**Original Effective Date: 09/25/2024**
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**Last P&T Approval/Version: 07/30/2025**
**Next Review Due By: 07/2026**
**Policy Number: C28289-A**

# Xolremdi (mavorixafor)

## PRODUCTS AFFECTED

Xolremdi (mavorixafor)

## COVERAGE POLICY

*Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.*

***Documentation Requirements:***
*Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.*

**DIAGNOSIS:**
Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) Syndrome

**REQUIRED MEDICAL INFORMATION:**
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. WHIM SYNDROME:
   1. Documented diagnosis of Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome
      AND

2. Documentation diagnosis was confirmed by genetic testing showing a CXCR4 variant [DOCUMENTATION REQUIRED]
   AND
3. Documentation of prescriber baseline disease activity evaluation which includes, but not limited to, absolute neutrophil count (ANC) and number of infections requiring treatment in the past 12 months and goals for treatment to be used to evaluate efficacy of therapy at renewal.
   AND
4. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Xolremdi (mavorixafor) include: Use with drugs highly dependent on CYP2D6 for clearance, avoid concomitant use with strong CYP3A4 inducer]

**CONTINUATION OF THERAPY:**

A. WHIM SYNDROME:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation
   AND
2. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity
   AND
3. Documentation of positive clinical response as demonstrated by improvement in ANC on two separate days within the last 6 months OR ALC improvement on two separate days within the last 6 months OR a reduction from baseline in infections requiring treatment

**DURATION OF APPROVAL:**

Initial authorization: 12 months, Continuation of Therapy: 12 months

**PRESCRIBER REQUIREMENTS:**

Prescribed by or in consultation with a board-certified geneticist, infectious disease specialist, immunologist or hematologist [If prescribed in consultation, consultation notes must be submitted with the initial request and reauthorization requests]

**AGE RESTRICTIONS:**

12 years of age and older

**QUANTITY:**

Weight >50 kg: 400 mg orally once daily
Weight ≤50 kg: 300 mg orally once daily

**PLACE OF ADMINISTRATION:**

The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

## DRUG INFORMATION

**ROUTE OF ADMINISTRATION:**

Oral

**DRUG CLASS:**

CXCR4 Receptor Antagonist

**FDA-APPROVED USES:**
Indicated in 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.

**COMPENDIAL APPROVED OFF-LABELED USES:**
None

## APPENDIX

**APPENDIX:**
None

## BACKGROUND AND OTHER CONSIDERATIONS

**BACKGROUND:**
Warts, hypogammaglobulinemia, infections and myelokathexis (WHIM) syndrome is an ultra-rare, hereditary immune deficiency caused by gain of function mutations in the chemokine receptor (CXCR4) gene. This leads to increased responsiveness to the CXCR4 ligand, CXCL12, and retention of leukocytes in the bone marrow.
Patients with WHIM syndrome may also have trouble with distributing other types of immune cells to the blood and as a result, are predisposed to frequent viral and bacterial infections, skin and genital warts, and are at an increased risk of developing cancer caused by human papillomavirus (HPV). WHIM syndrome is inherited in an autosomal-dominant pattern. Some individuals with the characteristic symptoms of WHIM syndrome do not have a detectable mutation in the CXCR4 gene, which suggests that the disorder may have other genetic causes. However, the majority of patients identified with WHIM syndrome do have this detectable mutation. Some patients have mild expression of WHIM syndrome while others develop potentially life-threatening complications. Symptoms often develop in early childhood, with children experiencing repeated bacterial infections that can be mild or severe but usually respond promptly to antibiotic therapy. However, chronic infections can potentially lead to additional complications (e.g. chronic ear infections and hearing loss, dental infection and tooth loss, pneumonia and bronchiectasis, atelectasis, and respiratory/heart failure).
The diagnosis of WHIM syndrome should be suspected in the patient with chronic verrucosis, recurrent sinopulmonary bacterial infections, and neutropenia, particularly in combination with a cardiac defect such as tetralogy of Fallot or laboratory evidence of hypogammaglobulinemia. The diagnosis can be confirmed by genetic testing in patients with pathogenic variants in the CXCR4 gene or by demonstration of enhanced leukocyte responsiveness to CXCL12 in patients without a confirmed CXCR4 defect. Some, but not all, newborns with WHIM syndrome are detected using expanded newborn screening for primary immunodeficiency disorders. One report describes low T cell receptor excision circle (TREC) levels in at least some newborns with WHIM syndrome
Treatment of WHIM syndrome depends upon disease severity and is based upon observational data and small clinical trials given the rarity of the disease. Management includes close monitoring for and aggressive treatment of sinopulmonary infections and warts, vaccination against HPV, and immunoglobulin replacement therapy for patients with hypogammaglobulinemia. Antibiotic prophylaxis is often used in patients with recurrent infections, particularly while awaiting the onset of action of other therapies. Potential additional treatment options include therapies to increase production of neutrophils (eg, a CXCR4 antagonist in patients ≥12 years of age or granulocyte colony-stimulating factor [G-CSF]) in patients with significant neutropenia and related infections and hematopoietic cell transplantation in patients with severe disease and life-threatening infections.

Xolremdi (mavorixafor) is an oral CXCR4 antagonist and the first FDA-approved treatment specifically indicated for patients with WHIM syndrome. Xolremdi works by blocking the binding of CXCL12, resulting in increased mobilization of neutrophils and lymphocytes from the bone marrow into peripheral circulation.

**CLINICAL STUDY-**

The efficacy of XOLREMDI in patients aged 12 years and older with WHIM syndrome was demonstrated in the 52-week, randomized, double-blind, placebo-controlled portion of Study 1 [NCT03995108]. Enrolled patients had a genotype-confirmed variant of CXCR4 consistent with WHIM syndrome, and a confirmed absolute neutrophil count (ANC) ≤400 cells/μL. Patients were permitted to continue (but not initiate) immunoglobulin therapy at the same dose.

Thirty-one patients were randomized 1:1 to receive either placebo (N=17) or XOLREMDI (N=14) once daily for 52 weeks. The efficacy of XOLREMDI in the treatment of patients with WHIM syndrome was based on improvement in absolute neutrophil counts (ANC), improvement in absolute lymphocyte counts (ALC), and a reduction in infections.

For ANC, the mean time (hours) above ANC threshold (TATANC) of 500 cells/μL over a 24-hour period was assessed 4 times throughout the study (every 3 months for 12 months). The results over the 52- week period showed that TATANC 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)

| | | XOLREMDI (N = 14) | Placebo (N = 17) |
|---|---|---|---|
| **$TAT_{ANC}$** (hours) | | | |
| Baseline | Mean (SD) | 0.0 (0.0) | 3.6 (5.7) |
| Overall MMRM results | LS mean (SE) | 15.0 (1.89) | 2.8 (1.52) |
| | LS mean 95% CI | (11.2, 18.9) | (0.0, 5.9) |
| | Difference from placebo: | | |
| | LS mean difference (SE) | 12.3 (2.49) | - |
| | LS mean difference 95% CI | (7.2, 17.4) | - |
| | P-value[1] | <0.0001 | - |

Abbreviations: ANC = absolute neutrophil count; CI = confidence interval; LS = least squares; MMRM = mixed-model repeated measures; SD = standard deviation; SE = standard error; TAT = time above threshold of 500 cells/μL.

[1] The results are based on an MMRM analysis with time above threshold as a dependent variable; treatment, visit (Weeks 13, 26, 39 and 52), treatment*visit, Ig use (randomization strata), and baseline time above threshold as covariates; and patient as the repeated random effect.

For ALC, the mean time (hours) above ALC threshold (TATALC) of 1,000 cells/μL over a 24-hour period was assessed 4 times throughout the study (every 3 months for 12 months). The results over the 52-week period showed that TATALC 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.”

| Category | n** | Win-Ratio (95% CI) |
|---|---|---|
| XOLREMDI wins on total infection score | 174 | 2.76 (1.60, 4.76) |
| Placebo wins on total infection score | 63 | |
| XOLREMDI wins on total wart change score | 0 | |
| Placebo wins on total wart change score | 0 | |
| None of the above (tie) | 1 | |

*The method compared each XOLREMDI-treated patient to each placebo-treated patient in a pair-wise manner that proceeded in a hierarchical fashion using total infection score, followed by total wart change score if patients could not be differentiated based on total infection score. The total infection score was calculated by summing up the number of infection events weighted by severity and divided by the total exposure time (in years). Total wart change score was calculated by summing up the regional wart change scores from 3 target regions (lesions).
** n is number of 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 by 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.

**CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:**
All other uses of Xolremdi (mavorixafor) are considered experimental/investigational and therefore, will follow Molina's Off-label policy. Contraindications to Xolremdi (mavorixafor) include: Use with drugs highly dependent on CYP2D6 for clearance, avoid concomitant use with strong CYP3A4 inducers.

**OTHER SPECIAL CONSIDERATIONS:**
Administer Xolremdi on an empty stomach after an overnight fast, and ≥30 minutes before food.

X4 has launched X4Connect, a patient support program that includes copay assistance for eligible patients, a Quick Start program that offers a temporary supply of Xolremdi in the event of an insurance-related delay, a bridge program that provides a temporary supply of Xolremdi in the event of insurance coverage interruptions, and a patient assistance program.

## CODING/BILLING INFORMATION

***CODING DISCLAIMER.*** *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

| HCPCS CODE | DESCRIPTION |
|---|---|

| | |
|---|---|
| NA | |

**AVAILABLE DOSAGE FORMS**:
Xolremdi CAPS 100MG

## REFERENCES


1. Xolremdi (mavorixafor) capsules, for oral use [prescribing information]. Boston, MA: X4 Pharmaceuticals Inc; September 2024.
2. Badolato R, et al; WHIM Research Group. How I treat warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. Blood. 2017;130(23):2491-2498. doi:10.1182/blood-2017-02-708552
3. Dotta L, et al. Long-term outcome of WHIM syndrome in 18 patients: High risk of lung disease and HPV- related malignancies. J Allergy Clin Immunol Pract. 2019;7(5):1568-1577. doi:10.1016/j.jaip.2019.01.045
4. Heusinkveld LE, et al. Pathogenesis, diagnosis and therapeutic strategies in WHIM syndrome immunodeficiency. Expert Opin Orphan Drugs. 2017;5(10):813-825. doi:10.1080/21678707.2017.1375403
5. Heusinkveld LE, et al. WHIM Syndrome: from pathogenesis towards personalized medicine and cure. J Clin Immunol. 2019; 39(6):532-556. doi:10.1007/s10875-019-00665-w McDermott DH, et al. A phase III randomized crossover trial of plerixafor versus G-CSF for treatment of WHIM syndrome. J Clin Invest. 2023;133(19):e164918. doi:10.1172/JCI164918
6. McDermott DH, et al. Plerixafor for the treatment of WHIM syndrome. N Engl J Med. 2019;380(2):163-170. doi:10.1056/NEJMoa1808575


| SUMMARY OF REVIEW/REVISIONS | DATE |
|---|---|
| REVISION- Notable revisions:<br>Required Medical Information<br>Continuation of Therapy<br>Duration of Approval<br>Appendix<br>References | Q3 2025 |
| NEW CRITERIA CREATION | Q3 2024 |