PDL DRUG REVIEW

Proprietary Name: Xcopri®
Common Name: cenobamate
PDL Category: Anticonvulsants

Comparable Products	Preferred Drug List Status
Lamotrigine	Preferred
Levetiracetam	Preferred
Topiramate	Preferred

Summary

Pharmacology/Usage: Cenobamate, the active ingredient of Xcopri®, has been shown to reduce repetitive neuronal firing by inhibiting voltage-gated sodium currents. It is also a positive allosteric modulator of the γ-aminobutyric acid (GABA-A) ion channel. However, the exact mechanism by which it exerts its therapeutic effects for its approved indication is not known.

Xcopri® is a Schedule V controlled substance.

Indication: For the treatment of partial-onset seizures in adult patients.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no adequate data on the developmental risk associated with the use of Xcopri® in pregnant women. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptics, such as Xcopri®, during pregnancy. Women of reproductive potential concomitantly using oral contraceptives should use additional or alternative non-hormonal birth control. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Tablets: 12.5mg, 25mg, 50mg, 100mg, 150mg, 200mg

Recommended Dosage: Administer once daily and swallow tablets whole with liquid. Do not crush or chew. Start at 12.5mg QD weeks 1 and 2, 25mg QD weeks 3 and 4, 50mg QD weeks 5 and 6, 100mg QD weeks 7 and 8, and 150mg QD weeks 9-10. The maintenance dose is 200mg QD after the 10 weeks of dose titration. The maximum dose, if needed based on clinical response and tolerability is 400mg QD, increasing the 200mg dose by increments of 50mg QD every 2 weeks to 400mg.

Use with caution and consider dose reduction in patients with mild to moderate (CrCl 30 to <90ml/min) and severe (CrCl <30ml/min) renal impairment. Use in patients with end-stage renal disease undergoing dialysis is not recommended. Xcopri® should be used with caution in patients with mild to moderate hepatic impairment. In these patients, the maximum recommended dosage is 200mg QD and additional dosage reduction may be considered. Use of Xcopri® with severe hepatic impairment is not recommended.

As with most antiepileptic drugs, Xcopri® should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.

Drug Interactions: Use caution when administering Xcopri® and other drugs that shorten the QT interval.

Concomitant use of Xcopri® with other CNS depressants, including alcohol, may increase the risk of neurological adverse reactions, including sedation and somnolence.

Due to the potential for reduced efficacy of lamotrigine and carbamazepine if used concomitantly with Xcopri®, increase the dosage of lamotrigine or carbamazepine, as needed, if used concomitantly with Xcopri®.

Due to a potential 2-fold increase in phenytoin levels if used concomitantly with Xcopri®, gradually decrease phenytoin dosage by up to 50% as Xcopri® is being titrated.

Due to the potential for an increase in the risk of adverse reactions from these drugs, consider a reduction in dosage of phenobarbital or clobazam, as clinically appropriate, when used concomitantly with Xcopri®.

Due to the potential for reduced efficacy of these drugs, increase the dosage of CYP2B6 or CYP3A4 substrates, as needed, when used concomitantly with Xcopri®.

Due to the potential for reduced efficacy of oral contraceptives, women should use additional or alternative non-hormonal birth control while taking Xcopri®.

Due to the potential for an increase in the risk of adverse reactions from these drugs, consider a reduction in dosage of CYP2C19 substrates, as clinically appropriate, when used concomitantly with Xcopri®.

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 (Xcopri® 200mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The reported adverse events included palpitations (0%), vertigo (0%), diplopia (5%), vision blurred (2%), nausea (3%), constipation (4%), diarrhea (3%), vomiting (4%), dry mouth (1%), abdominal pain (2%), dyspepsia (2%), nasopharyngitis (1%), pharyngitis (2%), urinary tract infection (3%), head injury (0%), alanine aminotransferase increased (1%), aspartate aminotransferase increased (1%), weight decreased (0%), decreased appetite (0%), back pain (0%), musculoskeletal chest pain (1%), somnolence (11%), dizziness (7%), fatigue (7%), headache (3%), balance disorder (4%), gait disturbance (2%), dysarthria (1%), nystagmus (7%), ataxia (1%), aphasia (1%), asthenia (0%), dysgeusia (0%), memory impairment (1%), migraine (0%), sedation (1%), tremor (2%), confusional state (2%), euphoric mood (0%), irritability (0%), suicidal ideation (1%), pollakiuria (1%), dysmenorrhea (2%), hiccups (1%), dyspnea (3%), pruritus (1%), and rash papular (0%).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as multiorgan hypersensitivity, has been reported in patients taking Xcopri®. DRESS has occurred, including one fatality, when Xcopri® was titrated rapidly. No cases of DRESS were reported in an open-label study that included seizure patients when Xcopri® was initiated at 12.5mg daily and titrated every two weeks. This finding does not establish that the risk of DRESS is prevented by a slower titration; however, Xcopri® should be initiated at 12.5mg once daily and titrated every 2 weeks. Monitor for signs and symptoms.

In a placebo-controlled trial of the QT interval, more taking Xcopri® (31% at 200mg and 66% at 500mg) had a QT shortening of greater than 20msec compared to placebo (6-17%). Reductions of the QTc interval below 300msec were not seen. Patients with Familial Short QT syndrome should not be treated with Xcopri®. Caution should be used when administering Xcopri® and other drugs that shorten the QT interval.

Antiepileptic drugs, including Xcopri®, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with an antiepileptic drug for any indication should be monitored for the

emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Neurological adverse reactions, including somnolence and fatigue, as well as dizziness, disturbance in gait and coordination, and cognitive dysfunction have been reported with Xcopri®. In addition, visual changes including diplopia, blurred vision, and impaired vision have been reported with Xcopri®. Visual change led to discontinuation in 0.5% of subjects treated with Xcopri® compared to none treated with placebo.

Contraindications: Familial Short QT syndrome; Hypersensitivity to cenobamate or any of the inactive ingredients of the product.

Manufacturer: SK Life Science, Inc

Analysis: The safety and efficacy of Xcopri® were assessed for the treatment of partial-onset seizures in two multicenter, randomized, double-blind, placebo-controlled studies that included adults with partial-onset seizures with or without secondary generalization and who were not adequately controlled with 1 to 3 concomitant antiepileptic drugs (AEDs). During an 8-week baseline period, patients were required to have at least 3 or 4 partial-onset seizures per 28 days on average with no seizure-free period exceeding 3 to 4 weeks. In these studies, patients had a mean duration of epilepsy of about 24 years and median baseline seizure frequency of 8.5 seizures per 28 days. More than 80% of patients were taking 2 more concomitant AEDs.

Study 1 compared doses of Xcopri® 200mg/day with placebo, while study 2 compared doses of Xcopri® 100mg/day, 200mg/day and 400mg/day with placebo. Both studies had an 8-week baseline period to establish a baseline seizure frequency, after which patients were randomized to a treatment. Patients entered a treatment period consisting of an initial titration phase (6 weeks) and a subsequent maintenance phase (6 weeks for study 1 and 12 weeks for study 2).

The primary efficacy outcome of both studies was the percent change from baseline in seizure frequency per 28 days in the treatment period. The results can be seen in the table below, which was adapted from the prescribing information.

	N	Median percent change from baseline in seizure frequency per 28 days	p-value
Study 1			
Placebo	108	-21.5%	-
Xcopri® 200mg/day	113	-55.6%	<0.0001
Study 2			
Placebo	106	-24.3%	-
Xcopri® 100mg/day	108	-36.3%	0.006
Xcopri® 200mg/day	109	-55.2%	<0.001
Xcopri® 400mg/day	111	-55.3%	<0.001

In study 2, 4% in the Xcopri® 100mg/day group, 11% in the Xcopri® 200mg/day group, and 21% in the Xcopri® 400mg/day group and 1% in the placebo group reported no partial seizures during the maintenance phase.

Place in Therapy: Xcopri® is an oral tablet indicated for the treatment of partial-onset seizures in adult patients. It is a Schedule V controlled substance and is subject to abuse and dependence. Xcopri® is contraindicated in patients with Familial Short QT syndrome. In two clinical trials compared with placebo, Xcopri® was found to be significantly more effective than placebo for the percent change from baseline in seizure frequency per 28 days in the treatment period. Comparator studies with other active treatments were not found.

There is no evidence at this time to support that Xcopri® is safer or more effective than the currently preferred, more cost-effective medications. It is therefore recommended that Xcopri® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

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

References

[1] Xcopri [package insert]. Paramus, NJ: SK Life Science, Inc; 2020.