-use ampule</td>
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<td>56 single-dose ampules/28 days</td>
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<tr>
<td>tobramycin (TOBI Podhaler)</td>
<td>28mg inhalation capsule</td>
<td></td>
<td>224 inhalation capsules/28 days</td>
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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 FEV₁ >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.

References

1. KITABIS PAK package insert. Catalent Pharma Solutions, LLC Woodstock, IL 60098. 12/06/2019
2. TOBI Podhaler package insert. Novartis Pharmaceuticals Corporation (10/02/2015)
3. TOBI inhalation solution package insert. Novartis Pharmaceuticals Corporation (10/05/2018)

Policy Implementation/Update:

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<td>12/2019</td>
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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

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<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
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<tbody>
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<td>tolvaptan (Jynarque)</td>
<td>15 mg tablets</td>
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<td>28 tablets/28 days</td>
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<td></td>
<td>30 mg tablets</td>
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<td>60 tablets/30 days</td>
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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 (ADPKD)** 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 **investigational** when used for all other conditions, including but not limited to:
   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 m2); the group difference was 1.27 mL/min/1.73 m2 (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 eGFR 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 euvoletic 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
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:

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<th>Date</th>
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<td>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).</td>
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Washington State Rx Services is administered by Medicaid

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.

October 01, 2020
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 (aquarexis), a decrease in urine osmolality, and a resulting increase in serum sodium concentrations.

Length of Authorization
- Initial: one month
- Renewal: no renewal

Quantity limits

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<th>Product Name</th>
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<tr>
<td>tolvaptan (Samsca)</td>
<td>15 mg tablet</td>
<td>Hypervolemic or euvolemic hyponatremia</td>
<td>30 tablets/30 days*</td>
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<tr>
<td></td>
<td>30 mg tablet</td>
<td></td>
<td>60 tablets/30 days*</td>
</tr>
</tbody>
</table>

*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

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

I. Per the label, tolvaptan (Samsca) is indicated for the treatment of clinically significant hypervolemic and euvoletic 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 quadriaparesis, 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


Policy Implementation/Update:

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<th>Date</th>
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<tr>
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Washington State Rx Services is administered by moda HEALTH

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

UMP POLICY

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

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<tr>
<td>trametinib (Mekinist)</td>
<td>0.5 mg tablet</td>
<td>Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy</td>
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<td>2 mg tablet</td>
<td>Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy</td>
<td>30 tablets/30 days</td>
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<tr>
<td></td>
<td>50 mg capsule</td>
<td>Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy</td>
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<tr>
<td>dabrafenib (Tafinlar)</td>
<td>75 mg capsule</td>
<td>Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, monotherapy in BRAF treatment naïve patients</td>
<td>120 capsules/30 days</td>
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<tr>
<td></td>
<td></td>
<td>Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy</td>
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</tr>
</tbody>
</table>
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. Hepatocellular 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

References


Policy Implementation/Update:

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<td>November, 2013</td>
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<tr>
<td>Last Updated</td>
<td>October, 2019</td>
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<td>Last Reviewed</td>
<td>01/2015, 06/2018</td>
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**Action and Summary of Changes**

| 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 |

**Washington State Rx Services is administered by**

These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.
Policy Type: PA/SP  Pharmacy Coverage Policy: UMP069

Description
Trifluridine 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

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<td>trifluridine/tipiracil (Lonsurf)</td>
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<td>Stomach or esophagogastric adenocarcinoma – metastatic, previously treated</td>
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<td>20 mg – 8.19 mg tablets</td>
<td>Colorectal cancer – metastatic, previously treated</td>
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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; \textbf{AND}

v. The member has been previously treated with an anti-VEGF biological therapy (e.g., bevacizumab); \textbf{OR}

\begin{enumerate}
\item \textbf{Gastric or gastroesophageal junction adenocarcinoma; AND}
\item The disease is metastatic (i.e., stage IV); \textbf{AND}
\item The member has been tested and has documentation of HER2/neu negative status; \textbf{OR}
\begin{enumerate}
\item The member has been tested and has documentation of HER2/neu positive status; \textbf{AND}
\item Has received prior HER2/neu targeted therapy (e.g., trastuzumab); \textbf{AND}
\end{enumerate}
\item The member has been previously treated with at least two prior lines of chemotherapy; \textbf{AND}
\item 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
\end{enumerate}

\textbf{II. Trifluridine/tipiracil (Lonsurf) is considered investigational when used for all other conditions, including but not limited to:}
\begin{enumerate}
\item Combination therapy with other oncolytic agents.
\item 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.
\item Colorectal, gastric, or gastroesophageal cancer at a dose <20 mg/m2 orally twice daily.
\item Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type).
\item 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.
\item Biliary track cancers.
\item Tumors that are not colorectal, gastric or gastroesophageal in nature.
\end{enumerate}

\textbf{Renewal Evaluation}
\begin{enumerate}
\item The medication is prescribed by or in consultation with an oncologist or gastroenterologist; \textbf{AND}
\item Trifluridine/tipiracil (Lonsurf) continues to be used as monotherapy; \textbf{AND}
\item Body surface area is provided in meters squared; \textbf{AND}
\item Trifluridine/tipiracil (Lonsurf) is being used at or above a dose of 20 mg/m2; \textbf{AND}
\item The member is not experiencing unacceptable toxicity from the therapy; \textbf{AND}
\item The patient has not experienced disease progression while on trifluridine/tipiracil (Lonsurf); \textbf{OR}
\end{enumerate}
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 shown 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


**Policy Implementation/Update:**

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<td>September 2019</td>
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<td>Last Reviewed</td>
<td>09/05/2019</td>
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**Action and Summary of Changes**

| 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 |
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

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<th>Dosage Form</th>
<th>Indication</th>
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<tbody>
<tr>
<td>tucatinib (Tukysa)</td>
<td>50 mg tablets</td>
<td>Metastatic breast cancer</td>
<td>60 tablets/30 days</td>
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<tr>
<td></td>
<td>150 mg tablets</td>
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<td>120 tablets/30 days</td>
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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

8. UpToDate, Inc. Lapatinib: Drug information. UpToDate [database online]. Waltham, MA. Available at: http://www.uptodate.com/home/index.htm

Policy Implementation/Update:

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<td>08/2020</td>
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vemurafenib (Zelboraf®)
UMP POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: UMP070

Description
Vemurafenib (Zelboraf) is an orally administered BRAF kinase inhibitor used for the treatment of unresectable or metastatic melanoma, or Erdheim-Chester Disease in patients with a BRAFV600E mutation.

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

Quantity limits

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<td>240 mg tablets</td>
<td>Unresectable or metastatic melanoma; Erdheim-Chester Disease</td>
<td>240 tablets/30 days</td>
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</table>
I. Member has previously received treatment with vemurafenib (Zelboraf); AND
II. Continues to meet criteria identified in section I of the Initial Evaluation; AND
III. Absence of disease progression; AND
IV. Absence of unacceptable toxicity from the medication

Supporting Evidence

I. FDA-approved companion diagnostic for BRAF V600E mutation includes FoundationOne CDx and Cobas® 4800 V600 Mutation Test
II. A Cochrane Review meta-analysis concluded that vemurafenib (Zelboraf) used in combination with cobimetinib (Cotellic) is superior over monotherapy vemurafenib (Zelboraf) in the setting of unresectable or metastatic melanoma.
III. 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.

Investigational or Not Medically Necessary Uses

I. Thyroid cancers (e.g. anaplastic thyroid carcinoma, advanced papillary thyroid cancers with BRAF v600 mutation)
   A. Evidence for the use of vemurafenib (Zelboraf) in the setting of thyroid cancers are limited to phase I trials
II. Non-small cell lung cancer (NSCLC) with BRAF V600E mutation
   A. Evidence for the use of vemurafenib (Zelboraf) in the setting of NSCLC is limited to case studies.
III. Hairy cell leukemia
   A. Evidence for the use of vemurafenib (Zelboraf) in the setting of hairy cell leukemia are limited to phase II trials

References


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<td>- After review of evidence regarding safety, the removal of split fill management is clinically appropriate.</td>
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<td>- Updated renewal duration from 3 months to 12 months to align with usual oncolytic renewal approval duration.</td>
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<td>- Convert criteria format into policy format</td>
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Clarified use of concomitant medication

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

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<tr>
<th>Product Name</th>
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<td>10 mg tablets</td>
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<td>28 tablets/28 days 192576</td>
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<td>120 tablets/30 days 192579</td>
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<td>100 mg tablets</td>
<td>Acute myeloid leukemia</td>
<td>180 tablets/30 days 192579</td>
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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

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October 01, 2020
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.

- Age 75 years and older; OR
- Have comorbidities that preclude use of intensive induction chemotherapy such as:
  - Baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3
  - Severe cardiac or pulmonary comorbidity
  - Moderate hepatic impairment
  - CrCl ≥30 to <45 mL/min
  **AND**
- 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 idelalisib (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. Approval is based on 2 phase Ib/II trials in this setting. Continued approval of venetoclax (Venclexta) in AML is contingent on the results of a confirmatory trial.

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. 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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<td>06/2016, 08/2018, 12/2018, 06/2019</td>
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<tr>
<td>Added new FDA approval in untreated CLL/SLL in combination with obinutuzumab (Gazyva)</td>
<td>06/2019</td>
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<tr>
<td>Added new FDA approval in Acute Myeloid Leukemia.</td>
<td>12/2018</td>
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<tr>
<td>Included new FDA expanded indication in CLL/SLL without 19p deletion and expanded initial approval to 6 months.</td>
<td>08/2018</td>
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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

October 01, 2020
Description
Vigabatrin (Sabril) is an orally administered agent that has irreversible inhibition of gamma-aminobutyric acid transaminase (GABA-T) but the full mechanism of action is unknown at this time.

Length of Authorization
- Initial: Three months for complex partial epileptic seizure, and one month for West Syndrome
- Renewal: 12 months

Quantity limits

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<td>500 mg/packet oral powder for solution</td>
<td>Refractory complex partial epileptic seizure, adjunct therapy.</td>
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<td>500 mg/packet oral powder for solution</td>
<td>West Syndrome</td>
<td>120 packets/30 days</td>
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Initial Evaluation
I. Vigabatrin (Sabril) 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 is prescribed, or documentation is provided regarding clinical rationale as to why generic vigabatrin 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) 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, tigabine; AND
         ii. A trial and failure of at least two anti-epileptic medications listed above; AND
         iii. Member is 10 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)** 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. Medication is prescribed by or in consultation with a neurologist; **AND**  
II. Ophthalmologic examination has been completed at baseline and every three months since initiation of therapy; **AND**  
III. Generic vigabatrin is prescribed, or documentation is provided regarding clinical rationale as to why generic vigabatrin is not appropriate or is contraindicated **AND**  
IV. 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, tigabine; **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) 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) administration. This medication is available through a Risk Evaluation Mitigation Strategy (REMS) Program, and a specialist shall be involved in prescribing to ascertain if the benefits of vigabatrin (Sabril) outweigh the risk of vision loss.  
II. Recommended ophthalmologic monitoring shall start at baseline or within four weeks of initiating therapy, every three months during therapy through three to six months post discontinuation.  
III. Vigabatrin (Sabril) is FDA-approved for complex partial epileptic seizures (focal onset impaired awareness seizure) for ages 10 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 shall be used in addition to at least one other anti-epileptic (i.e., vigabatrin [Sabril] is an adjunct therapy).
IV. The max dose of vigabatrin (Sabril) is 3000 mg/day for complex partial epileptic seizure and a maximum of 150 mg/kg/day for West Syndrome.

V. For West Syndrome, significant clinical benefit should be realized within four weeks of therapy initiation, and the medication shall be discontinued if not. Due to the risks associated with the medication, continuation of therapy shall not be granted 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 vigabaril (Sabril).

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


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Von Willebrand factor (Vonvendi®)

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

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<th>Dosage Form</th>
<th>Indication/ FDA Labeled Dosing</th>
<th>Quantity Limit</th>
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| 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)

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 ratios 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


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Policy Implementation/Update:

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

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

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Dosage Form</th>
<th>Indication</th>
<th>Quantity Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>voxelotor (Oxbryta™)</td>
<td>500 mg tablets</td>
<td>Sickle Cell Disease</td>
<td>90 tablets/30 days</td>
</tr>
</tbody>
</table>

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

Washington State Rx Services is administered by moda HEALTH

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

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

References


Policy Implementation/Update:

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<th>Action and Summary of Changes</th>
<th>Date</th>
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<tr>
<td>Policy created</td>
<td>02/2020</td>
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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

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<tr>
<th>Product Name</th>
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<th>Quantity Limit</th>
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</thead>
<tbody>
<tr>
<td>zanubrutinib (Brukinsa)</td>
<td>80 mg tablets</td>
<td>Treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy</td>
<td>120 tablets/30 days</td>
</tr>
</tbody>
</table>

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 investigational when used for all other conditions, including but not limited to:
   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 Macroglobulinemia (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 (Venclexta).

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 Macroglobulinemia (WM)
   J. MCL first-line therapy
   K. MCL combination therapy

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

References


Policy Implementation/Update:

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<th>02/2020</th>
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<td>Date</td>
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<tr>
<td>Policy created</td>
<td>02/2020</td>
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The UMP POLICY NAME: **UMP007 SUVOREXANT**

**Affected Medications:** BELSOMRA® (SUVOREXANT, ORAL)

**Effective Date (date PA/Step UM edit effective):** 1/27/2016

**Last Review Date:** 12/27/15

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<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF INSOMNIA.</th>
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<tbody>
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<td>Required Medical Documentation</td>
<td>FAILURE OF NON-PHARMACOLOGIC THERAPIES (E.G., SLEEP HYGEINE, PSYCHOLOGICAL THERAPIES, BEHAVIORAL THERAPIES); FAILURE OF OR CONTRAINDICATION TO ZOLPIDEM, ESZOPICLONE, AND ONE ADDITIONAL MEDICATION USED FOR THE TREATMENT OF INSOMNIA (E.G., TEMAZEPAM, ZALEPLON).</td>
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<tr>
<td>Exclusion and Restrictions</td>
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<td>Exclusion</td>
<td>DIAGNOSIS OF NARCOLEPSY</td>
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<td>Quantity Limits</td>
<td>30 TABLETS PER 30 DAYS.</td>
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<td>Additional Information</td>
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POLICY NAME: **UMP009 COBIMETINIB**

**Affected Medications**: COTELLIC® (COBIMETINIB FUMARATE, ORAL)

**Effective Date (date PA/Step UM edit effective)**: 2/4/2016

**Last Review Date**: 2/4/16

<table>
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<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF UNRESECTABLE OR METASTATIC MELANOMA WITH BRAF V600F OR V600K MUTATION IN COMBINATION WITH VEMURAFENIB.</th>
</tr>
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<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>CONCURRENT USE WITH VEMURAFENIB. CONFIRMED BRAF V600E OR V600K MUTATION. RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON COBIMETINIB AND CONTINUED CONCURRENT USE WITH VEMURAFENIB.</td>
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<td>Provider restriction: PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST.</td>
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<td>Coverage Duration</td>
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<td>USE OF SAMPLES DO NOT CIRCUMVENT POLICY REQUIREMENTS FOR COVERAGE.</td>
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**POLICY NAME:** **UMP031 ENFUVIRIDETIDE**

**Affected Medications:** FUZEON® (ENFUVIRIDETIDE, SUBCUTANE.)

**Effective Date (date PA/Step UM edit effective):** 3/1/2012

**Last Review Date:**

<table>
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<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF HIV-1 INFECTION.</th>
</tr>
</thead>
</table>

**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 PHOTOTYPIC) INCLUDING AT LEAST THREE HIV DRUGS.

<table>
<thead>
<tr>
<th>Exclusion and Restrictions</th>
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<tbody>
<tr>
<td>Patient restriction</td>
<td>MUST BE SIX YEARS OF AGE OR OLDER.</td>
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<tr>
<td>Provider restriction</td>
<td>PRESCRIBED OR SUPERVISED BY A SPECIALIST IN THE TREATMENT OF HIV INFECTION.</td>
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<tr>
<th>Coverage Duration</th>
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| Additional Information | |
|------------------------| |
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

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<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF NON-NEUROPATHIC GAUCHER'S DISEASE, CHRONIC (MILD TO MODERATE).</th>
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<tbody>
<tr>
<td>Required Medical Documentation</td>
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<tr>
<td>Exclusion and Restrictions</td>
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<tr>
<td>Patient restriction</td>
<td>IMIGLUCERASE: PATIENT AGE 2 YEARS OR OVER; MIGLUSTAT: PATIENT AGE 18 YEARS OR OLDER; VELAGLUCERASE ALFA: PATIENT AGE 4 YEARS OR OLDER.</td>
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<td>ONE YEAR.</td>
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<tr>
<td>Quantity Limits</td>
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<tr>
<td>Additional Information</td>
<td>PATIENTS TAKING MIGLUSTAT MUST NOT BE A CANDIDATE FOR ENZYME REPLACEMENT THERAPY. PATIENTS TAKING IMIGLUCERASE AND VELAGLUCERASE ALFA MUST BE MONITORED FOR HYPERSENSITIVITY REACTIONS.</td>
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**Policy Name:** UMP040 PEGYLATED INTERFERON

**Affected Medications:** PEGASYS PROCLICK® (PEGINTERFERON ALFA-2A, SUBCUTANE.); PEGASYS® (PEGINTERFERON ALFA-2A, SUBCUTANE.); PEG-INTRON® (PEGINTERFERON ALFA-2B)

**Effective Date (date PA/Step UM edit effective):** 12/4/2012

**Last Review Date:** 1/27/14

<table>
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<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF HEPATITIS C</th>
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</thead>
</table>

**Required Medical Documentation**

FOR PATIENTS WITH A HISTORY OF A SEVERE PSYCHIATRIC DISORDER, SUICIDAL IDEATIONS OR SEVERE DEPRESSION- AFFIRMATION THE CONDITION IS CURRENTLY CONTROLLED. AFFIRMATION THAT NONE OF THE FOLLOWING APPLY: PATIENT HAS DECOMPENSATED LIVER DISEASE, HAS NOT MAINTAINED SOBRIETY FOR THE LAST SIX MONTHS, IS AN INFANT OR NEONATE, HAS AUTOIMMUNE HEPATITIS, HAS A HISTORY OF HEMOGLOBINOPATHIES, HAS HYPERSENSITIVITY TO PEGYLATED INTERFERON OR ANY COMPONENT OF THE PRODUCT, IS PREGNANT OR WHOSE PARTER IS PREGNANCY AND LESS THAN TWO METHODS OF CONTRACEPTION WILL BE USED. NO CONTRAINDICATION TO COMBINATION OF RIBAVIRING AND PEGINTERFERON. IF RIBAVIRIN IS USED IN COMBINATION WITH PEGINTERFERON, THE PATIENT HAS BEEN COUNSELED ON THE TERATOGENIC EFFECTS OF THERAPY, IS WILLING TO PRACTICE CONTRACEPTION DURING AND FOR SIX MONTHS AFTER COMPLETION OF THERAPY AND HAS HAD A NEGATIVE PREGNANCY TEST (APPLIED TO FEMALE PATIENTS ONLY). DETECTABLE VIRAL LOAD IS REQUIRED, DEFINED AS 50 IU/ML OR GREATER. FOR GENOTYPE 1 AND 4, LIVER BIOPSY INDICATING CHRONIC HEPATITIS WITH SIGNIFICANT FIBROSIS (E.G., META VIR SCORE OF 2 OR GREATER, ISHAK SCORE OF 3 OR GREATER). PATIENTS WITH A CURRENT/RECENT HISTORY OF ILLICIT DRUG USE, HEAVY ALCOHOL CONSUMPTION OR CURRENTLY ENROLLED IN A METHADONE MAINTENANCE PROGRAM WILL BE ENROLLED IN A SUBSTANCE ABUSE TREATMENT PROGRAM DURING THERAPY. PATIENT OR CAREGIVER HAS BEEN EDUCATED ON THE IMPORTANCE OF MEDICATION ADHERENCE AND AFFIRMS WILLINGNESS TO ADHERE TO THE REGIMEN FOR THE FULL COURSE OF THERAPY. PEGASYS IS THE PREFERRED PEGINTERFERON FOR WHICH TRIAL/FAILURE OF OR CONTRAINDICATION TO IS REQUIRED.

**Exclusion and Restrictions**

**Exclusion**

PAYMENT WILL NOT BE PROVIDED FOR RETREATMENT WITH THE SAME REGIMEN DEFINED AS: PREVIOUS TREATMENT WITH THE PRESCRIBED MEDICATION REGIMEN WHERE EARLY VIROLOGIC RESPONSE (EVR) WAS NOT ACHIEVED AT 12 OR 24 WEEKS; ACHIEVED EVR OR END TREATMENT RESPONSE BUT NOT SUSTAINED VIRAL RESPONSE AT SIX MONTHS POST THERAPY. RENEWAL IS RESERVED FOR PATIENTS WITH HIV-COINFECTION OR THOSE WITH GENOTYPE 1 OR 4 WHO HAVE ACHIEVED GREATER THAN 2 LOG REDUCTION IN HCV RNA FROM BASELINE VALUE (EVR) AFTER 12 WEEKS OF THERAPY. PEGINTERFERON RENEWALS REQUIRE A 60 DAY GAP IN THERAPY.
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**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:**

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<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
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<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>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.</td>
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<td>Provider restriction</td>
<td>PRESCRIBED OR SUPERVISED BY A GASTROENTEROLOGIST, HEPATOLOGIST, OR INFECTIOUS DISEASE SPECIALIST.</td>
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<td>Coverage Duration</td>
<td>INITIATION THERAPY: FOUR MONTHS. RENEWAL THERAPY FOR GENOTYPE 1 OR 4: 8 MONTHS; FOR GENOTYPE 2 OR 3: 2 MONTHS.</td>
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<td>TABLETS/CAPSULES: 180/30; ORAL SOLUTION: 900ML/30.</td>
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**Additional Information**
**POLICY NAME:** UMP044 ADEFOVIR

**Affected Medications:** ADEFOVIR DIPIVOXIL, ORAL (HEPSERA®)

**Effective Date (date PA/Step UM edit effective):** 1/1/2011

**Last Review Date:**

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</thead>
</table>

| Required Medical Documentation | PATIENTS PREGNANT OR OF CHILDBEARING POTENTIAL COUNSELED 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 (GREATER 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 (GREATER 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. |

<table>
<thead>
<tr>
<th>Exclusion and Restrictions</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient restriction</strong></td>
<td>18 YEARS OF AGE OR OLDER.</td>
</tr>
<tr>
<td><strong>Provider restriction</strong></td>
<td>PRESCRIBED BY A GASTROENTEROLOGIST, INFECTIOUS DISEASE SPECIALIST OR SPECIALIST IN THE TREATMENT OF HEPATITIS B VIRUS.</td>
</tr>
</tbody>
</table>

| Coverage Duration | ONE YEAR. |

| Quantity Limits | Additional Information |
**POLICY NAME:** **UMP047 PRAMINTIDE ACETATE**

**Affected Medications:** SYMLINPEN 120® (PRAMINTIDE ACETATE, SUBCUTANE.); SYMLINPEN 60® (PRAMINTIDE ACETATE, SUBCUTANE.)

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 7/21/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF TYPE I OR TYPE II DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>FAILED TO REACH TREATMENT GOALS WITH INSULIN (ALONE OR IN COMBINATION WITH ORAL MEDICATIONS), REQUIRING MEALTIME INSULIN OR CONTINUOUS INSULIN INFUSION (VIA INSULIN PUMP), HbA1C VALUE LESS THAN 9% WITHIN THE LAST 3 MONTHS,</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>DIAGNOSIS OF GASTROPARESIS OR REQUIRING USE OF MEDICATION TO STIMULATE GASTROINTESTINAL MOTILITY (I.E. METOCLOPRAMIDE OR ERYTHROMYCIN) OR POOR COMPLIANCE WITH INSULIN REGIMEN, BLOOD GLOCOSE MONITORING REGIMEN OR EXPERIENCING SEVERE HYPOCLYCEMIA REQUIRING ASSISTANCE WITHIN THE LAST 6 MONTHS</td>
</tr>
<tr>
<td>Patient restriction</td>
<td></td>
</tr>
<tr>
<td>Provider restriction</td>
<td></td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>LENGTH OF BENEFIT</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**Policy Name:** UMP064 Vitamin D Analogues

**Affected Medications:** CALCIEX® (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:**

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td></td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion for end-stage renal disease (ESRD) for calcitriol, hectorol, ZEMPLAR rejecting for &quot;Bill Medicare Part B&quot;: 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</td>
</tr>
<tr>
<td>Patient restriction</td>
<td></td>
</tr>
<tr>
<td>Provider restriction</td>
<td></td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>1 year</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**Policy Name:** UMP067 UMP Extended Duration Multiple Copay Specialty Drugs

**Affected Medications:** ILARIS® (CANAKINUMAB, SUBCUTANEOUS); LILETTA® (LEVONORGESTREL, VAGINAL); MIRENA® (LEVONORGESTREL, VAGINAL); NEXPLANON® (ETONOGESTREL, SUBCUTANEOUS); 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, INTRAOCULAR); ZOLADEX® (GOSERELIN ACETATE, SUBCUTANEOUS)

**Effective Date (Date PA/Step UM edit effective):**

**Last Review Date:** 8/18/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>Diagnosis of FDA approved indication per package labeling; for TRELSTAR and TRELSTAR MIXJET: Transgender/Gender Reassignment/Gender Dysphoria also covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>Documentation of Treatment Dose, Follow up Monitoring Plan, Prior Therpay for the Submitted Diagnosis, Planned Treatment Duration and Submission of Chart Notes for Review</td>
</tr>
</tbody>
</table>
| 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 implant 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 |
**POLICY NAME:** **UMP075 ACITRETIN**

**Affected Medications:** ACITRETIN, ORAL; SORIATANE® (ACITRETIN, ORAL)

**Effective Date (date PA/Step UM edit effective):** 9/28/2011

**Last Review Date:** 8/15/13

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF SEVERE PSORIASIS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>FAILURE OF OR CONTRAINDICATION TO A TOPIC AGENT FOR THE TREATMENT OF PSORIASIS (E.G., CORTICOSTEROIDS, CALCIPOTRIENE/CALCITRIOL, CALCIPOTIENE-STEROID COMBINATION, TAZAROTENE, CALCINEURIN INHIBITORS, TARGETED PHOTOTHERAPY). FAILURE OF OR CONTRAINDICATION TO METHOTREXATE OR CYCLOSPORINE.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>CONTRAINDICATED IN PATIENTS WITH SEVERELY IMPAIRED LIVER OR KIDNEY FUNCTION. CONCOMITANT USE OF ACITRETIN AND METHOTREXATE OR TETRACYCLINE IS CONTRAINDICATED.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>SIX MONTHS.</td>
</tr>
</tbody>
</table>
| Quantity Limits                    | 10mg capsules: up to 90 capsules per 30 days  
17.5mg capsules: up to 30 capsules per 30 days  
25mg capsules: up to 60 capsules per 30 days |
| Additional Information             | PER THE MANUFACTURER, SMALL AMOUNTS OF THE DRUG ARE FOUND IN THE SEMEN OF MALES. THE AMOUNT NEEDED IN SEMEN TO CAUSE A BIRTH DEFECT IS UNKNOWN. IN ADDITION, ALL PATIENTS SHOULD BE COUNSELED THAT THEY CANNOT DONATE BLOOD WHILE THEY ARE TAKING SORIATANE AND FOR AT LEAST 3 YEARS AFTER STOPPING THERAPY. |
POLICY NAME: UMP076 GABAPENTIN EXTENDED RELEASE (GRALISE®)

Affected Medications: GRALISE® (GABAPENTIN, ORAL)

Effective Date (date PA/Step UM edit effective): 11/28/2011

Last Review Date: 9/23/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF POSTHERPETIC NEURALGIA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>FAILURE OF OR CONTRAINDICATION TO AT LEAST A 30 DAY TRIAL OF 1800 MG PER DAY OR MORE OF IMMEDIATE-RELEASE GABAPENTIN.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>CONTRAINDICATED IN PATIENTS WITH A CREATININE CLEARANCE OF LESS THAN 30 ML/MIN OR THOSE RECEIVING HEMODIALYSIS.</td>
</tr>
<tr>
<td>Patient restriction</td>
<td>18 YEARS OF AGE OR OLDER.</td>
</tr>
<tr>
<td>Provider restriction</td>
<td></td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>ONE YEAR.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>90 TABLETS PER 30 DAYS.</td>
</tr>
<tr>
<td>Additional Information</td>
<td>USE OF SAMPLES DO NOT CIRCUMVENT POLICY REQUIREMENTS FOR COVERAGE.</td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP077 GABAPENTIN EXTENDED RELEASE (HORIZANT®)

**Affected Medications:** HORIZANT® (GABAPENTIN ENACARBIL, ORAL)

**Effective Date (date PA/Step UM edit effective):** 11/29/2011

**Last Review Date:** 9/13/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF MODERATE TO SEVERE RESTLESS LEGS SYNDROME.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>FAILURE OF OR CONTRAINDICATION TO ROPINOROLE (REQUIP®) AND PRAMIPEXOLE (MIRAPEX®)</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>ONE YEAR.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>30 TABLETS PER 30 DAYS</td>
</tr>
<tr>
<td>Additional Information</td>
<td>USE OF SAMPLES DO NOT CIRCUMVENT POLICY REQUIREMENTS FOR COVERAGE.</td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP084 VORINOSTAT

**Affected Medications:** ZOLINZA® (VORINOSTAT, ORAL)

**Effective Date (date PA/Step UM edit effective):** 3/14/2012

**Last Review Date:** 12/31/12

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF CUTANEOUS T-CELL LYMPHOMA, PROGRESSIVE, PERSISTENT OR RECURRENCE ON OR FOLLOWING TWO SYSTEMIC THERAPIES.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: FAILURE OF AT LEAST 2 SYSTEMIC THERAPIES PRIOR TO VORINOSTAT INITIATION. RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION.</td>
</tr>
<tr>
<td>Exclusion Restrictions</td>
<td><strong>Exclusion</strong></td>
</tr>
<tr>
<td></td>
<td>PATIENT AGE 18 YEARS AND OLDER.</td>
</tr>
<tr>
<td></td>
<td><strong>Provider restriction</strong></td>
</tr>
<tr>
<td></td>
<td>PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST OR DERMATOLOGIST.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: THREE MONTHS. RENEWAL: SIX MONTHS.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>100 MG CAPSULES, 120 CAPSULES PER 30 DAYS.</td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**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:**

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>INSOMNIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>TRAIL AND FAILURE OF ZOLPIDEM IR AND ZALEPLON</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>ONE YEAR</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>TWENTY TABLETS PER THIRTY DAYS</td>
</tr>
<tr>
<td>Additional Information</td>
<td>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</td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP090 VISMODEGIB

**Affected Medications:** ERIVEDGE® (VISMODEGIB, ORAL)

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 12/31/12

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF BASAL CELL CARCINOMA OF SKIN, METASTATIC OR LOCALLY ADVANCED, AFTER SURGERY OR FOR THOSE THAT ARE NOT CANDIDATES FOR SURGERY OR RADIATION.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: BASAL CELL CARCINOMA OF SKIN, METASTATIC OR LOCALLY ADVANCED. DISEASE RETURN AFTER SURGERY OR PATIENT IS NOT A CANDIDATE FOR SURGERY. PATIENT IS NOT A CANDIDATE FOR RADIATION. RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON THERAPY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td><strong>Exclusion</strong> EMBRYO-FETAL TOXICITY; EDUCATION ON THE NECESSITY OF CONTRACEPTION. <strong>Patient restriction</strong> AT LEAST 18 YEARS OF AGE. <strong>Provider restriction</strong> PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST OR UNDER THE SUPERVISION OF A SPECIALIST.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: THREE MONTHS. RENEWAL: THREE MONTHS.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>150 MG CAPSULES, 30 CAPSULES PER 30 DAYS.</td>
</tr>
</tbody>
</table>
**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

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF: HEPATITIS C, CHRONIC (PEGINTRON); MELANOMA: ADJUVANT (SYLATRON).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: HEPATITIS C, CHRONIC (PEGINTRON); MELANOMA: DIAGNOSIS WITH MICROSCOPIC OR GROSS NODAL INVOLVEMENT WITHIN 84 DAYS OF DEFINITIVE SURGICAL RESECTION INCLUDING COMPLETE LYMPHADENECTOMY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion: SYLATRON: AUTOIMMUNE HEPATITIS, HEPATIC DECOMPENSATION.</td>
</tr>
<tr>
<td></td>
<td>Patient restriction:</td>
</tr>
<tr>
<td></td>
<td>Provider restriction: PRESERVED OR SUPERVISED BY A GASTROENTEROLOGIST, HEPATOLOGIST, INFECTIOUS DISEASE SPECIALIST, ONCOLOGIST OR TRANSPLANT SPECIALIST</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>3 MONTHS</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP100 PONATINIB  

**Affected Medications:** ICLUSIG® (PONATINIB HCL, ORAL)  

**Effective Date (date PA/Step UM edit effective):** 5/19/2013  

**Last Review Date:** 5/9/13

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF CHRONIC MYELOID LEUKEMIA, CHRONIC, ACCELERATED, OR BLAST PHASE; FOR WHOM NO OTHER TYROSINE KINASE INHIBITOR THERAPY IS INDICATED; CHRONIC MYELOID LEUKEMIA, T315I-POSITIVE, CHRONIC, ACCELERATED, OR BLAST PHASE; PHILADELPHIA CHROMOSOME-POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (PH+ ALL).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: TRIAL AND FAILURE OF OR INTOLEANCE TO IMATINIB, BOSUTINIB, NILOTINIB OR OTHER TYROSINE KINASE INHIBITOR, IF INDICATED. RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON ICLUSIG.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: THREE MONTHS. RENEWAL: SIX MONTHS.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>15 MG TABLETS, 60 TABLETS PER 30 DAYS. 45 MG TABLETS, 30 TABLETS PER 30 DAYS.</td>
</tr>
<tr>
<td>Additional Information</td>
<td>ROUTINE EVALUATION HEPATIC ENZYMES, SERUM LIPASE TEST AND COMPLETE BLOOD COUNTS DURING TREATMENT.</td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP107

**Affected Medications:** FULYZAQ® (CROFELEMER, ORAL)

**Effective Date (date PA/Step UM edit effective):** 8/16/2013

**Last Review Date:** 8/16/13

**Uses Considered Medically Necessary:**
- HIV INFECTION, RECEIVING ANTI-RETROVIRAL THERAPY - NON-INFECTION DIARRHEA

**Required Medical Documentation:**
- DIAGNOSIS OF HIV/AIDS AND CURRENT REGIMENT OF ANTIRETROVIRAL THERAPY;
- DOCUMENTATION OF WATERY BOWEL MOVEMENTS;
- DOCUMENTATION INFECTIOUS DIARRHEA HAS BEEN RULED OUT;
- TRAIL AND FAILURE OF AN ALTERNATIVE THERAPY (E.G. LOPERAMIDE, DIPhenoxylATE/ATROPINE)

**Exclusion and Restrictions:**
- **Exclusion**
  - PATIENT 18 YEARS OF AGE OR OLDER

**Coverage Duration:**
- INITIAL: 3 MONTHS; CONTINUATION: 6 MONTHS

**Quantity Limits:**
- 60 TABLETS PER 30 DAYS

**Additional Information:**
- RENEWAL CRITERIA: DOCUMENTATION OF REDUCTION IN THE FREQUENCY AND QUANTITY OF WATERY BOWEL MOVEMENTS
**Policy Name:** UMP108 BEDAQUILINE FUMARATE

**Affected Medications:** SIRTURO® (BEDAQUILINE FUMARATE, ORAL)

**Effective Date (date PA/Step UM edit effective):** 8/29/2013

**Last Review Date:** 8/29/14

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF: MULTI-DRUG RESISTANT TUBERCULOSIS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: ACTIVE PULMONARY TUBERCULOSIS THAT IS RESISTANT TO ISONIAZID AND RIFAMPIN, USED IN COMBINATION WITH 3 OTHER MEDICATIONS TO WHICH THE INFECTION IS SUSCEPTIBLE.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td><strong>Exclusion</strong> LACK OF QT PROLONGATION.</td>
</tr>
<tr>
<td></td>
<td><strong>Patient restriction</strong> 18 YEARS OF AGE AND OLDER.</td>
</tr>
<tr>
<td></td>
<td><strong>Provider restriction</strong></td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>SIX MONTHS</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>100 MG TABLETS, 68 TABLETS FOR 28 DAYS, THEN 24 TABLETS FOR 28 DAYS FOR MONTHS FOUR ADDITIONAL MONTHS.</td>
</tr>
<tr>
<td>Additional Information</td>
<td>SIRTURO USED IN COMBINATION WITH AT LEAST 3 OTHER ANTIBIOTICS FOR IN THE TREATMENT OF PULMONARY MULTI-DRUG RESISTANT TUBERCULOSIS.</td>
</tr>
</tbody>
</table>
POLICY NAME: **UMP113**

**Affected Medications:** VECAMYL® (MECAMYLAMINE HCL, ORAL)

**Effective Date** *(date PA/Step UM edit effective):* 11/18/2103

**Last Review Date:**

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>MODERATELY SEVERE TO SEVERE ESSENTIAL HYPERTENSION; UNCOMPPLICATED MALIGNANT HYPERTENSION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>DIAGNOSIS OF MODERATELY SEVERE TO SEVERE ESSENTIAL HYPERTENSION OR UNCOMPPLICATED CASES OF MALIGNANT HYPERTENSION; TRIAL AND FAILURE OF A DIURETIC AND FOUR ALTERNATIVE ANTIHYPERTENSIVE MEDICATIONS (E.G. ACE, ARB, BETA BLOCKER, CALCIUM CHANNEL BLOCKER); TRIAL AND FAILURE OF A PARENTERAL ANTIHYPERTENSIVE (E.G. NICARDIPINE)</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion: CORONARY INSUFFICIENCY, MYOCARDIAL INFARCTION, ELEVATED BUN, RENAL INSUFFICIENCY, UREMIA, GLAUCOMA, PYLORIC STENOSIS, CURRENTLY RECEIVING SULFONAMIDES OR ANTIBIOTICS.</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>ONE YEAR</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
POLICY NAME: **UMP114**

**Affected Medications:** CHENODAL® (CHENODIOL, ORAL)

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 02/06/2014

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>RADIOLUCENT GALLSTONES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>DIAGNOSIS OF RADIOLUCENT CHOLESTEROL GALLSTONE; TRIAL AND FAILURE OF URSODIOL; DOCUMENTATION OF ELIGIBILITY FOR SURGERY (E.G. EXTRACORPOREAL SHOCKWAVE LITHIOTRIPSY)</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>HISTORY OF LIVER DISEASE, BILE DUCT ABNORMALITY, PRIMARY BILIARY CIRRHOSIS, SCERLOSING CHOLANGITIS</td>
</tr>
<tr>
<td>Patient restriction</td>
<td>18 YEARS OF AGE OR OLDER</td>
</tr>
<tr>
<td>Provider restriction</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coverage Duration</th>
<th>3 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**POLICY NAME:** **UMP119**

**Affected Medications:** HETLIOZ® (TASIMELTEON, ORAL)

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 5/14/14

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>NON-24 HOUR SLEEP-WAKE DISORDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>DIAGNOSIS OF NON-24 HOUR SLEEP-WAKE DISORDER.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td>Patient restriction</td>
<td>18 YEARS OF AGE OR OLDER</td>
</tr>
<tr>
<td>Provider restriction</td>
<td>EVALUATION BY OR IN CONSULTATION WITH A NEUROLOGIST; SLEEP SPECIALIST; PYCHIATRIST</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>THREE MONTHS</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>30 CAPSULES PER 30 DAYS</td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
POLICY NAME: **UMP123**

**Affected Medications:** ZONTIVITY® (VORAPAXAR SULFATE, ORAL)

**Effective Date (date PA/Step UM edit effective):** 9/1/2014

**Last Review Date:**

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>THROMBOSIS, HISTORY OF MYOCARDIAL INFARCTION OR WITH PERIPHERAL ARTERIAL DISEASE; PROPHYLAXIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>DIAGNOSIS OF MYOCARDIAL INFARCTION OR PERIPHERAL ARTERIAL DISEASE; DOCUMENTATION THE PATIENT IS TAKING VORAPAXAR WITH ASPIRIN AND/OR CLOPIDOGREL</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion PRIOR HISTORY OF TIA, STROKE, INTRACRANIAL HEMORRHAGE, OR ACTIVE PATHOLOGICAL BLEEDING.</td>
</tr>
<tr>
<td></td>
<td>Patient restriction PATIENT AGE 18 YEARS AND OLDER</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>ONE YEAR</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>30 TABLETS PER 30 DAYS</td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>

October 01, 2020
**Policy Name:** UMP128 ELGLUSTAT

**Affected Medications:** CERDELGA® (ELGLUSTAT TARTRATE, ORAL)

**Effective Date (date PA/Step UM edit effective):** 11/23/2014

**Last Review Date:**

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF NON-NEUROPATHIC GAUCHER’S DISEASE, CHRONIC (GAUCHER DISEASE TYPE 1).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td></td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion CONCOMITANT USE WITH A STRONG CYP2D6 INHIBITOR (E.G., BUPROPION, FLUOXETINE, PAROXETINE, QUINIDINE) IS CONTRAINDICATED. THESE MEDICATIONS SHOULD BE DISCONTINUED PRIOR TO STARTING CERDELGA.</td>
</tr>
<tr>
<td>Patient restriction</td>
<td></td>
</tr>
<tr>
<td>Provider restriction</td>
<td></td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: 3 MONTHS. RENEWAL: ONE YEAR.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>CYP2D6 POOR METABOLIZERS: ONE 84 MG CAPSULE PER DAY. CYP2D6 INTERMEDIATE AND EXTENSIVE METABOLIZERS: TWO 84 MG CAPSULES PER DAY.</td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP130 METHYLTESTOSTERONE

**Affected Medications:** ANDROID® (METHYLTESTOSTERONE, ORAL); TESTRED® (METHYLTESTOSTERONE, ORAL)

**Effective Date (date PA/Step UM edit effective):** 9/28/2014

**Last Review Date:**

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF DELAY IN SEXUAL DEVELOPMENT AND/OR PUBERTY, MALE; HYPOGONADOTROPIC HYPOGONADISM, MALE; PRIMARY HYPOGONADISM, MALE; METASTASIS FROM MALIGNANT TUMOR OF BREAST, INOPERABLE METASTATIC DISEASE (SKELETAL) IN WOMEN 1 TO 5 YEARS POSTMENOPAUSAL; BREAST CANCER IN PREMENOPAUSAL WOMEN WHO HAVE BENEFITED FROM OOPHORECTOMY AND ARE CONSIDERED TO HAVE A HORMONE-RESPONSIVE TUMOR.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>FOR MALES WITH DIAGNOSIS OF DELAY IN SEXUAL DEVELOPMENT AND/OR PUBERTY, HYPOGONADOTROPIC HYPOGONADISM, OR PRIMARY HYPOGONADISM: FAILURE OF OR CONTRAINDICATION TO BOTH INJECTABLE AND TOPICAL TESTOSTERONE; FOR DIAGNOSIS OF METASTASIS FROM MALIGNANT TUMOR OF BREAST, INOPERABLE METASTATIC DISEASE (SKELETAL) IN WOMEN 1 TO 5 YEARS POSTMENOPAUSAL: FAILURE OF OR CONTRAINDICATION TO INJECTABLE TESTOSTERONE ENANTHATE</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td>Patient restriction</td>
<td>FOR DIAGNOSIS OF DELAY IN SEXUAL DEVELOPMENT AND/OR PUBERTY, MALE; HYPOGONADOTROPIC HYPOGONADISM, MALE; PRIMARY HYPOGONADISM, MALE: PATIENT AGE 18 YEARS OF AGE OR OLDER</td>
</tr>
<tr>
<td>Provider restriction</td>
<td>FOR DIAGNOSIS OF METASTASIS FROM MALIGNANT TUMOR OF BREAST, INOPERABLE METASTATIC DISEASE (SKELETAL) IN WOMEN 1 TO 5 YEARS POSTMENOPAUSAL; BREAST CANCER IN PREMENOPAUSAL WOMEN WHO HAVE BENEFITED FROM OOPHORECTOMY AND ARE CONSIDERED TO HAVE A HORMONE-RESPONSIVE TUMOR: PRESCRIBED BY AN ONCOLOGIST.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>1 YEAR</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>MALES: UP TO 150 TABLETS PER 30 DAY SUPPLY; FEMALES: UP TO 600 TABLETS PER 30 DAY SUPPLY</td>
</tr>
</tbody>
</table>

**Additional Information**
**POLICY NAME:** **UMP135 PANOBINOSTAT LACTATE**

**Affected Medications:** FARYDAK® (PANOBINOSTAT LACTATE, ORAL)

**Effective Date (date PA/Step UM edit effective):** 3/13/2015

**Last Review Date:** 3/13/15

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF MULTIPLE MYELOMA, IN COMBINATION WITH BORTEZOMIB AND DEXAMETHASONE, RELAPSED AFTER 2 PRIOR THERAPIES INCLUDING BORTEZOMIB AND AN IMMUNOMODULATING AGENT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: TRIAL AND FAILURE OF TWO PRIOR THERAPIES INCLUDING BORTEZOMIB AND AN IMMUNOMODULATORY AGENT. USE IS IN COMBINATION WITH DEXAMETHASONE AND BORTEZOMIB. RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON THERAPY.</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Exclusion</td>
</tr>
<tr>
<td>Patient restriction</td>
<td>Prescribed or supervised by an oncologist or hematologist.</td>
</tr>
<tr>
<td>Provider restriction</td>
<td>Prescribed or supervised by an oncologist or hematologist.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: SIX MONTHS. RENEWAL: SIX MONTHS.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>10 MG, 16 MG, 20 MG CAPSULES, 6 CAPSULES PER 21 DAYS.</td>
</tr>
<tr>
<td>Additional Information</td>
<td>LACK OF PATIENT RECENT HISTORY OF MYOCARDIAL INFARCTION OR UNSTABLE ANGINA.</td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP138 ISAVUCONAZONIUM SULFATE

**Affected Medications:** CRESEMBA® (ISAVUCONAZONIUM SULFATE, ORAL)

**Effective Date (date PA/Step UM edit effective):** 4/20/2015

**Last Review Date:** 4/20/15

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF: ASPERGILLOSIS, INVASIVE; MUCORMYCOSIS, INVASIVE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: INVASIVE ASPERGILLOSIS, TRIAL AND FAILURE OR CONTRAINDICATION TO VORICONAZOLE.</td>
</tr>
<tr>
<td>Exclusion</td>
<td>Exclusion</td>
</tr>
<tr>
<td>Patient restriction</td>
<td>MUST BE 18 YEARS OF AGE OR OLDER.</td>
</tr>
<tr>
<td>Provider restriction</td>
<td></td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>ONE YEAR</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
# POLICY NAME: UMP145

**Affected Medications:** CARBAGLU® (CARGLUMIC ACID, ORAL)

**Effective Date** *(date PA/Step UM edit effective):* 12/3/2015

**Last Review Date:**

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>ADJUNCTIVE THERAPY, ACUTE HYPERAMMONEMIA, NAGS DEFICIENCY; MAINTENANCE THERAPY, CHRONIC HYPERAMMONEMIA, NAGS DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>DOCUMENTATION OF N-ACETYLGlutamate SYNTHASE (NAGS) DEFICIENCY CONFIRMED BY DNA TESTING; DOCUMENTATION OF AMMONIA LEVEL; DOCUMENTATION OF PATIENT WEIGHT</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td><strong>Provider restriction</strong> PRESCRIBED OR SUPERVISED BY A METABOLIC SPECIALIST</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>3 MONTHS</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td>RENEWAL: DOCUMENTATION OF AMMONIA LEVEL, DOCUMENTATION OF PATIENT WEIGHT</td>
</tr>
</tbody>
</table>
**POLICY NAME:** **UMP173 LOMUSTINE**

**Affected Medications:** CEENU® (LOMUSTINE, ORAL)

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 8/25/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: BRAIN TUMORS, FOLLOWING APPROPRIATE SURGICAL AND/OR RADIOTHERAPEUTIC PROCEDURES; HODGKIN’S LYMPHOMA, AS A COMPONENT OF COMBINATION CHEMOTHERAPY, AFTER PROGRESSION FOLLOWING INITIAL CHEMOTHERAPY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions Patient restriction</td>
<td>PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST OR NEUROLOGIST.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: SIX MONTHS. RENEWAL: SIX MONTHS.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
POLICY NAME: **UMP178 MITOTANE**

**Affected Medications:** LYSODREN® (MITOTANE, ORAL)

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 8/25/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF ADRENAL CORTICAL CARCINOMA, INOPERABLE, FUNCTIONAL OR NON-FUNCTIONAL.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: DIAGNOSIS OF INOPERABLE ADRENAL CORTICAL CARCINOMA. RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON THERAPY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td></td>
<td>PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: 6 MONTHS. RENEWAL: ONE YEAR.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP179 PROCARBAZINE HCL

**Affected Medications:** MATULANE® (PROCARBAZINE HCL, ORAL)

**Effective Date (date PA/Step UM edit effective):**

Last Review Date: 8/25/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF HODGKIN'S DISEASE, STAGE III AND IV, USED AS PART OF THE MOPP (NITROGEN MUSTARD, VINCristine, PROCarBAZINE, PREDNISONE) REGIMEN.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: USE IN COMBINATION WITH NITROGEN MUSTARD, VINCristine AND PREDNISONE. RENEWAL: DOCUMENTATION SHOW LACK OF DISEASE PROGRESSION ON THERAPY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction PREScribed or supervised by an oncoLOGIST.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: SIX MONTHS. RENEWAL: ONE YEAR.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>50 MG CAPSULE, WEIGHT BASED DOSING INITIAL: 2-4 MG/KG/DAY, RENEWAL: 1-2 MG/KG/DAY.</td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP181 THIOGUANINE

**Affected Medications:** TABLOID® (THIOGUANINE, ORAL)

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 8/25/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF ACUTE NONLYMPHOCYTIC LEUKEMIAS, FOR REMISSION INDUCTION AND REMISSION CONSOLIDATION.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION ON THERAPY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td></td>
<td>PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: 3 MONTHS. RENEWAL: SIX MONTHS.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>40 MG TABLET, WEIGHT BASED DOSING 2-3 MG/KG/DAY.</td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP183 TOPOTECAN HCL

**Affected Medications:** Hycamtin® (Topotecan HCL, ORAL)

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 8/25/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF SMALL CELL LUNG CANCER, RELAPSED, IN PATIENTS WITH PRIOR COMPLETE OR PARTIAL RESPONSE WHO ARE AT LEAST 45 DAYS FROM THE END OF FIRST-LINE THERAPY.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation Initiation</td>
<td>INITIAL: PRIOR COMPLETE OR PARTIAL RESPONSE FROM FIRST-LINE THERAPY. RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON THERAPY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions Exclusion</td>
<td>Exclusion</td>
</tr>
<tr>
<td>Patient restriction</td>
<td>Patient restriction</td>
</tr>
<tr>
<td>Provider restriction</td>
<td>Prescribed or supervised by an oncologist.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: THREE MONTHS. RENEWAL: ONE YEAR.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>0.25 MG, 1 MG CAPSULE, WEIGHT BASED THERAPY 2.3 MG/M2 ON DAYS 1-5 OF A 21 DAY CYCLE.</td>
</tr>
</tbody>
</table>

**Additional Information**
**POLICY NAME:** UMP187 MERCAPTOPURINE MONOHYDRATE

**Affected Medications:** PURIXAN® (MERCAPTOPURINE, ORAL)

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 8/25/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF ACUTE LYMPHOCYTIC LEUKEMIA.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON THERAPY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td></td>
<td>PREScribed OR SUPERvised BY AN ONCOLOGIST.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: THREE MONTHS. RENEWAL: ONE YEAR.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>2000 MG/100 ML SOLUTION, WEIGHT BASED DOSING 1.5 TO 2.5 MG/KG/DAY</td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: POST TREATMENT WITH HIGH DOSE METHOTREXATE THERAPY IN OSTEOSARCOMA; COLORECTAL CANCER, IN COMBINATION WITH 5-FLUOROURACIL. RENEWAL: DOCUMENTATION OF TREATMENT BENEFIT FROM THERAPY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: ONE YEAR. RENEWAL: ONE YEAR.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
POLICY NAME: **UMP190 RUFINAMIDE**

**Affected Medications:** BANZEL® (RUFINAMIDE, ORAL)

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 8/16/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF SEIZURE ASSOCIATED WITH LENNOX-GASTAUT SYNDROME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>DOCUMENTATION OF TREATMENT DOSE, FOLLOW UP MONITORING PLAN, PRIOR THERPAY FOR THE SUBMITTED DIAGNOSIS, PLANNED TREATMENT DURATION AND SUBMISSION OF CHART NOTES FOR REVIEW</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>1 YEAR</td>
</tr>
</tbody>
</table>

**Additional Information**
**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

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF: USE AS AN ANTI-INFLAMMATORY OR IMMUNOSUPPRESSIVE AGENT, TREATMENT OF CERTAIN ENDOCRINE CONDITIONS OR PALLIATE OF CERTAIN NEOPLASTIC CONDITIONS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: TRIAL AND FAILURE OF OR CONTRAINDICATIONS TO IMMEDIATE RELEASE PREDNISONE. RENEWAL: DOCUMENTATION INDICATING CLINICAL BENEFIT FROM TREATMENT.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>ONE YEAR</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>1 MG, 2 MG, 5 MG TABLETS: 30 TABLETS PER 30 DAYS</td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
POLICY NAME: **UMP205**

**Affected Medications:** XURIDEN® (URIDINE TRIACETATE, ORAL)

**Effective Date (date PA/Step UM edit effective):** 5/4/2016

**Last Review Date:**

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>HEREDITARY OROTIC ACIDURIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Required Medical Documentation</strong></td>
<td>DIAGNOSIS OF HEREDITARY OROTIC ACIDURIA; DOCUMENTATION OF PATIENTS WEIGHT; DOCUMENTATION OF STARTING DOSE AT 60 MG/KG ONCE DAILY</td>
</tr>
<tr>
<td><strong>Exclusion and Restrictions</strong></td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td><strong>Coverage Duration</strong></td>
<td>ONE YEAR</td>
</tr>
<tr>
<td><strong>Quantity Limits</strong></td>
<td>For up to 35kg weight: 1 carton (60 grams) per 30-day supply</td>
</tr>
<tr>
<td></td>
<td>For 36-75kg weight: 2 cartons (120 grams) per 30-day supply</td>
</tr>
<tr>
<td></td>
<td>for greater than 75kg weight: 3 cartons (180 grams) per 30-day supply</td>
</tr>
<tr>
<td><strong>Additional Information</strong></td>
<td>RENEWAL: PATIENTS CURRENT WEIGHT; DOSAGE FOR ADMINISTRATION; FOR DOSES OF 120 MG/KG - TRIAL AND FAILURE OF 60MG/KG AS DEFINED BY AT LEAST ONE OF THE FOLLOWING: LEVELS OF OROTIC ACID IN URINE REMAIN ABOVE NORMAL OR INCREASE ABOVE THE USUAL OR EXPECTED RANGE, LABORATORY VALUES (E.G. RBC, WBC) SHOW EVIDENCE OF WORSENING, WORSENING OF OTHER SIGNS OR SYMPTOMS OF DISEASE</td>
</tr>
</tbody>
</table>
**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

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF INTERSTITIAL CYSTITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>DOCUMENTATION OF TREATMENT DOSE, FOLLOW UP MONITORING PLAN, PRIOR THERPAY FOR THE SUBMITTED DIAGNOSIS, PLANNED TREATMENT DURATION AND SUBMISSION OF CHART NOTES FOR REVIEW</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td>Patient restriction</td>
<td></td>
</tr>
<tr>
<td>Provider restriction</td>
<td></td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>1 YEAR</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**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

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF ABORTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>DOCUMENTATION OF TREATMENT DOSE, FOLLOW UP MONITORING PLAN, PRIOR THERPAY FOR THE SUBMITTED DIAGNOSIS, PLANNED TREATMENT DURATION AND SUBMISSION OF CHART NOTES FOR REVIEW</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>1 MONTH</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td>Additional Information</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF: ACUTE IRON INTOXICATION AND OF CHRONIC IRON OVERLOAD DUE TO TRANSFUSION-DEPENDENT ANEMIAS.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: ACUTE IRON INTOXICATION AND OF CHRONIC IRON OVERLOAD DUE TO TRANSFUSION-DEPENDENT ANEMIAS. RENEWAL: DOCUMENTATION INDICATING CLINICAL BENEFIT FROM THERAPY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>THREE MONTHS</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**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

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF: NEUROPATHIC PAIN ASSOCIATED WITH POSTHERPETIC NEURALGIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: TREATMENT OF NEUROPATHIC PAIN ASSOCIATED WITH POSTHERPETIC NEURALGIA. RENEWAL: DOCUMENTATION INDICATING CLINICAL BENEFIT FROM TREATMENT.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>ONE YEAR</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**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

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>PERNICIOUS ANEMIA IN PATIENTS WHO ARE IN REMISSION FOLLOWING INTRAMUSCULAR VITAMIN B12 THERAPY AND HAVE NO NERVOUS SYSTEM INVOLVEMENT; VITAMIN B12 DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INABILITY TO ABSORB VITAMIN B12 ORALLY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td></td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td>DOSING IS ONE SPRAY IN ONE NOSTRIL ONCE WEEKLY.</td>
</tr>
</tbody>
</table>
**POLICY NAME:** **UMP221 FACTOR XIII A-SUBUNIT RECOMBINANT**

**Affected Medications:** TRETEN® (FACTOR XIII A-SUBUNIT,RECOMB, INTRAVEN.)

**Effective Date (date PA/Step UM edit effective):** 10/12/2016

**Last Review Date:** 10/12/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>USE IN ROUTINE PROPHYLAXIS FOR BLEEDING IN PATIENTS WITH CONGENITAL FACTOR XIII A-SUBUNIT DEFICIENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td></td>
</tr>
<tr>
<td>Coverage Duration</td>
<td></td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td>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.</td>
</tr>
</tbody>
</table>
POLICY NAME: **UMP225 ETOPOSIDE**

**Affected Medications:** ETOPOSIDE, ORAL

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 8/26/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF SMALL CELL LUNG CANCER, IN COMBINATION WITH OTHER CHEMOTHERAPEUTIC AGENTS, AS FIRST LINE TREATMENT.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: SMALL CELL LUNG CANCER IN COMBINATION WITH OTHER CHEMOTHERAPEUTIC AGENTS. RENEWAL: DOCUMENTATION SHOWING LACK OF DISEASE PROGRESSION WHILE ON THERAPY.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td></td>
<td>PRESCRIBED OR SUPERVISED BY AN ONCOLOGIST.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>INITIAL: THREE MONTHS. RENEWAL: ONE YEAR.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
POLICY NAME: **UMP229 DESMOPRESSIN**

**Affected Medications:** DDAVP® (DESMOPRESSIN ACETATE, INJECTION); DESMOPRESSIN ACETATE, INJECTION

**Effective Date (date PA/Step UM edit effective):**

**Last Review Date:** 8/16/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF CENTRAL DIABETES INSIPIDUS; HEMOPHILIA A; VON WILLEBRAND DISEASE (TYPE 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>DOCUMENTATION OF TREATMENT DOSE, FOLLOW UP MONITORING PLAN, PRIOR THERPAY FOR THE SUBMITTED DIAGNOSIS, PLANNED TREATMENT DURATION AND SUBMISSION OF CHART NOTES FOR REVIEW</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>1 YEAR</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**POLICY NAME:** UMP231 CHLORAMBUCIL

**Affected Medications:** LEUKERAN® (CHLORAMBUCIL, ORAL)

**Effective Date (date PA/Step UM edit effective):** 10/24/2016

**Last Review Date:** 10/24/16

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF: LYMPHATIC LEUKEMIA, CHRONIC; MALIGNANT LYMPHOMAS INCLUDING LYMPHOSARCOMA, GIANT FOLLICULAR LYMPHOMA, HODGKIN’S DISEASE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: LYMPHATIC LEUKEMIA, CHRONIC; MALIGNANT LYMPHOMAS INCLUDING LYMPHOSARCOMA, GIANT FOLLICULAR LYMPHOMA, HODGKIN’S DISEASE.</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td><strong>Exclusion</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Patient restriction</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Provider restriction</strong> MUST BE PRESCRIBED BY AN ONCOLOGIST.</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>SIX MONTHS.</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**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

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>TREATMENT FOR: TOXOPLASMOsis AND MALARIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>TRIAL OF COMPOUNDED PYRIMETHAMINE</td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>3 MONTHS</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
POLICY NAME: UMP250 URIDINE TRIACETATE
Affected Medications: URIDINE TRIACETATE (VISTOGARD®), ORAL TABLET
Effective Date (date PA/Step UM edit effective): 5/4/2016
Last Review Date: 3/7/16
Uses
Considered
Medically
Necessary
Required
Medical
Documentation
Exclusion and
Restrictions

Coverage
Duration
Quantity Limits
Additional
Information

EMERGENCY TREATMENT FOR: FLUOROURACIL OR CAPCITABINE OVERDOSE REGARDLESS
OF SYMPTOMS OR EARLY-ONSET, SEVERE, OR LIFE-THREATENING TOXICITY AFFECTING
THE CARDIAC OR CENTRAL NERVOUS SYSTEMS, AND/OR EARLY-ONSET, UNUSUALLY
SEVERE ADVERSE REACTIONS (I.E. GASTROINTESTINAL TOXICITY AND/OR NEUTROPENIA)
WITHIN 96 HOURS FOLLOWING THE END OF FLUOROURACIL OR CAPECITABINE
ADMINISTRATION

Exclusion
Patient
restriction
Provider
restriction
1 TIME FILL OF 20 SINGLE DOSE PACKETS

Page 779 of 790

October 01, 2020


POLICY NAME: **UMP256 VIR AZOLE**

**Affected Medications**: RIBAVIRIN INHALATION SOLUTION (VIRAZOLE®)

**Effective Date (date PA/Step UM edit effective)**: 01/27/17

**Last Review Date**: 01/27/17

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF HOSPITALIZED INFANTS AND YOUNG CHILDREN WITH SEVERE LOWER RESPIRATORY TRACT INFECTIONS DUE TO RESPIRATORY SYNCTIAL VIRUS (RSV).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td></td>
</tr>
<tr>
<td>Exclusion and Restrictions</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Patient restriction</td>
</tr>
<tr>
<td></td>
<td>Provider restriction</td>
</tr>
<tr>
<td>Coverage Duration</td>
<td>ONE MONTH</td>
</tr>
<tr>
<td>Quantity Limits</td>
<td></td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>
**POLICY NAME: UMP265 NALOXONE**

**Affected Medications**: EVZIO® (NALOXONE, SUBCUTANE.)

**Effective Date (date PA/Step UM edit effective)**: 08/01/2017

**Last Review Date**: 08/01/2017

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>DIAGNOSIS OF OPIOID OVERDOSE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>TRIAL AND FAILURE OF NALOXONE INJECTION SOLUTION OR NARCAN NASAL SPRAY OR DEMONSTRATED INABILITY OF PERSONS ADMINISTERING NALOXONE INJECTION SOLUTION OR NARCAN NASAL SPRAY; CLINICAL RATIONALE AND DOCUMENTATION OF MEDICAL NECESSITY FOR USE OF EVZIO AUTO-INJECTOR.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion and Restrictions</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient restriction</td>
<td></td>
</tr>
<tr>
<td>Provider restriction</td>
<td></td>
</tr>
</tbody>
</table>

| Coverage Duration | 1 YEAR. |

| Quantity Limits | 2 AUTO-INJECTORS PER 30 DAYS. |

| Additional Information | |
|------------------------||
**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 |  |
POLICY NAME: **UMP163 DUVELISIB**

**Affected Medications:** COPIKTRA™ (DEVELISIB)

**Effective Date (date PA/Step UM edit effective):** 11/7/2018

**Last Review Date:** 11/7/2018

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>FDA APPROVED INDICATIONS OF RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) OR SMALL LYMPHOCYTIC LYMPHOMA (SLL) AFTER TWO PRIOR THERAPIES, OR RELAPSED OR REFRACTORY FOLLICULAR LYMPHOMA (FL) AFTER AT LEAST TWO PRIOR SYSTEMIC THERAPIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Required Medical Documentation</td>
<td>INITIAL: CLL/SLL – PROPHYLAXIS FOR PNEUMOCYSTISJIROVECII PNEUMONIA (PCP) ADMINISTERED DURING AND FOLLOWING TREATMENT; NO HISTORY OF ALLOGENIC STEM CELL TRANSPLANT; NO HISTORY OF HISTOLOGICAL TRANSFORMATION; TREATMENT WITH AT LEAST TWO PRIOR THERAPIES FOR CLL/SLL; IBRUTINIB AND/OR VENETOCLAX ARE NOT APPROPRIATE TREATMENT OPTIONS. FL - PROPHYLAXIS FOR PNEUMOCYSTISJIROVECII PNEUMONIA (PCP) ADMINISTERED DURING AND FOLLOWING TREATMENT; NO HISTORY OF ALLOGENIC STEM CELL TRANSPLANT; NO HISTORY OF HISTOLOGICAL TRANSFORMATION; REFRACTORY TO RITUXIMAB AND REFRACTORY TO EITHER CHEMOTHERAPY OR RADIOIMMUNOTHERAPY; PATIENT DOES NOT HAVE GRADE 3B DISEASE. RENEWAL: CLINICAL DOCUMENTATION OF RESPONSE TO TREATMENT, SUCH AS STABILIZATION OF DISEASE OR DECREASE IN SIZE OF TUMOR OR TUMOR SPREAD.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exclusion and Restrictions</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient restriction</strong></td>
<td>MEDICATION PRESCRIBED BY, OR IN CONSULTATION WITH A HEMATOLOGIST OR ONCOLOGIST</td>
</tr>
<tr>
<td><strong>Provider restriction</strong></td>
<td>MEDICATION PRESCRIBED BY, OR IN CONSULTATION WITH A HEMATOLOGIST OR ONCOLOGIST</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coverage Duration</th>
<th>INITIAL: 3 MONTHS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RENEWAL: 12 MONTHS</td>
</tr>
</tbody>
</table>

| Quantity Limits                    | 56 CAPSULES PER 28 DAYS |

| Additional Information             | SPLIT FILL REQUIREMENTS APPLY |
**POLICY NAME:** UMP167 LANADELUMAB

**Affected Medications:** TAKHYZRO™ (LANADELUMAB)

**Effective Date (date PA/Step UM edit effective):** 11/07/2018

**Last Review Date:** 11/07/2018

<table>
<thead>
<tr>
<th>Uses Considered Medically Necessary</th>
<th>HEREDITARY ANGIOEDEMA (HAE) PROPHYLAXIS.</th>
</tr>
</thead>
</table>

| Required Medical Documentation | INITIAL: MEDICATION IS PRESCRIBED BY A SPECIALIST (ALLERGIST, IMMUNOLOGIST, DERMATOLOGIST, HEMATOLOGIST, PULMONOLOGIST, MEDICAL GENETICIST); CONFIRMATION VIA LABORATORY VALUES THE PATIENT HAS CONFIRMED HAE TYPE 1 OR TYPE 2; THE PATIENT IS BEING EVALUATED FOR TREATABLE TRIGGERS OF HAE ATTACKS AND IS BEING MANAGED TO AVOID THEM; PATIENT IS 12 YEARS OF AGE OR OLDER; THE MEDICATION WILL NOT BE USED IN COMBINATION WITH OTHER HAE PREVENTIVE TREATMENTS; HISTORY OF FAILURE OF ON-DEMAND THERAPY, OR CONTRAINDICATION, UNSATISFACTORY CONTROL WITH OR LIMITED ACCESS TO THE ON-DEMAND THERAPIES; PATIENT HAS A HISTORY OF ONE OF THE FOLLOWING: HISTORY OF TWO OR MORE SEVERE HAE ATTACKS PER MONTH (I.E., AIRWAY SWELLING, DEBILITATING CUTANEOUS OR GASTROINTESTINAL EPISODES), PATIENT IS DISABLED MORE THAN FIVE DAYS PER MONTH BY HAE, OR HISTORY OF LARYNGEAL ATTACKS CAUSED BY HAE. RENEWAL: DOCUMENTATION OF IMPROVEMENT IN SEVERITY/DURATION OF ATTACKS AND FUNCTIONAL IMPROVEMENT OR STABILITY WITH THE MEDICATION; CONSIDERATION FOR DOSE DE-ESCALATING TO 300 MG EVERY FOUR WEEKS. |

<table>
<thead>
<tr>
<th>Exclusion and Restrictions</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient restriction</td>
<td>PATIENTS UNDER 12 YEARS OF AGE</td>
</tr>
<tr>
<td>Provider restriction</td>
<td>SPECIALIST: ALLERGIST, IMMUNOLOGIST, DERMATOLOGIST, HEMATOLOGIST, PULMONOLOGIST, MEDICAL GENETICIST.</td>
</tr>
</tbody>
</table>

| Coverage Duration | INITIAL: 6 MONTHS  
                       RENEWAL: 1 YEAR |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity Limits</td>
<td>4 ML PER 28-DAY SUPPLY</td>
</tr>
<tr>
<td>Additional Information</td>
<td></td>
</tr>
</tbody>
</table>

October 01, 2020
<table>
<thead>
<tr>
<th>MEDICATION NAME</th>
<th>Step Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADAPALENE 0.1% Med Swab</td>
<td>Must have tried and failed Tretinoin, Adapalene gel, cream, OR lotion</td>
</tr>
<tr>
<td>ADAPALENE-BENZOYL PEROXIDE</td>
<td>Must have tried and failed Tretinoin OR Adapalene</td>
</tr>
<tr>
<td>ALMOTRIPTAN MALATE</td>
<td>Must have tried and failed 2 of the following: generic Sumatriptan, Naratriptan, OR Rizatriptan</td>
</tr>
<tr>
<td>ALOGLIPTIN</td>
<td>Must have tried and failed Metformin</td>
</tr>
<tr>
<td>ALOGLIPTIN-METFORMIN</td>
<td>Must have tried and failed Metformin</td>
</tr>
<tr>
<td>ALOGLIPTIN-PIOGLITAZONE</td>
<td>Must have tried and failed Metformin</td>
</tr>
<tr>
<td>BIMATOPROST</td>
<td>Must have tried and failed generic Latanoprost</td>
</tr>
<tr>
<td>BRIMONIDINE TARTRATE 0.15%</td>
<td>Must have tried and failed Brimonidine Tartrate 0.20% drops</td>
</tr>
<tr>
<td>BUPROPION XL 450 mg</td>
<td>Must have tried and failed Bupropion XL 150MG OR 300MG</td>
</tr>
<tr>
<td>BUTALBITAL-ACETAMINOPHEN 25MG-325MG TABLET</td>
<td>Must have tried and failed butalbital-acetaminophen 50/325mg tablet</td>
</tr>
<tr>
<td>BYETTA</td>
<td>Must have tried and failed generic metformin</td>
</tr>
<tr>
<td>CALCIPOTRIENE-BETAMETHASONE SUSPENSION</td>
<td>Must have tried and failed calcipotriene cream/ointment/solution AND one topical corticosteroid</td>
</tr>
<tr>
<td>CALCIPOTRIENE FOAM</td>
<td>Must have tried and failed calcipotriene solution</td>
</tr>
<tr>
<td>CARISOPRODOL</td>
<td>Must have tried and failed 2 of the following: Cyclobenzaprine, Tizanidine, Methocarbamol, Orphenadrine Citrate</td>
</tr>
<tr>
<td>CARVEDILOL ER</td>
<td>Must have tried and failed Bisoprolol OR Metoprolol OR Carvedilol IR</td>
</tr>
<tr>
<td>CHLORZOXAZONE 375 mg and 750 mg</td>
<td>Must have tried and failed two of the following: Baclofen tablets, Methocarbamol tablets, Chlorzoxazone 500MG tablets, Cyclobenzaprine 5 OR 10 MG tablets, Orphenadrine Citrate ER tablets, Tizanidine tablets</td>
</tr>
<tr>
<td>CLINDAMYCIN PHOSPHATE 1%</td>
<td>Must have tried and failed generic Cleocin (Clindamycin Phosphate)</td>
</tr>
<tr>
<td>CLINDAMYCIN PHOS-TRETINOIN</td>
<td>Must have tried and failed topical clindamycin OR tretinoin</td>
</tr>
<tr>
<td>COLESEVELAM HCL</td>
<td>Must have tried and failed Colestipol AND Cholestyramine</td>
</tr>
<tr>
<td>CYCLOBENZAPRINE HCL ER</td>
<td>Must have tried and failed cyclobenzaprine IR 5mg tablets AND cyclobenzaprine 10mg tablets</td>
</tr>
<tr>
<td>DANTROLENE SODIUM</td>
<td>Must have tried and failed 2 of the following: Cyclobenzaprine, Tizanidine, Methocarbamol, Orphenadrine Citrate</td>
</tr>
<tr>
<td>DARIFENACIN ER</td>
<td>Must have tried and failed two of the following: Oxybutynin, Tolterodine, Trospium</td>
</tr>
<tr>
<td>DICLOFENAC SODIUM-MISOPROSTOL</td>
<td>Must have tried and failed a PPI PLUS two generic NSAIDS</td>
</tr>
<tr>
<td>Medication</td>
<td>Must have tried and failed</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>DICYCLOMINE HCL vial</td>
<td>oral Dicyclomine HCL</td>
</tr>
<tr>
<td>DIFICID</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>DIHYDROERGOTAMINE MESYLATE</td>
<td>generic Sumatriptan OR Naratriptan</td>
</tr>
<tr>
<td>DOXYCYCLINE HYCLATE 75MG AND 150MG TABLET</td>
<td>Doxycycline Monohydrate tablets</td>
</tr>
<tr>
<td>DOXYCYCLINE IR-DR</td>
<td>generic Doxycycline Monohydrate OR Doxycycline Hyclate</td>
</tr>
<tr>
<td>DUTASTERIDE-TAMSULOSIN</td>
<td>Tamsulosin AND Finasteride</td>
</tr>
<tr>
<td>ELETRIPTAN HBR</td>
<td>generic Sumatriptan, Naratriptan, OR Rizatriptan</td>
</tr>
<tr>
<td>ENTRESTO</td>
<td>one generic ACE Inhibitor OR ARB</td>
</tr>
<tr>
<td>EZETIMIBE-SIMVASTATIN</td>
<td>Atorvastatin, Lovastatin, Pravastatin, Simvastatin, OR Rosuvastatin</td>
</tr>
<tr>
<td>FAMOTIDINE</td>
<td>Ranitidine 15MG/ML, Cimetidine 300MG/5ML, OR Nizatidine 150MG/10ML</td>
</tr>
<tr>
<td>FARXIGA</td>
<td>generic metformin</td>
</tr>
<tr>
<td>FENOFIBRATE</td>
<td>any of the following: Fenofibrate, Fenofibrate Nanocrystalized 48 MG OR 145 MG</td>
</tr>
<tr>
<td>FENOPROFEN CALCIUM</td>
<td>Ibuprofen, Diclofenac, Etodolac</td>
</tr>
<tr>
<td>FLUOXETINE HCL 60MG TABLET</td>
<td>Fluoxetine oral capsules</td>
</tr>
<tr>
<td>FLURBIPROFEN SODIUM DROPS</td>
<td>Diclofenac 0.1% drops OR 0.5% Keterolac drops</td>
</tr>
<tr>
<td>FLUVASTATIN ER</td>
<td>Atorvastatin, Lovastatin, Pravastatin, Simvastatin, OR Rosuvastatin</td>
</tr>
<tr>
<td>FLUVASTATIN SODIUM</td>
<td>Lovastatin Sodium, Atorvastatin Calcium, Simvastatin, OR Rosuvastatin Calcium</td>
</tr>
<tr>
<td>FROVATRIPTAN SUCCINATE</td>
<td>Sumatriptan, Naratriptan, OR Rizatriptan</td>
</tr>
<tr>
<td>GLYCOPYRROLATE 1.5MG</td>
<td>Glycopyrrolate 2 MG</td>
</tr>
<tr>
<td>GLYXAMBI</td>
<td>Metformin</td>
</tr>
<tr>
<td>HALCINONIDE</td>
<td>Betamethasone, Desoximetasone, Fluocinonide</td>
</tr>
<tr>
<td>HYDROMORPHONE ER</td>
<td>Morphine sulfate ER AND Fentanyl Patches</td>
</tr>
<tr>
<td>INDOMETHACIN</td>
<td>indomethacine 25/50/75 mg capsules AND ibuprofen or diclofenac</td>
</tr>
<tr>
<td>IVERMECTIN</td>
<td>generic Doxycycline, Metronidazole Gel OR Cream</td>
</tr>
<tr>
<td>JARDIANE</td>
<td>Metformin</td>
</tr>
<tr>
<td>HYDROCODONE BITARTRATE ER</td>
<td>Morphine sulfate ER AND Fentanyl Patches</td>
</tr>
<tr>
<td>KETOROLAC TORMETHAMINE SPRAY</td>
<td>ketorolac tablets, ibuprofen, diclofenac</td>
</tr>
<tr>
<td>LEVORPHANOL TARTRATE</td>
<td>Hydromorphone IR, Oxydalone, Oxydalone-Acetaminophen, Oxydalone-Ibuprofen, Oxydalone-Aspirin, Hydrocodone/Acetaminophen, Hydrocodone-Ibuprofen</td>
</tr>
<tr>
<td>MEMANTINE HCL ER</td>
<td>Memantine IR</td>
</tr>
<tr>
<td>METAXALL</td>
<td>Cyclobenzaprine, Tizanidine, Methocarbamol, Orphenadrine Citrate</td>
</tr>
<tr>
<td>Medicine</td>
<td>Requirement</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>METAXALONE</strong></td>
<td>Must have tried and failed Cyclobenzaprine, Tizanidine, Methocarbamol, Orphenadrine Citrate</td>
</tr>
<tr>
<td><strong>METFORMIN ER GASTRIC</strong></td>
<td>Consider lower cost alternatives generic Glucophage XR OR Fortamet ER</td>
</tr>
<tr>
<td><strong>METFORMIN HCL 500mg/5mL</strong></td>
<td>Must have tried and failed a 60-day supply generic extended release Metformin</td>
</tr>
<tr>
<td><strong>METOPROLOL SUCCINATE ER-HCTZ</strong></td>
<td>Must have tried and failed any of the following: Bisoprolol, Propanolol, Metoprolol Succinate, Nadolol, OR Metoprolol/Hydrochlorothiazide</td>
</tr>
<tr>
<td><strong>MINOCYCLINE HCL ER</strong></td>
<td>Must have tried and failed Minocycline IR</td>
</tr>
<tr>
<td><strong>MODERIBA</strong></td>
<td>Must have tried and failed Ribavirin OR Pegintron OR Pegasys</td>
</tr>
<tr>
<td><strong>MORPHINE SULFATE ER CAPSULE</strong></td>
<td>Must have tried and failed Morphine Sulfate Tablet ER</td>
</tr>
<tr>
<td><strong>NAMENDA XR DOSEPAK</strong></td>
<td>Must have tried and failed generic memantine IR</td>
</tr>
<tr>
<td><strong>NATEGLINIDE</strong></td>
<td>Must have tried and failed generic Metformin</td>
</tr>
<tr>
<td><strong>OLMESARTAN-AMLODIPINE-HCTZ</strong></td>
<td>Must have tried and failed any of the following: Irbesartan, Irbesartan HCTZ, Losartan, Losartan HCTZ, Valsartan, OR Valsartan HCTZ</td>
</tr>
<tr>
<td><strong>OXYCODONE HCL ER</strong></td>
<td>Must have tried and failed Morphine Sulphate ER tablets AND Fentanyl Transdermal patches</td>
</tr>
<tr>
<td><strong>PENICILLAMINE</strong></td>
<td>Must have tried and failed brand Depen</td>
</tr>
<tr>
<td><strong>PIOGLITAZONE-GLIMEPIRIDE</strong></td>
<td>Must have tried and failed Metformin</td>
</tr>
<tr>
<td><strong>POSACONAZOLE</strong></td>
<td>Must have tried and failed any of the following medications: generic fluconazole, Itraconazole, OR Voriconazole</td>
</tr>
<tr>
<td><strong>POTIGA</strong></td>
<td>Must have tried and failed generic oral anticonvulsant</td>
</tr>
<tr>
<td><strong>PRAMIPEXOLE ER</strong></td>
<td>Must have tried and failed pramipexole IR</td>
</tr>
<tr>
<td><strong>PRAMIPEXOLE ER 3.75 mg</strong></td>
<td>Must have tried and failed pramipexole IR</td>
</tr>
<tr>
<td><strong>QTERN</strong></td>
<td>Must have tried and failed generic metformin or metformin combinations</td>
</tr>
<tr>
<td><strong>RAMELTEON</strong></td>
<td>Must have tried and failed 2 of the following: generic Zaleplon, generic zolpidem</td>
</tr>
<tr>
<td><strong>REXULTI</strong></td>
<td>Must have tried and failed one generic antidepressant OR one generic antipsychotic</td>
</tr>
<tr>
<td><strong>RIBASPHERE RIBAPAK</strong></td>
<td>Must have tried and failed Ribavirin OR Pegintron OR Pegasys</td>
</tr>
<tr>
<td><strong>RIBATAB</strong></td>
<td>Must have tried and failed Ribavirin OR Pegintron OR Pegasys</td>
</tr>
<tr>
<td><strong>ROPINIROLE ER</strong></td>
<td>Must have tried and failed Ropinirole IR tablets</td>
</tr>
<tr>
<td><strong>SOLIFENACIN SUCCINATE</strong></td>
<td>Must have tried and failed 2 of the following: Oxybutynin, Tolterodine, Trospium</td>
</tr>
<tr>
<td><strong>SOLOXIDE</strong></td>
<td>Must have tried and failed Doxycycline Monohydrate tablets</td>
</tr>
<tr>
<td><strong>SUMATRIPTAN SUCC-NAPROXEN SOD</strong></td>
<td>Must have tried and failed any of the following medications: Sumatriptan, Naratriptan, OR Rizatriptan</td>
</tr>
<tr>
<td><strong>SYNJARDY/ SYNJARDY XR</strong></td>
<td>Must have tried and failed Metformin</td>
</tr>
<tr>
<td><strong>TELMISARTAN-HYDROCHLOROTHIAZID</strong></td>
<td>Must have tried and failed any of the following: Losartan, Losartan/HCTZ, Irbesartan, OR Irbesartan/HCTZ</td>
</tr>
<tr>
<td><strong>TIGLUTIK</strong></td>
<td>Must have tried and failed Riluzole</td>
</tr>
<tr>
<td>Product</td>
<td>Must have tried and failed</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>TIMOLOL MALEATE SOL-GEL</td>
<td>non-gel form</td>
</tr>
<tr>
<td>TIMOLOL MALEATE 0.50% DROPS DAILY</td>
<td>generic Timoptic</td>
</tr>
<tr>
<td>TOLSURA</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>TOUJEO MAX SOLOSTAR</td>
<td>Basaglar Kwikpen</td>
</tr>
<tr>
<td>TRAMADOL HCL ER</td>
<td>Tramadol HCL</td>
</tr>
<tr>
<td>TRAZODONE HCL</td>
<td>Trazodone 100MG OR 150MG tablets</td>
</tr>
<tr>
<td>TRESIBA</td>
<td>Basaglar Kwikpen</td>
</tr>
<tr>
<td>TRETINOIN MICROSPHERE</td>
<td>generic tretinoin OR adapalene</td>
</tr>
<tr>
<td>TRIAMTERENE</td>
<td>Spironolactone OR Amiloride</td>
</tr>
<tr>
<td>VICTOZA</td>
<td>Metformin</td>
</tr>
<tr>
<td>VIMPAT</td>
<td>any generic oral anticonvulsants</td>
</tr>
<tr>
<td>XERMELO</td>
<td>Octreotide OR Lanreotide</td>
</tr>
<tr>
<td>XIGDUO XR</td>
<td>generic metformin</td>
</tr>
<tr>
<td>ZENZEDI</td>
<td>one generic IR stimulant (Dexamethylphenidate, Methlypheniate, Amphetamine salt combo, Dextroamphetamine)</td>
</tr>
<tr>
<td>ZILEUTON ER</td>
<td>generic montelukast</td>
</tr>
<tr>
<td>ZOSTAVAX</td>
<td>Shingrix</td>
</tr>
</tbody>
</table>
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PO Box 40168
Portland, OR 97240-0168
Fax: 1-866-923-0412

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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:
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Chief Compliance Officer
601 SW Second Ave.
Portland, OR 97204
855-232-9111
compliance@modahealth.com