PDL DRUG REVIEW

Proprietary Name: Xolremdi®
Common Name: mavorixafor
PDL Category: Hematopoietic Agents

Pharmacology/Usage: Mavorixafor, the active ingredient of Xolremdi®, is an orally bioavailable CXC Chemokine Receptor 4 (CXCR4) antagonist that blocks the binding of the CXCR4 ligand, stromal-derived factor-1α (SDF-1α)/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 lead to increased responsiveness to CXCL12 and retention of leukocytes in the bone marrow. Mavorixafor inhibits the response to CXCL12 in both wild-type and for mutated CXCR4 variants associated with WHIM syndrome. Treatment with mavorixafor results in increased mobilization of neutrophils and lymphocytes from the bone marrow into the peripheral circulation.

Indication: 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.

There is no pregnancy category for this medication; however, the risk summary indicates that based on its mechanism of action, Xolremdi® is expected to cause fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women informing the risk of embryo-fetal developmental toxicities. Advise pregnant women of the potential risk to the fetus and to use effective contraception. Verify the pregnancy status in female patients of reproductive potential prior to starting Xolremdi®. Advise females of reproductive potential to use an effective form of contraception during treatment and for three weeks after the final dose. The safety and efficacy of use in the pediatric population younger than 12 years of age have not been established.

Dosage Form: Capsules: 100mg.

Recommended Dosage: The recommended dosage is:

- Weight more than 50kg: 400mg PO QD on an empty stomach after an overnight fast, and at least 30 minutes before food.
- Weight less than or equal to 50kg: 300mg PO QD on an empty stomach after an overnight fast, and at least 30 minutes before food.
- Swallow the capsules whole; do not open, break, or chew capsules.

If a dose is missed, the next dose should be taken as scheduled. Do not take more than one dose each day.

Dose adjustments are not recommended with mild to moderate renal impairment; however, Xolremdi® use is not recommended in patients with severe renal impairment or end-stage renal disease. Dosage adjustments are not recommended with mild hepatic impairment; however, Xolremdi® use is not recommended with moderate to severe hepatic impairment.

Drug Interactions: Mavorixafor is a CYP3A4 substrate. Concomitant use with a strong CYP3A4 inhibitor increases mavorixafor maximal concentrations, which may increase the risk of Xolremdi® adverse reactions. Reduce Xolremdi® daily dosage when used concomitantly with a strong CYP3A4 inhibitor to

200mg daily. Monitor more frequently for Xolremdi® adverse reactions that may be associated with an increase in mavorixafor exposure when used concomitantly with a moderate CYP3A4 inhibitor and reduce the Xolremdi® daily dosage by steps of 100mg, if necessary, but not to a dose less than 200mg.

Avoid concomitant use of Xolremdi® with a strong CYP3A4 inducer.

Mavorixafor is a P-gp substrate. Monitor more frequently for Xolremdi® adverse reactions that may be associated with an increase in mavorixafor exposure when used concomitantly with P-gp inhibitors and reduce the Xolremdi® daily dosage by steps of 100mg, if necessary, but not to a dose less than 200mg.

Mavorixafor is a CYP2D6 inhibitor. The use of Xolremdi® with drugs that are highly dependent on CYP2D6 for clearance is contraindicated.

Mavorixafor is an inhibitor of CYP3A4. Monitor for CYP3A4 substrate related adverse reactions more frequently, unless otherwise recommended in the substrate's prescribing information, when Xolremdi® is used concomitantly with CYP3A4 substrates where minimal substrate concentration changes may lead to serious adverse reactions.

Monitor for P-gp substrate related adverse reactions more frequently, unless otherwise recommended in the substrate prescribing information, when Xolremdi® is used concomitantly with P-gp substrates where minimal substrate concentration changes may lead to serious adverse reactions.

Measure serum digoxin concentrations before starting concomitant use with Xolremdi® and continue monitoring serum digoxin concentrations as recommended in the prescribing information for digoxin.

Mavorixafor is an inhibitor of P-gp. Mavorixafor may increase the Cmax and AUC of P-gp substrates, which may increase the risk of adverse reactions from the P-gp substrate.

Mavorixafor may decrease the mean Cmax and AUC of metformin, which may reduce metformin's effectiveness. Monitor for glycemic control and adjust the dose of metformin as necessary if use in combination with Xolremdi®.

Xolremdi® causes QTc interval prolongation. Concomitant use of Xolremdi® with other products that prolong the QTc interval may result in a greater increase in the QTc interval and adverse reactions associated with QTc interval prolongation, including Torsade de Pointes, other serious arrythmias, and sudden death. Obtain an electrocardiogram when starting, during concomitant use, and as clinically indicated in patients receiving concomitant medications with a known potential to prolong the QTc interval.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Xolremdi®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included thrombocytopenia (21%), pityriasis (14%), rash (14%), rhinitis (14%), epistaxis (8%), vomiting (8%), and dizziness (8%).

Xolremdi® causes concentration-dependent QTc interval prolongation. QT interval prolongation may occur when Xolremdi® is taken with concomitant medications that increase Xolremdi® exposure and/or drug products with a known potential to prolong QT. Correct any modifiable risk factors for QTc prolongation (e.g., hypokalemia), assess QTc at baseline, and monitor QTc during treatment as clinically indicated in patients with risk factors for QTc prolongation such as those receiving concomitant medications that increase Xolremdi® exposure and drug products with a known potential to prolong the QTc interval. A dose reduction in Xolremdi® or discontinuation of Xolremdi® may be required.

Contraindications: Use of Xolremdi® is contraindicated with drugs that are highly dependent on CYP2D6 for clearance.

Manufacturer: X4 Pharmaceuticals, Inc.

Analysis: The efficacy of Xolremdi® was assessed in a randomized, double-blind, placebo-controlled portion of Study 1 that included patients aged 12 years and older with WHIM syndrome. This 52-week study included patients that had a genotype-confirmed variant of CXCR4 consistent with WHIM syndrome, and a confirmed absolute neutrophil count (ANC) ≤400 cells/µL. Patients were allowed to continue (but not start) immunoglobulin therapy at the same dose.

The mean age of patients in the Xolremdi® vs placebo group was 22.1 years vs 30.9 years, while 64.3% vs 52.9% were females, respectively. In addition, 93% vs 94% were white, the baseline mean ANC was 155 vs 281 cells/µL, and the baseline mean absolute lymphocyte count (ALC) was 501 vs 563 cells/µL.

The efficacy of Xolremdi® was based on improvement in ANC, improvement in ALC, and a reduction in infections. For ANC, the mean time (hours) above ANC threshold (TAT-ANC) 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 demonstrated that TAT-ANC was statistically significantly greater in patients treated with Xolremdi® (least squares [LS] mean 15 hours) compared with placebo (2.8 hours; p<0.0001). Results of the mean time above ANC threshold are presented in the table below, which was adapted from the prescribing information.

Clinical Endpoints		Xolremdi® (N=14)	Placebo (N=17)
TAT-ANC (hours)			
Mean Baseline		0.0	3.6
Overall mixed-model repeated measures (MMRM) results	LS mean	15.0	2.8
	LS mean 95% CI	(11.2, 18.9)	(0.0, 5.9)
	Difference from placebo:		
	LS mean difference	12.3	
	LS mean difference 95% CI	(7.2, 17.4)	
	p-value	<0.0001	

For ALC, the mean time (hours) above ALC threshold (TAT-ALC) 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 demonstrated that TAT-ALC was statistically significantly greater in patients treated with Xolremdi® (LS mean 15.8 hours) compared with placebo (4.6 hours; p<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”. Results of the Win-Ratio analysis for the composite clinical efficacy endpoint based on total infection score and total wart change score are presented in the table below, which was adapted from the prescribing information.

Category	N (number of wins)	Win-Ratio
Xolremdi® wins on total infection score	174	2.76
Placebo wins on total infection score	63	
Xolremdi® wins on total wart change score	0	
Placebo wins on total wart change score	0	

Category	N (number of wins)	Win-Ratio
None of the above (tie)	1	

Analyses of the individual components of this composite endpoint demonstrated an approximately 40% reduction of total infection score, weighted by infection severity, in Xolremdi®-treated patients as compared to placebo-treated patients. The annualized infection rate was reduced about 60% in Xolremdi®-treated patients (LS mean 1.7) compared with placebo-treated patients (LS mean 4.2). There was no difference in total wart change scores between the Xolremdi® and placebo treatment arms over the 52 week period.

Place in Therapy: Xolremdi® is an oral CXC chemokine receptor 4 antagonist 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. It is contraindicated with drugs that are highly dependent on CYP2D6 for clearance. In addition, Xolremdi® causes concentration-dependent QTc interval prolongation and should be monitored. The efficacy of Xolremdi® was assessed in a double-blind, placebo-controlled study that included patients with WHIM syndrome. The results over the 52-week period demonstrated that TAT-ANC was statistically significantly greater in patients treated with Xolremdi® compared with placebo (15 hrs vs 2.8 hrs; $p<0.0001$). Xolremdi® is the first targeted therapy FDA approved for WHIM syndrome.

Summary

It is recommended that Xolremdi® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Xolremdi [package insert]. Boston, MA: X4 Pharmaceuticals, Inc; 2024.