Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Xphozah®
Common Name: tenapanor
PDL Category: Gastrointesinal Agents

Comparable Products	Preferred Drug List Status
Fosrenol	Non-Preferred
Sevelamer	Preferred

Pharmacology/Usage: Tenapanor, the active ingredient of Xphozah®, is a locally acting inhibitor that targets the sodium/hydrogen exchanger 3 (NHE3), an antiporter expressed on the apical surface of the epithelium of the small intestine and colon. Inhibition of NHE3 by tenapanor results in reduced sodium absorption and decreased phosphate absorption by reducing phosphate permeability through the paracellular pathway.

Indication: To reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

There is no pregnancy category for this medication; however, the risk summary indicates that tenapanor is essentially non-absorbed systemically. Thus, maternal use is not expected to result in fetal exposure to the drug. The available data on exposure from a small number of pregnant women have not identified any drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. The safety and efficacy of use in the pediatric population have not been established. Furthermore, use is contraindicated in patients less than 6 years of age.

Dosage Form: Film-Coated Tablets: 10mg (not currently listed in the drug file), 20mg, 30mg.

Recommended Dosage: Take 30mg PO BID before the morning and evening meals. Monitor serum phosphorus and adjust the dosage as needed to manage gastrointestinal tolerability. If a dose is missed, skip the missed dose and take the next dose at the regular time.

Instruct patients not to take Xphozah® right before a hemodialysis session, and instead take right before the next meal following dialysis, as patients may experience diarrhea after taking Xphozah®.

Drug Interactions: Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1. Drugs which are substrates of OATP2B1 may have reduced exposures when concomitantly taken with Xphozah®. Monitor for signs related to loss of efficacy and adjust the dose of concomitantly administered drug as needed.

Enalapril is a substrate of OATP2B1. When enalapril was co-administered with Xphozah® (30mg BID X5 days), the peak exposure (Cmax) of enalapril and its active metabolite (enalaprilat) decreased by about 70% and total systemic exposures (AUC) decreased by 50 to 65% compared to when enalapril was administered alone. However, the decrease in enalaprilat's exposure with Xphozah® may be offset by the inherently higher exposures observed in patients with CKD on dialysis due to its reduced renal clearance. Thus, a lower starting dose of enalapril, which is otherwise recommended in patients with CKD on dialysis, is not required when enalapril is co-administered with Xphozah®.

Separate the administration of Xphozah® and sodium polystyrene sulfonate (SPS) by at least 3 hours.

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 (Xphozah®). There was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included diarrhea, which occurred in 43-53% of patients. It was the only adverse reaction reported in at least 5% of patients treated with Xphozah®. Most diarrhea events were mild-to-moderate in severity and resolved over time, or with dose reduction.

Diarrhea was the most common adverse reaction in Xphozah®-treated patients with CKD on dialysis. In clinical trials, diarrhea was reported as severe in 5%, and associated with dehydration and hyponatremia in less than 1% of patients. Discontinue Xphozah® in patients who develop severe diarrhea.

Contraindications: In patients:

- Under 6 years of age because of the risk of diarrhea and serious dehydration.
- With known or suspected mechanical gastrointestinal obstruction.

Manufacturer: Ardelyx, Inc.

Analysis: The efficacy of Xphozah® for the ability to lower serum phosphorus in adults with CKD on dialysis was assessed in 3 trials, including TEN-02-201, TEN-02-301, and TEN-02-202. Across these trials, the mean age of patients treated with Xphozah® was 56 years (range 24 to 88), while 61% were males, and 44% were white. Both monotherapy trials (TEN-02-201 and TEN-02-301) enrolled patients who, following a 3-week washout period, had an increase in serum phosphorus of at least 1.5mg/dL (compared to pre-wash out value) and a serum phosphorus level of at least 6.0mg/dL and not more than 10mg/dL.

Study TEN-02-301 included a 26-week randomized, active-controlled, open-label treatment period that was followed by a 12-week, blinded placebo-controlled randomized withdrawal period. Patients (N=564) were randomized into the 26-week treatment period (N=423® to Xphozah® and N=141 to control arm which was intended to provide controlled safety data). Of the 423 randomized to Xphozah®, 255 patients (60%) completed the 26-week treatment period and were re-randomized to remain on Xphozah® (N=128) or placebo (N=127). During the randomized withdrawal phase, the phosphorus concentration rose in the placebo group by 0.7mg/dL (p=0.002) relative to patients who remained on Xphozah®.

Study TEN-02-201 included an 8-week, randomized, double-blind period that assessed 3 dosing regimens of Xphozah® (3mg BID, 10mg BID or a titration regimen). This period was followed by a 4-week placebo-controlled randomized-withdrawal phase, during which patients were re-randomized to their current Xphozah® treatment or to placebo. Of the patients (N=219) included in the trial, 164 patients (75%) completed the 8-week randomized treatment period and were re-randomized to received Xphozah® (N=82) or placebo (N=82). During the randomized withdrawal phase, the phosphorus concentration rose in the placebo group by 0.7mg/dL (p=0.003) relative to patients who remained on Xphozah®.

Study TEN-02-202 was a randomized, parallel-group, double-blind, placebo-controlled study that assessed the effect of Xphozah® on the change in serum phosphorus when used as add-on therapy in patients on stable phosphate-binder therapy with serum phosphorus greater than or equal to 5.5mg/dL. Patients (N=236) were randomized to receive Xphozah® (N=117) or placebo BID (N=119) for 4 weeks. During the 4-week period, the serum phosphorus decreased by 0.7mg/dL (p=0.0004) in the add-on Xphozah® group as compared to the add-on placebo group.

Place in Therapy: Xphozah® is a sodium hydrogen exchanger 3 (NHE3) inhibitor indicated to reduce serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy. Xphozah® is a first in-class agent that acts as a blocker (an NHE3 inhibitor, resulting in reduced sodium absorption and decreased phosphate absorption) and to be taken only twice a day rather than with meals as with most traditional phosphate binders. Data from the two phase 3 monotherapy studies suggested that during the randomized

withdrawal period, phosphorus levels significantly rose in the placebo group relative to patients who remained on Xphozah®.

Study Ten-02-202 was also called the AMPLIFY study. These patients were already receiving phosphate binder therapy (sevelamer, non-sevelamer, sevelamer plus non-sevelamer, or multiple non-sevelamer binders) who were then randomly assigned to receive oral tenapanor or placebo. Per the full text study by Pergola et al[2], tenapanor plus binder resulted in a significantly larger mean change in serum phosphorus concentration from baseline to week 4 compared with placebo and binder, and a significantly larger proportion of patients receiving tenapanor plus binder achieved a serum phosphorus level below 5.5mg/dl starting at week 1 (49.1% vs 21%, p<0.001), and each week through week 4 (37.1% vs 21.8%, respectively; p=0.01) compared with placebo plus binder.

There is some evidence in a phase 3 study to suggest that Xphozah® in combination with phosphate binder may be more effective for lowering serum phosphorus compared to placebo plus phosphate binder; however, there is no evidence at this time to support that Xphozah® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Xphozah® 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] Xphozah [package insert]. Waltham, MA: Ardelyx, In; 2023.
[2] Pergola PE, Rosenbaum DP, Yang Y, et al. A randomized trial of tenapanor and phosphate binders as a dual-mechanism treatment for hyperphosphatemia in patients on maintenance dialysis (AMPLIFY). *J Am Soc Nephrol.* 2021; 32(6): 1465-1473.