mavorixafor (Xolremdi™)

Policy # 00896
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider mavorixafor (Xolremdi™)‡ for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for mavorixafor (Xolremdi) will be considered when the following criteria are met:

- Initial (6 months)
  - Patient is ≥ 12 years of age or older; AND
  - Patient has a diagnosis of WHIM syndrome confirmed by documentation of genetic testing demonstrating pathogenic and/or likely pathogenic variants in the *CXCR4* gene; AND
  - Documentation is provided of an absolute neutrophil count (ANC) ≤ 400 cells/μL obtained while the patient has no clinical evidence of infection; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Patient exhibits at least one other clinical manifestation of disease (i.e., warts, hypogammaglobulinemia, infections, myelokathexis, lymphopenia, monocytopenia); AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*

  - If the patient is a female of reproductive potential, provider attests that the patient is NOT currently pregnant and is willing to use effective contraception; AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Xolremdi will not be used concurrently with plerixafor (Mozobil®)‡.
- Continuation
  - Patient has an initial authorization for Xolremdi; AND
  - Patient has experienced significant improvement or stabilization in clinical signs and symptoms of the disease while on Xolremdi including, but not limited to, reduction in the frequency, duration, or severity of infections, fewer warts, improvement in absolute neutrophil count (ANC), improvement in white blood cell count (WBC), or improvement in absolute lymphocyte count [ALC]); AND
    *(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)*
  - Xolremdi will not be used concurrently with plerixafor (Mozobil).

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of mavorixafor (Xolremdi) when ANY of the following criteria listed below are NOT met to be **not medically necessary.****

- For Initial Requests:
  - Documentation is provided of an absolute neutrophil count (ANC) ≤ 400 cells/μL obtained while the patient has no clinical evidence of infection
  - Patient exhibits at least one other clinical manifestation of disease (i.e., warts, hypogammaglobulinemia, infections, myelokathexis, lymphopenia, monocytopenia)
  - If the patient is a female of reproductive potential, provider attests that the patient is NOT currently pregnant and is willing to use effective contraception
- For Continuation Requests:
  - Patient has experienced significant improvement or stabilization in clinical signs and symptoms of the disease while on Xolremdi including, but not limited to, reduction in the frequency, duration, or severity of infections, fewer warts, improvement in absolute neutrophil count (ANC), improvement in white blood cell count (WBC), or improvement in absolute lymphocyte count [ALC])

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers mavorixafor (Xolremdi) when the patient selection criteria are not met (with the exception of those denoted above as **not medically necessary****) to be **investigational.***

Background/Overview

Xolremdi, a selective CXC chemokine receptor 4 (CXCR4) antagonist, is indicated for patients 12 years of age and older with WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes. It is the first FDA-approved treatment specifically indicated for patients with WHIM syndrome and received a Rare Pediatric Disease Priority Review Voucher with its approval. Xolremdi blocks the CXCL12 ligand from activating CXCR4 resulting in increased mobilization of neutrophils and lymphocytes from the bone marrow into peripheral circulation. Xolremdi, available in 100 mg capsules, should be administered by mouth on an empty stomach after an overnight fast and at least 30 minutes before food. The capsules should not be opened, broken or chewed. For patients weighing more than 50 kg, the recommended dose is 400 mg once daily, and for patients weighing ≤ 50 kg, the recommend dose is 300 mg once daily. Xolremdi is expected to cause fetal harm when administered to a pregnant woman based on its mechanism of action. The prescribing information for Xolremdi recommends verifying the pregnancy status of female patients of reproductive potential prior to initiation of Xolremdi and advising females of reproductive potential to use an effective method of contraception during treatment with Xolremdi and for three weeks after the final dose. Xolremdi is contraindicated with drugs that are highly dependent on CYP2D6 for clearance and also carries a warning of concentration dependent QTc interval prolongation.

WHIM Syndrome

WHIM syndrome is an ultra-rare autosomal primary immunodeficiency caused by gain-of-function mutations in chemokine receptor CXCR4 thereby preventing normal CXCR4 receptor downregulation and causing hyperactivation of the CXCR4-CXCL12 pathway. Hyperactivation in this pathway leads to retention of leukocytes in the bone marrow (myelokathexis), resulting in neutropenia, leukopenia, and in some cases, hypogammaglobulinemia. WHIM syndrome occurs in

about 1 in 5 million live births with most diagnosed individuals being heterozygous carriers of a CXCR4 mutation. In the US, it is thought that at least 1000 individuals are affected by WHIM syndrome, but due to the rare nature of the disease, it is likely underdiagnosed. Clinical presentation includes recurrent pneumonia, sinusitis, and severe or chronic neutropenia that begins in infancy or early childhood. Individuals with WHIM syndrome also have an unusual susceptibility to human papillomavirus (HPV), predisposing these patients to the development of skin and genital warts. There is no cure for WHIM syndrome, and prior to the approval of Xolremdi, management was based upon clinical symptoms. Previous therapies have included granulocyte colony-stimulating factor (G-CSF) to normalize neutrophil counts, intravenous immune globulin (IVIG) to treat hypogammaglobulinemia and reduce recurrent infections, and antibiotics. Plerixafor (Mozobil) has been studied in WHIM syndrome, but hast not been FDA approved for its treatment.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Xolremdi was approved in April of 2024 for patients 12 years of age and older with WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Xolremdi in patients aged 12 and older with WHIM syndrome was demonstrated in a 52-week, randomized, double-blind, placebo-controlled pivotal study. Enrolled patients had a genotype-confirmed variant of CXCR4 consistent with WHIM syndrome, and a confirmed absolute neutrophil count (ANC) $\leq$ 400 cells/μL. Patients were allowed to continue (but not initiate) immunoglobulin therapy at the same dose, but use of other CXCR4 antagonists was not permitted. Thirty-one patients were randomized 1:1 to receive either placebo or Xolremdi once daily for 52 weeks. The primary endpoint was the number of hours above ANC threshold of 500 cells/μL over a 24-hour period, assessed prior to treatment, and 4 times throughout the study (every 3 months over

the 52-week randomized period). The results showed that the mean time (hours) above ANC threshold (TAT_{ANC}) was statistically significantly greater in patients treated with Xolremdi (LS mean [SE] 15.0 [1.89] hours) compared with placebo (2.8 [1.52] hours) (p value <0.0001).

A key secondary efficacy endpoint was time above threshold absolute lymphocyte count (ALC), defined similarly to TAT_{ANC} but with an ALC threshold of 1,000 cells/µL (TAT_{ALC}). The results over the 52-week period showed that TAT_{ALC} was statistically significantly greater in patients treated with Xolremdi (LS mean [SE] 15.8 [1.39] hours) compared with placebo (4.6 [1.15] hours) (p value <0.0001). The efficacy of Xolremdi was further assessed in a composite endpoint consisting of total infection score and total wart change score using a Win-Ratio method. The Win-Ratio of 2.76 is the number of pairs of Xolremdi-treated patient "wins" divided by the number of pairs of placebo patient "wins." Analyses of the individual components of this composite endpoint showed an approximately 40% reduction of total infection score, weighted by infection severity, in Xolremdi-treated patients compared with placebo-treated patients. The annualized infection rate was reduced approximately 60% in Xolremdi-treated patients [LS mean (SE) 1.7(0.5)] compared with placebo-treated patients [LS mean (SE) 4.2(0.7)]. There was no difference in total wart change scores between the Xolremdi and placebo treatment arms over the 52-week period.

References

1. Xolremdi [package insert]. X4 Pharmaceuticals, Inc. Boston, MA. April 2024.
2. Badolato R., et al. A phase 3 randomized trial of mavorixafor, a CXCR4 antagonist, for WHIM syndrome. Blood. 2024 Jul 4;144(1):35-45.
3. Heusinkveld LE., et al. Pathogenesis, diagnosis and therapeutic strategies in WHIM syndrome immunodeficiency. Expert Opin Orphan Drugs. 2017;5(10):813-825.
4. Rodríguez-Frade JM., et al. The complex nature of CXCR4 mutations in WHIM syndrome. Front Immunol. 2024 Jul 5;15:1406532.
5. Xolremdi (mavorixafor) New Drug Review. IPD Analytics. May 2024.

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10/03/2024 Medical Policy Committee review
10/08/2024 Medical Policy Implementation Committee approval. New policy.
Next Scheduled Review Date: 10/2025

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.