BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

XOLREMDI™ (mavorixafor)
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Xolremdi (mavorixafor) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist, Hematologist, Geneticist, Immunologist, or Dermatologist

2. Individual is 12 years of age or older

3. Individual has a confirmed diagnosis of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis)

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Documentation of pathogenic gain-of-function mutation in the *CXCR4* gene
    b. Absolute neutrophil count (ANC) is less than or equal to 400 cells/microL
    c. Electrocardiogram
    d. Risk factors for QT interval prolongation have been corrected (i.e., hypokalemia, drug interaction, changing to other medications that do not increase QT interval if clinically appropriate)
    e. Negative pregnancy test in a woman of childbearing potential

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. There are **NO** FDA-label contraindications such as use with drugs that are highly dependent on CYP2D6 for clearance such as codeine, dextromethorphan, tamoxifen, tramadol, clozapine, desipramine, flecainide, haloperidol, nortriptyline, others (see Definitions section)

7. Individual is not currently taking strong CYP3A4 inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, others)

8. Individual does not have severe renal impairment (creatinine clearance (CrCl) 15 to less than 30 mL/min) or end stage renal disease (CrCl less than 15 mL/min)

9. Individual does not have moderate to severe hepatic impairment

10. Individual is not on other CXCR4 antagonists (e.g., Aphexda (motixafortide), Mozobil (plerixafor))

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Xolremdi (mavorixafor) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist, Hematologist, Geneticist, Immunologist, or Dermatologist

2. Individual's condition has responded while on therapy with response defined as **TWO** of the following:
    a. Increase in absolute neutrophil count
    b. Increase in absolute lymphocyte count
    c. Reduced number of infections
    d. Reduced wart numbers

3. Individual has been adherent with the medication

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic

should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as QT interval prolongation

6. There are **NO** FDA-label contraindications such as use with drugs that are highly dependent on CYP2D6 for clearance such as codeine, dextromethorphan, tamoxifen, tramadol, clozapine, desipramine, flecainide, haloperidol, nortriptyline, others (see Definitions section)

7. Individual is not currently taking strong CYP3A4 inducers (e.g., rifampin, rifabutin, phenobarbital, carbamazepine, others)

8. Individual does not have severe renal impairment (creatinine clearance (CrCl) 15 to less than 30 mL/min) or end stage renal disease (CrCl) less than 15 mL/min)

9. Individual does not have moderate to severe hepatic impairment

10. Individual is not on other CXCR4 antagonists (e.g., Aphexda (motixafortide), Mozobil (plerixafor))

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Xolremdi (mavorixafor) is a CXC chemokine receptor 4 (CXCR4) antagonist indicated in individuals12 years of age and older with WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes. WHIM syndrome presents in childhood, with severe congenital neutropenia, lymphopenia, hypogammaglobulinemia, recurrent infections, and warts due to human papilloma virus infection. A mutant CXCR4 chemokine receptor causes abnormal apoptosis and migratory function, with retention of mature neutrophils in the bone marrow. Individuals are severely neutropenic even though the bone marrow may be hypercellular, suggesting impaired release of neutrophils from the bone marrow.

Immune globulin replacement therapy is effective for reducing bacterial infections. Mavorixafor, a selective CXCR4 antagonist, was shown to decrease the yearly infection rates and reduce the number of cutaneous warts in individuals with WHIM syndrome. Treatment with mavorixafor results in increased mobilization of neutrophils and lymphocytes from the bone marrow into peripheral circulation. Mavorixafor is FDA-indicated in individuals 12 years of age and older with WHIM syndrome to increase the number of circulating mature neutrophils and lymphocytes.

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XOLREMDI™ (mavorixafor) Generic Equivalent (if available)

Mavorixafor is an orally bioavailable CXC Chemokine Receptor 4 (CXCR4) antagonist that blocks the binding of the CXCR4 ligand, stromal-derived factor-1a (SDF-1a)/CXC Chemokine Ligand 12 (CXCL12). SDF-1/CXCR4 plays a role in trafficking and homing of leukocytes to and from the bone marrow compartment. Gain of function mutations in the CXCR4 receptor gene that occur in patients with WHIM syndrome led to increased responsiveness to CXCL12 and retention of leukocytes in the bone marrow. Mavorixafor inhibits the response to CXCL12 in both wild-type and mutated CXCR4 variants associated with WHIM syndrome.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Cytochrome P450 Interactions
https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

Resources:

Xolremdi (mavorixafor) product information, revised by X4 Pharmaceuticals, Inc. 04-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 15, 2024.

Coates TD. Congenital neutropenia. In: UpToDate, Newburger P, Rosmarin AG (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated on November 30, 2023. Accessed May 17, 2024.

Hand JL. Epidermodysplasia verruciformis. In: UpToDate, Orange JS, Corona R, TePas E (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through April 2024. Topic last updated on June 29, 2022. Accessed May 17, 2024.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03995108: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Mavorixafor in Patients With WHIM Syndrome With Open-Label Extension. Available from: http://clinicaltrials.gov. Last update posted May 02, 2024. Last verified October 2023. Accessed May 16, 2024.

Badolato R, Alsina L, Azar A, et al.: Phase 3 randomized trial of mavorixafor, CXCR4 antagonist, in WHIM syndrome. Blood 2023. Available at http://ashpublications.org/blood/article-pdf/doi/10.1182/blood.2023022658/2222739/blood.2023022658.pdf. Accessed May 15, 2024.

Dale DC, Firkin F, Bolyard AA, et al.: Results of a phase 2 trial of an oral CXCR4 antagonist, mavorixafor, for treatment of WHIM syndrome. Blood 2020 Dec 24; 136(26): 2994–3003. Accessed May 17, 2024.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.

ORIGINAL EFFECTIVE DATE: 08/15/2024 | ARCHIVE DATE: | LAST REVIEW DATE: | LAST CRITERIA REVISION DATE: