09-J4000-91

Original Effective Date: 10/01/24

Reviewed: 08/14/24

Revised: 00/00/00

Subject: Mavorixafor (Xolremdi) Capsule

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Mavorixafor (Xolremdi), a CXC chemokine receptor 4 (CXCR4) antagonist, was approved by the U.S. Food and Drug Administration (FDA) in June 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. Mavorixafor was previously granted orphan drug designation for the treatment of WHIM syndrome in 2018. WHIM syndrome is an extremely rare autosomal dominant primary immunodeficiency that causes excessive CXCR4 signaling leading to failure to release neutrophils from bone marrow. Only about 180 cases have been reported in the medical literature, and the estimated incidence is thought to be 0.2 per million livebirths.

Clinical presentation includes recurrent bacterial infections (respiratory tract and skin infections are most common) and severe or chronic neutropenia that begins in infancy or early childhood. Cutaneous warts, most often on the hand and feet, typically develop during childhood due to increased susceptibility to human papillomavirus (HPV). Anogenital warts generally appear in early adulthood and can progress to dysplasia and neoplasia. Hypogammaglobulinemia is the least consistently occurring syndromic feature and is usually mild to moderate. Outside of an allogeneic hematopoietic stem cell transplant (HSCT), there is no cure for WHIM syndrome. Prior to the approval of mavorixafor, treatment was based on patient's symptoms, and included preventing and/or treating bacterial infections and warts to improve quality of life and avoid serious complications. Treatments include immunoglobulin (IgG) replacement therapy, granulocyte colony-stimulating factors (G-CSF), short- or long-term antimicrobial prophylaxis, vaccination against HPV, and destruction/removal of warts.

The safety and efficacy of mavorixafor leading to initial FDA approval was evaluated in a 52-week, randomized, double-blind, placebo-controlled portion of Study 1 [NCT03995108] in patients aged 12 and older with WHIM syndrome. Enrolled patients had a genotype-confirmed variant of CXCR4 consistent with WHIM syndrome, and a confirmed absolute neutrophil count (ANC) ≤400 cells/mcL. Patients were

permitted to continue (but not initiate) immunoglobulin therapy at the same dose. Use of other CXCR4 antagonists was not permitted. Thirty-one patients were randomized 1:1 to receive either placebo (n=17) or mavorixafor (n=14) once daily for 52 weeks. Efficacy 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 (TAT ANC) of 500 cells/mcL over a 24-hour period was assessed 4 times throughout the study (every 3 months for 12 months). During the 24-hour period, measurements were taken a time 0 (pre-dose, up to 15 minutes prior), 30, 60, and 90 min (each ± 5 min) and 2, 3, 4, 8, 12, 16, and 24 hours (each ± 15 min) post-dose. The results over the 52-week period showed that TAT ANC was statistically significantly greater in patients treated with mavorixafor (LS mean [SE] 15 [1.89] hours) vs. placebo (2.8 [1.52] hours) ($p<0.0001$). For ALC, the mean time (hours) above ALC threshold (TAT ALC) of 1,000 cells/mcL 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 TAT ALC was statistically significantly greater in patients treated with mavorixafor (LS mean [SE] 15.8 [1.39] hours) compared with placebo (4.6 [1.15] hours) (p value <0.0001).

The efficacy of mavorixafor 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 mavorixafor-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 mavorixafor-treated patients compared with placebo-treated patients. The annualized infection rate was reduced approximately 60% in mavorixafor-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 mavorixafor and placebo treatment arms over the 52-week period.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of mavorixafor (Xolremdi) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “8”):

1. The member has a diagnosis of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis)
2. The member diagnosis has been confirmed by pathogenic or likely pathogenic variants in the CXC chemokine receptor type 4 (CXCR4) gene - *genetic testing results must be submitted*
3. The member has a baseline (within the past 90 days and prior to treatment with mavorixafor) absolute neutrophil count (ANC) or total white blood cell (WBC) count less than or equal to 400 cells/mcL, **AND** the member had no evidence of infection at the time of the measurement and the member has not received G-CSF therapy or systemic corticosteroids within 30 days of the

measurement (unless the member is on continuous, chronic therapy with either) - *laboratory results or documentation from the medical record must be submitted*

4. The prescriber has assessed the member's baseline (prior to treatment with mavorixafor) immune status regarding the total number of infections occurring with the past 12 months - *medical records documenting the number of infections occurring past 12 month must be submitted*
5. Treatment is prescribed by an immunologist, geneticist, hematologist, or dermatologist with experience in the management of WHIM syndrome
6. The member will **NOT** use mavorixafor in combination with another CXCR4 antagonists [e.g., motixafortide (Aphexda) or plerixafor (Mozobil)] for the treatment of WHIM syndrome
7. The member is 12 years of age or older, **OR** meets the minimum age as listed in the FDA-approved product labeling for mavorixafor
8. The dosage of mavorixafor does not exceed the following based on the member's body weight:
    a. Greater than 50 kg (110 lbs) - 400 mg once daily [four 100 mg capsules/day]
    b. 50 kg (110 lbs) or less – 300 mg once daily [three 100 mg capsules/day]

Approval duration: 12 months

Continuation of mavorixafor (Xolremdi) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1' to "5"):

1. An authorization or reauthorization for mavorixafor has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of WHIM syndrome (if another health plan, documentation of a health plan-paid claim for mavorixafor during the 90 days immediately before the request must be submitted), **OR** the member has previously met **ALL** indication-specific criteria (except for requirement #3 and #4 regarding baseline ANC and infections)
2. The member has had a beneficial response to mavorixafor treatment as evidence by **EITHER** of the following depending on duration of treatment ("a" or "b"):
    a. Less than 18 months of continuous treatment, **EITHER** of the following ("i" or "ii") - *supportive laboratory results or documentation from the medical record must be submitted:*
        i. Increase in absolute neutrophil counts (ANC) or absolute lymphocyte counts (ALC) as compared to baseline (prior to treatment with mavorixafor) as confirmed by at least **TWO** separate follow-up measurements at least one month apart, **AND** the member had no evidence of infection at the time of the repeat measurements and the member had not received G-CSF therapy or systemic corticosteroids within 30 days of the measurements (unless the member is on continuous, chronic therapy with either)
        ii. Reduction in the number of infections per year as compared to baseline (prior to treatment with mavorixafor)
    b. Continuous treatment of 18 or more months - the prescriber attests that the member continues to have a beneficial response to treatment with mavorixafor
3. Treatment is prescribed by an immunologist, geneticist, hematologist, or dermatologist with experience in the management of WHIM syndrome

4. The member will **NOT** use mavorixafor in combination with another CXCR4 antagonists [e.g., motixafortide (Aphexda) or plerixafor (Mozobil)] for the treatment of WHIM syndrome
5. The member is 12 years of age or older, **OR** meets the minimum age as listed in the FDA-approved product labeling for mavorixafor
6. The dosage of mavorixafor does not exceed the following based on the member's body weight:
    a. Greater than 50 kg (110 lbs) - 400 mg once daily [four 100 mg capsules/day]
    b. 50 kg (110 lbs) or less – 300 mg once daily [three 100 mg capsules/day]

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 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
- The recommended dosage is:
    - Weight more than 50 kg: 400 mg orally once daily
    - Weight less than or equal to 50 kg: 300 mg orally once daily
- Administer on an empty stomach after an overnight fast, and at least 30 minutes before food

Dose Adjustments

- Hepatic Impairment - Mavorixafor is not recommended in persons with moderate to severe hepatic impairment. No dosage adjustment is recommended in persons with mild hepatic impairment.
- Renal Impairment - Mavorixafor is not recommended in persons with severe renal impairment (CrCl 15 to less than 30 mL/minute) or end-stage renal disease (ESRD) (CrCl less than 15 mL/minute). No dosage adjustment is recommended in persons with mild to moderate renal impairment (CrCl 30 to less than 90 mL/minute).
- Drug Interactions - Reduce daily dosage of mavorixafor to 200 mg when used concomitantly with strong CYP3A4 inhibitors.

Drug Availability

- 100 mg white capsules in 60-count and 120-count child-resistant bottles
- Store refrigerated at 2°C to 8°C (36°F to 46°F). Keep bottle tightly closed. Store in and dispense from original container to protect from moisture.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Use with drugs that are highly dependent on CYP2D6 for clearance

Precautions/Warnings

- **Embryo-fetal toxicity**: Expected to cause fetal harm. Advise women of reproductive potential to use effective contraception.
- **QTc Interval Prolongation**: Correct any modifiable risk factors, assess QTc at baseline and monitor QTc during treatment as clinically indicated. Mavorixafor dose reduction or discontinuation may be required due to drug-drug interactions.
- **Drug Interactions**:
  - Strong CYP3A4 inhibitors: Reduce mavorixafor daily dosage
  - P-gp inhibitors or moderate CYP3A4 inhibitors: Monitor more frequently for mavorixafor adverse reactions and reduce mavorixafor daily dosage if necessary
  - Strong CYP3A4 Inducers: Avoid concomitant use
  - CYP3A4 or P-gp substrates: Monitor more frequently for substrate adverse reactions unless otherwise recommended

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

D81.8	Other combined immunodeficiencies

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

myelokathexis - retention of mature neutrophils in bone marrow, resulting in bone marrow hypercellularity and neutropenia.

RELATED GUIDELINES:

None

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 08/14/24.

GUIDELINE UPDATE INFORMATION:

10/01/24	New Medical Coverage Guideline.