mavorixafor (Xolremdi™)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO307

Description

Mavorixafor (Xolremdi) is an oral selective CXC chemokine receptor 4 (CXCR4) antagonist.

Length of Authorization

- Initial: 6 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
mavorixafor (Xolremdi)	Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome	100 mg tablets	Weight > 50 kg: 120 tablets/30 days Weight ≤ 50 kg: 60 tablets/20 days

Initial Evaluation

I. **Mavorixafor (Xolremdi)** may be considered medically necessary when the following criteria are met:
   A. Member is 12 years of age or older; **AND**
   B. Documentation of member's weight is provided (kg); **AND**
   C. Medication is prescribed by, or in consultation with, a hematologist or immunology specialist; **AND**
   ~~D.~~ Medication will not be used in combination with another CXCR4 antagonist (e.g., plerixafor (Mozobil), motixafortide (Aphexda)); **AND**
   E. Member has a diagnosis of **warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome** when the following are met:
      1. Documentation of genotype-confirmed mutation of *CXCR4* consistent with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) phenotype; **AND**
      2. Documentation of severe symptoms and complications associated with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome (e.g., history of recurrent infections, chronic neutropenia, history of lymphopenia, history of hypogammaglobulinemia, detected myelokathexis, refractory or recalcitrant warts, etc.); **AND**
      3. Documentation of absolute neutrophil count (ANC) < 500 cells/µL that is not related to medication, chemotherapy, or secondary to viral infections; **AND**

F. Treatment with a granulocyte-colony stimulating factor (G-CSF) (e.g., filgrastim-sndz (Zarxio), pegfilgrastim-apgf (Nyvepria), pegfilgrastim-jmdb (Fulphila) etc.) has been ineffective, contraindicated, or not tolerated.

II. Mavorixafor (Xolremdi) is considered investigational when used for all other conditions, including but not limited to:
   A. Chronic neutropenia (congenital, acquired primary autoimmune, and idiopathic)
   B. Melanoma
   C. Renal Cell Carcinoma
   D. Waldenstrom macroglobulinemia
   E. Alzheimer's and Parkinson's diseases
   F. HIV-1

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Documentation of weight is provided (kg); **AND**
IV. Medication will not be used in combination with another CXCR4 antagonist (e.g., plerixafor (Mozobil), motixafortide (Aphexda)); **AND**
V. Member has exhibited sustained improvement in absolute neutrophile count (ANC) and/or absolute lymphocyte count (ALC); **OR**
   A. Member has exhibited improvement or stability of disease symptoms [e.g., reduced incidence or severity of infections from baseline, reduction from baseline or severity of warts, etc.]

Supporting Evidence

I. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is a rare immunodeficiency and a congenital neutropenic disorder that results from impaired leukocyte trafficking. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome presents with chronic neutropenia, lymphopenia, monocytopenia, recurrent infections, and warts. Individuals with WHIM syndrome are susceptible to bacterial infections, human papillomavirus (HPV) infections, and cancer. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome as an autosomal dominant condition is predominately caused by gain-of-function variants in CXCR4, which is a key regulator of the mobilization of white blood cells (neutrophils and lymphocytes) with a prevalence of less than 1 in 1,000,000.

II. Mavorixafor (Xolremdi) is a selective CXC chemokine receptor 4 (CXCR4) antagonist and the first FDA-approved treatment specifically indicated in patients with WHIM syndrome. Historically, treatment targeted symptoms of WHIM and included the use of granulocyte-colony stimulating factor (G-CSF), Immunoglobulin (Ig), and antibiotics requiring coordination between specialists, such as hematologists and immunologists. Confirmation of documented genotype-confirmed mutation of *CXCR4* consistent with WHIM phenotype should be done in those presenting with common symptoms of WHIM, such as history of recurrent infections, chronic neutropenia, lymphopenia, monocytopenia, hypogammaglobulinemia, recalcitrant or recurrent warts, etc.

III. As of August 2024, WHIM syndrome does not have a specific ICD-10 code; however, ICD-10 codes of D81.8 "Other combined immunodeficiencies" or D89.9 "Disorder involving the immune mechanism, unspecified" may apply to mavorixafor (Xolremdi). The prescriber must confirm that the member has a specific diagnosis of WHIM syndrome based on confirmation of the *CXCR4* gene, documentation of personal history of severe symptoms and complications associated with WHIM syndrome, and neutropenia based on absolute neutrophil count (ANC) count.

IV. The absolute neutrophil count (ANC) is the absolute number of segmented neutrophils (also called polys or segs) and band forms ([WBC count per microliter] × [percentage of neutrophils + band forms]). An ANC below 1000 cells/µL is defined as neutropenia and associated with increased risk of infection.

V. Approval for mavorixafor (Xolremdi) was based on results of the Phase 3, randomized, double-blind, placebo-controlled, 52-week multicenter study (4WHIM) that evaluated the efficacy and safety of mavorixafor (Xolremdi) in 31 participants. Patients 12 years of age and older were randomized in a 1:1 ratio to receive mavorixafor (N=14) based on weight (>50 kg, 400mg; ≤ 50 kg, 200mg) or placebo (N=17) orally once daily. Patients all had a genotype-confirmed variant of *CXCR4* consistent with WHIM syndrome, confirmed absolute neutrophil count (ANC) ≤400 cells/µL, and were eligible to continue on IVIG therapy. The primary endpoint was defined as number of hours above ANC threshold (500 cells/µL) over a 24-hour period, assessed every 3 months for 52 weeks. Mavorixafor (Xolremdi) achieved a mean time of 15.04 hours versus placebo at 2.75 hours ($p<0.0001$). The key secondary endpoint of number of hours above absolute lymphocyte count (ALC) of ≥1000 cells/µL over a 24-hour period was also met with mavorixafor (Xolremdi) having a mean time of 15.80 hours versus placebo at 4.55, ($p<0.0001$).

VI. Mavorixafor (Xolremdi) showed positive trends in secondary endpoints demonstrating less severe and fewer number of infections, a statistically significant reduction (~60%) in annualized infection rate versus placebo ($p<0.01$), 71% less time with infection, and lower rate of antibiotic usage compared with placebo. The use of mavorixafor (Xolremdi) on warts has uncertain benefit as there was no difference in total wart change scores between treatment arms; however, minor reduction in wart score occurred in both mavorixafor and placebo groups. Additionally, no new warts were observed in mavorixafor (Xolremdi) group for participants without warts at baseline.

VII. The safety was established by all patients receiving at least one dose of mavorixafor (Xolremdi). Seven (50%) of patients in mavorixafor (Xolremdi) compared to 3 (18%) patients in placebo experienced treatment-related adverse events (TEAEs). The most common adverse reactions (≥10% and at a frequency higher than placebo) in the mavorixafor (Xolremdi) arm were thrombocytopenia, pityriasis, rash, rhinitis, epistaxis, vomiting, and dizziness. The placebo arm had increased infections/infestations and respiratory disorders. Serious adverse reactions of thrombocytopenia occurred in 3 of the 14 patients who received mavorixafor (Xolremdi), two of which occurred in the setting of infection or febrile neutropenia. There were no TEAEs that led to discontinuations or death. Mavorixafor (Xolremdi) carries an embryo-fetal toxicity, QTc interval prolongation warning, and is contraindicated with drugs highly dependent on CYP2D6 for clearance.

VIII. Long-term efficacy and safety of G-CSF therapy has been demonstrated in treating neutropenia and preventing infection in various conditions, including in patients who have chronic neutropenia that are not caused by cancer treatment. Several case reports have been published on the off-label use of G-CSFs in WHIM syndrome, which resulted in a correction in neutropenia, however limited evidence to suggest efficacy in treating lymphopenia. While their use is off-label, the correction for neutropenia with G-CSF therapy has been the standard in treating patients with severe neutropenia; in absence of clinical guidelines or guidance on therapy sequencing, the use of G-CSF therapy is considered an appropriate first step in the treatment of severe neutropenia as it provides an efficacious and cost-effective treatment option for patients with WHIM syndrome.

IX. While G-CSF's have not been directly compared to mavorixafor (Xolremdi), they have been studied against another CXCR4 inhibitor, plerixafor, in WHIM syndrome (NCT02231879). In a Phase 3 crossover trial of plerixafor versus G-CSF (N = 19), no differences between the G-CSF and plerixafor arms were found for any infection outcome measures. In exploratory endpoints, plerixafor was noninferior to G-CSF for maintaining neutrophil counts of >500 cells/µL (P = 0.023) and was superior to G-CSF for maintaining lymphocyte counts >1000cells/µL (p <0.0001). There were no significant differences in drug preference, quality of life, or the incidence of drug failure or serious adverse events.

X. Mavorixafor (Xolremdi) has not been studied in combination with other CXCR4 antagonists such as plerixafor (Mozobil) or motixafortide (Aphexda). The combination use of these agents for safety and efficacy remains unknown at this time.

XI. There is moderate confidence that the medication provides a clinically objective and meaningful benefit as the medication provides a similar overall treatment profile balancing safety and efficacy relative to comparable treatment options, which include G-CSFs and other CXCR4 antagonists. Results from the 4WHIM trial demonstrate the ability for mavorixafor (Xolremdi) to raise and maintain ANC and ALC levels over a period of time. Absolute neutrophil count (ANC) and ALC values are used to predict the risk of serious bacterial infections in patients with neutropenia and lymphopenia. Mavorixafor (Xolremdi) provides a statistically significant difference in increasing the number of circulating mature neutrophils and lymphocytes in

patients with WHIM syndrome. Furthermore, mavorixafor (Xolremdi) showed positive trends in secondary endpoints compared with placebo. The full extent of efficacy and utility of mavorixafor (Xolremdi) will be realized in the real-world setting. An ongoing extension study is evaluating the long-term safety and efficacy of mavorixafor (Xolremdi).

Investigational or Not Medically Necessary Uses

I. Mavorixafor (Xolremdi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Chronic neutropenic disorders (congenital, acquired primary autoimmune, and idiopathic)
      i. Phase 3, 4WARD trial (NCT06056297) aims to evaluate the efficacy, safety, and tolerability of oral once-daily mavorixafor (Xolremdi) with or without granulocyte colony-stimulating factor (G-CSF) in participants with congenital or acquired primary autoimmune and idiopathic chronic neutropenia. The trial started enrolling 2024 and results are expected end of 2025. The current standard of care for treating severe chronic neutropenia is G-CSF therapy.
   B. Melanoma
   C. Renal Cell Carcinoma
   D. Waldenstrom macroglobulinemia
   E. Alzheimer's and Parkinson's diseases
   F. HIV-1

Appendix

I. Mavorixafor (Xolremdi) dosing:
   a. Weight >50 kg: 400 mg orally once daily
   b. Weight ≤50 kg: 300 mg orally once daily

I. Mavorixafor (Xolremdi) is contraindicated with drugs that are highly dependent on CYP2D6 for clearance.

II. Examples of G-CSF therapies:

Short-acting G-CSF	Long-acting G-CSF
filgrastim-sndz (Zarxio)*	pegfilgrastim-apgf (Nyvepria)*
filgrastim (Neupogen)	pegfilgrastim-jmdb (Fulphila)*
filgrastim-aafi (Nivestym)	Pegfilgrastim (Neulasta, Neulasta Onpro)
tbo-filgrastim (Granix)	pegfilgrastim-cbqv (Udenyca, Udencyca ON-BODY)
filgrastim-ayow (Releuko)	pegfilgrastim-bmez (Ziextenzo)
sargramostim (Leukine)	Pegfilgrastim (Neulasta)
	pegfilgrastim-pbbk (Fylnetra)
	pegfilgrastim-fpgk (Stimufend)

**as of July 2023, is a preferred G-CSF and does not require a prior authorization unless requesting above the plan's set quantity limits*

References

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7. McDermott DH, Velez D, Cho E, 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. Published 2023 Oct 2. doi:10.1172/JCI164918
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9. Tripathi R, Kumar P. Preliminary study to identify CXCR4 inhibitors as potential therapeutic agents for Alzheimer's and Parkinson's diseases. *Integr Biol (Camb).* 2023;15:zyad012. doi:10.1093/intbio/zyad012

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Short-acting Granulocyte-colony stimulating factor (CSF)	Severe chronic neutropenia
	WHIM syndrome
Long-acting Granulocyte Colony Stimulating Factor (G-CSF)	WHIM syndrome

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	08/2024