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Drug Class Update with New Drug Evaluation: Phosphate Binders

Date of Review: April 2024

Date of Last Review: August 2021
Dates of Literature Search: 05/19/2021 – 01/18/2024
Brand Name (Manufacturer): XPHOZAH® (Ardelyx)
Dossier Received: Not available

Generic Name: tenapanor

Current Status of Preferred Drug List (PDL) Class:
See **Appendix 1**.

Purpose for Class Update:
Review new evidence of efficacy and safety for the phosphate binder class, tenapanor (XPHOZAH), for the Oregon Health Plan (OHP) fee-for-service (FFS) program.

Plain Language Summary:
- People with kidney disease may experience increased levels of phosphate in the blood. High blood phosphate levels can decrease levels of calcium in the blood and lead to bone loss. High phosphate levels can also combine with calcium, leading to dangerous deposits in the blood vessels, lungs, eyes, and heart. Over time this can cause an increased risk for heart attack, stroke, or death.
- Phosphate binders are medicines that prevent phosphate in food from being absorbed into the body. Phosphate binders are all effective in lowering phosphate levels but have different side effects. Side effects include high calcium levels in the blood, nausea, constipation, and diarrhea.
- XPHOAZAH (tenapanor) is a new medication approved in 2023 that works differently than phosphate binders but can also lower phosphate levels when combined with a phosphate binder. Diarrhea is a common side effect of this medicine, but goes away after the first week of treatment.
- Two phosphate binders, calcium acetate and sevelamer, are preferred medications on the Oregon Health Plan fee-for-service Preferred Drug List. The other medications are not preferred and providers must receive prior authorization before the prescription is covered for the member.

Research Questions:
1. What is the comparative efficacy of phosphate binders (i.e., calcium acetate, calcium carbonate, sevelamer hydrochloride, sevelamer carbonate, lanthanum, sucroferric oxyhydroxide, and ferric citrate) to reduce serum phosphate?
2. What are the comparative harms of phosphate binders when used to reduce serum phosphate?
3. What is the evidence for the safety and efficacy of tenapanor when used as add-on therapy to reduce serum phosphate in patients with chronic kidney disease (CKD) on dialysis?
4. Do the phosphate binders differ in their effectiveness or harms based on age, race, ethnicity, gender, or patients with comorbidities?

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Conclusions:

- One guideline issued by the National Institute for Health and Care Excellence (NICE) was identified since the last P & T Committee review of this drug class.[1]
- In 2021, NICE updated guidance for assessment and management of people with CKD.[1]
    - Due to insufficient evidence, NICE recommendations for the use of phosphate binders in children and young people has not changed from the 2013 CKD guidance. Children and young people with CKD stage 4 or 5 and hyperphosphatemia should be offered a calcium-based phosphate binder to control serum phosphate levels.[1]
    - NICE recommendations for phosphate binders in adults are as follows:
        - Calcium acetate in adults with CKD stage 4 or 5 and hyperphosphatemia.[1]
        - Sevelamer carbonate if calcium acetate is not indicated (e.g., hypercalcemia or low serum parathyroid hormone [PTH] levels).[1]
        - If calcium acetate and sevelamer carbonate cannot be used, consider:
            - sucroferric oxyhydroxide for adults on dialysis if a calcium-based phosphate binder is not needed; or
            - calcium carbonate if a calcium-based phosphate binder is needed.[1]
        - Only consider lanthanum carbonate for adults with CKD stage 4 or 5 if other phosphate binders cannot be used.[1]
- Tenapanor (XPHOZAH) received FDA approval in October 2023 as an add-on therapy in adults with CKD on dialysis to reduce serum phosphate in patients who have had an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder.[2]
- The safety and efficacy of tenapanor was evaluated in three phase 3, randomized controlled trials (RCTs) conducted over 4 to 12 weeks.[2] In these trials, tenapanor combined with a phosphate binder was effective in reducing serum phosphate compared with placebo. The trials do not provide evidence for long-term safety and efficacy of tenapanor.
    - The first phase 3 (RCT) was conducted in 2 phases: an 8-week dose-finding phase (3 mg, 10 mg, and 30 mg twice daily) followed by a 4-week, withdrawal, placebo-controlled phase.[3] Enrolled participants were receiving hemodialysis and taking at least 3 doses of a phosphate binder per day.[3] In the 4-week withdrawal phase, the difference in serum phosphate change between the tenapanor plus phosphate binder group (n=82) and the placebo plus phosphate binder group (n=82) was statistically significant (mean increase ± standard deviation [SD] of 0.85 ± 1.68 mg/dL with placebo versus mean increase ± SD 0.02 ± 1.63 mg/dL with tenapanor; least squares mean difference [LSMD], −0.72 mg/dL; 95% confidence interval [CI], −1.19 to −0.25 mg/dL; p=0.003; moderate-quality evidence).[3]
    - The second phase 3 RCT (AMPLIFY) was a parallel-group, double-blind, placebo-controlled study that evaluated the effect of tenapanor on the change in serum phosphate when used as add-on therapy in adults maintained on hemodialysis or peritoneal dialysis and stable phosphate-binder therapy with serum phosphorus greater than or equal to 5.5 mg/dL.[4] Patients treated with tenapanor plus phosphate binder achieved a larger mean change in serum phosphate concentration from baseline to week 4 compared with placebo plus binder (−0.84 vs. −0.19 mg/dL; LSMD, -0.65; 95% CI -1.01 to -0.29; p<0.001; moderate-quality evidence).[4]
    - The final phase 3 RCT (PHREEDOM) had a complex study design conducted over 3 separate periods: a 26-week open-label randomized treatment period, a 12-week double-blind, placebo-controlled randomized withdrawal period, and a 14-week open-label safety extension period.[5] Forty weeks of this 52-week study were open-label. In the efficacy analysis set (n=131), the least square mean change in serum phosphate over 12 weeks was 0.4 mg/dL for the tenapanor group and 1.8 mg/dL for the placebo group (LSMD −1.37; 95% CI -1.92 to -0.82 mg/dL; p<0.001; moderate-quality evidence).[6]
    - In these trials, diarrhea was the most common adverse effect (AE) reported with tenapanor treatment.[4] Diarrhea was typically transient (less than 1 week in duration) and mild to moderate in severity.[4] Approximately two-thirds of cases occurred within 1 week of initiating treatment with tenapanor.[4]

- No evidence was identified to assess if the phosphate binders differ in their effectiveness or harms based on age, race, ethnicity, gender, or patients with comorbidities.

Recommendations:
- Revise name of the preferred drug list (PDL) class from "phosphate binders" to "phosphate binders and absorption inhibitors" due to unique mechanism of action for the newest product, tenapanor.
- Maintain tenapanor as nonpreferred and amend prior authorization (PA) criteria in **Appendix 4** to provide coverage for clinically appropriate use of tenapanor as add-on therapy in patients with hyperphosphatemia and CKD.
- Review costs in executive session.

Summary of Prior Reviews and Current Policy
The phosphate binder drug class was last reviewed by the P & T Committee at the August 2021 meeting. There is no comparative evidence that one phosphate binder is more effective or safer than another; however, there is more long-term evidence with sevelamer and lanthanum compared to sucroferric oxyhydroxide and ferric citrate. The Committee recommended removal of the PA requirement for preferred products. Preferred phosphate binders include calcium acetate, sevelamer hydrochloride, and sevelamer carbonate tablets. Non-preferred phosphate binders are listed in **Appendix 1.** The current PA criteria for phosphate binders (with amendments for tenapanor) are presented in **Appendix 4**.

In the fourth quarter of 2023 (September 1, 2023 to December 31, 2023), approximately 90% of FFS phosphate binder claims were for 2 preferred agents, calcium acetate (48%) and sevelamer carbonate (42%). Non-preferred utilization of phosphate binders was due to sucroferric oxyhydroxide (8%) and lanthanum (2%).

Background:
Phosphorous is an abundant mineral in the body and is predominantly an intracellular anion.[7] Ninety percent of the daily phosphate load is excreted by the kidneys, while the gastrointestinal (GI) tract excretes the other 10%.[7] Phosphate homeostasis is influenced by calcitriol, parathyroid hormone (PTH), and fibroblast growth factor-23 (FGF-23).[7] Fibroblast growth factor-23 is the most potent hormone regulating phosphate homeostasis, increasing urinary excretion of phosphate by inhibiting phosphate reabsorption in the renal proximal tubule.[7] Phosphate is essential for cellular energy production and bone mineralization.[8] Hyperphosphatemia can occur with excessive phosphate load, decreased renal excretion, or transcellular shifting.[7] High intake of phosphate due to excessive use of phosphate-containing laxatives or vitamin D can result in hyperphosphatemia.[7] Tissue breakdown due to tumor lysis syndrome or rhabdomyolysis can lead to the release of intracellular phosphate into extracellular fluid.[7] Other reasons for hyperphosphatemia include hypoparathyroidism, acromegaly, thyrotoxicosis, metabolic acidosis, lactic acidosis, and diabetic ketoacidosis. Some medications such as penicillin, corticosteroids, furosemide and thiazide diuretics can also cause hyperphosphatemia.[7]

In adults, hyperphosphatemia is defined as serum phosphate concentration greater than 4.5 mg/dL.[7] In children, normal serum phosphate levels range from 4 to 7 mg/dL.[7] People with CKD are at high risk for hyperphosphatemia due to impaired renal excretion of phosphate. In patients with end-stage renal disease, the prevalence of hyperphosphatemia ranges from 50 to 74%.[9] Hyperphosphatemia is common in late stages of CKD (i.e., glomerular filtration rate (GFR) less than 30 mL/min).[10] Elevated serum phosphate can cause secondary hyperparathyroidism, impaired bone metabolism, endothelial damage, and calcification of the blood vessels, heart valves, and myocardium.[11] Persistent hyperphosphatemia in CKD patients is associated with increased mortality in this population.[11]

Hyperphosphatemia is managed by restricting dietary phosphate, removing phosphate with dialysis, or minimizing phosphate absorption in the GI tract using phosphate binders. Phosphate binders are classified according to their molecular composition as: calcium-containing (calcium carbonate, calcium acetate), non-calcium-based (sevelamer carbonate, sevelamer hydrochloride, lanthanum), aluminum-containing (aluminum hydroxide) or iron-containing (sucroferric oxyhydroxide, ferric citrate).[11] The phosphate binders are all effective in lowering serum phosphorus, but they differ in their safety profiles.[11]

The first phosphate binders used in clinical practice were aluminum hydroxide preparations. With continued use, it became evident that these agents are associated with serious adverse effects due to aluminum accumulation, including osteomalacia, neurotoxicity, cognitive disturbances, and anemia.[11] Due to the risks of toxicity, aluminum hydroxide capsules are no longer manufactured. As calcium-based phosphate binders replaced aluminum preparations, increased risks for vascular calcification and arterial stiffness associated with calcium administration were identifed.[11] Excess exposure to calcium with calcium-based binders may be harmful in patients with any stage of CKD.[12] The first non-calcium containing phosphate binder, sevelamer hydrochloride, was approved by the FDA in 2000.[11] Sevelamer hydrochloride was found to worsen metabolic acidosis, so sevelamer carbonate was developed as an alternative.[11] Lanthanum carbonate, approved in 2004, also reduces phosphorus levels without increasing calcium load, which decreases the risk of treatment-related hypercalcemia.[6] The prescribing information for lanthanum includes a precaution for the risk of GI obstruction, ileus, GI perforation, and fecal impaction.[13] Iron-based phosphate binders include sucroferric hydroxide and ferric citrate. Sucroferric hydroxide was approved in 2013 and ferric citrate was approved in 2014.[14] Iron-containing agents can cause GI side effects including nausea, vomiting, diarrhea, and constipation.[11] Phosphate binder therapy is associated with poor GI tolerability, dosing up to 3 times per day, and a high pill burden.[5] The recently approved phosphate absorption inhibitor, tenapanor, has a unique mechanism of action and will be discussed in more depth later in this review. A summary of medications that inhibit phosphate absorption and their associated serious adverse effects is presented in **Table 1**.

Table 1. FDA-Approved Medications Which Inhibit Phosphate Absorption[14]

Generic Name (BRAND NAME)	Year of FDA Approval	FDA Approved Age Range	Serious Adverse Effects
Aluminum-Based Binders			
Aluminum Hydroxide (discontinued)	1970	N/A	Neurotoxicity, Cognitive Disorders, Osteomalacia, Anemia
Calcium-Based Binders			
Calcium Acetate (PHOSLO)	1990	Adults	Hypercalcemia which could lead to Vascular and Soft Tissue Calcification
Calcium Carbonate (TUMS)		Over-the-counter labeling includes dosing for pediatric patients	
Non-Calcium Based Binders			
Sevelamer Hydrochloride (RENAGEL)	2000	Adults	Metabolic Acidosis, GI Obstruction
Sevelamer Carbonate (RENVELA)			Ileus, Fecal Impaction, Bowel Obstruction, Bowel Perforation
Lanthanum Carbonate (FOSRENOL)	2004		Ileus, GI Obstruction, GI perforation, Fecal Impaction

Iron-Based Binders			
Sucroferric Oxyhydroxide (VELPHORO)	2013	Adults	Potential for Iron Overload
Ferric Citrate (AURYXIA)	2014		Potential for Iron Overload
Sodium-Hydrogen Exchanger			
Tenapanor (XPHOZAH)	2023	Adults	Severe Diarrhea
Abbreviations: FDA = Food and Drug Administration; GI = gastrointestinal; N/A = not available			

The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) work group concluded there is insufficient evidence for efficacy and safety of phosphate binders among patients not receiving dialysis with CKD Grades 3A through 5D.[12] The KDIGO panel suggested restricting the dose of calcium-based phosphate binders and stressed tolerance of mild and asymptomatic hypocalcemia, in order to avoid exogenous calcium loading.[12] The utility of calcium-free phosphate binders in reducing clinical events in CKD, balanced against their cost and potential harms has been controversial due insufficient and conflicting evidence.[15] Use of phosphate binders should be limited to patients with progressive or persistent hyperphosphatemia and not to prevent hyperphosphatemia.[12] For patients with CKD Grade 3a through 5, elevated phosphate levels should be reduced toward the normal range rather than normalized, while avoiding hypercalcemia for adult patients.[12] Most studies showed increasing risk of all-cause mortality with increasing levels of serum phosphate in a consistent and direct fashion, with moderate risk of bias and low quality of evidence.[12] Clinical trial evidence that treatments that lower serum phosphate improve patient-centered outcomes are still lacking, and therefore the strength of this recommendation remains weak.[12]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 7 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses),[16-20] wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled),[21-23] or outcome studied (e.g., non-clinical).

New Guidelines:
National Institute for Health and Care Excellence: Assessment and Management of Chronic Kidney Disease
In 2021 NICE updated guidance for assessment and management of people with CKD.[1] There was a significant amount of evidence (of varying quality) for the use of phosphate binders in adults with stage 5 CKD who are on dialysis.[1] However, evidence was limited for adults with stage 4 or 5 CKD not on dialysis, and for

children and young people.[1] The committee agreed to extrapolate from the evidence for adults with stage 5 CKD on dialysis, so they could make recommendations for the other populations.[1]

Phosphate Binders In Children And Young People

The committee reviewed the recommendations from the 2013 NICE guideline in the light of limited new evidence for the use of phosphate binders in children and young adults.[1]

NICE Recommendations:

- Offer children and young people with stage 4 or 5 CKD and hyperphosphatemia a calcium-based phosphate binder to control serum phosphate levels.[1]
- If serum calcium increases towards, or above, the age-adjusted upper normal limit:
    - Investigate possible causes other than the phosphate binder and
    - Consider reducing the dose of the calcium-based phosphate binder and adding sevelamer carbonate or switching to sevelamer carbonate alone. [1]
- For all children and young people who are taking more than a single phosphate binder, titrate the dosage to achieve the best possible control of serum phosphate while keeping serum calcium levels below the upper normal limit.[1]

Phosphate Binders In Adults

The committee reviewed the evidence for phosphate binders both in adults on dialysis and adults not receiving dialysis.[1] The committee agreed that diet and dialysis (when appropriate) had a large impact on serum phosphate levels.[1] Therefore, before offering phosphate binders it is important to provide dietary advice and ensure people are on the dialysis regimen that works best for them.[1]

The evidence summarized to support the guideline development showed no differences between phosphate binders for the impact on serum phosphate levels at 3, 6, and 12 months in adults with stage 5 CKD receiving dialysis.[24] However, calcium carbonate showed an increase in levels of serum calcium at 3, 6, and 12 months compared with sevelamer hydrochloride, an increase in levels of serum calcium at 6 months compared with magnesium carbonate, and a higher risk of hypercalcemia compared with lanthanum carbonate and sevelamer carbonate at 6 months in patients receiving dialysis.[24] People taking calcium acetate had higher risk of hypercalcemia, but there was no clinical difference on serum calcium levels at any of the time points compared with other phosphate binders.[24] Therefore, the committee agreed to keep calcium acetate as a first-line phosphate binder as it showed a clinically significant effect compared with placebo for increasing the proportion of adults achieving target (<1.78 mmol/L) phosphate levels.[24] The committee also made a recommendation to consider calcium carbonate if a calcium-based agent is required in adults who do not tolerate calcium acetate.[24] This decision was based on the data showing that, even though it carried a risk of hypercalcemia, calcium carbonate was effective at increasing the proportion of adults achieving phosphate control compared with placebo and at reducing the risk of constipation compared with calcium acetate and sevelamer hydrochloride.[24]

Evidence for sevelamer carbonate showed a clinically significant effect increasing the proportion of adults achieving phosphate control compared with placebo and a clinically significant effect reducing the risk of hypercalcemia compared with calcium carbonate and calcium acetate.[24] Lanthanum carbonate showed a clinically significant effect for increasing the proportion of adults achieving phosphate control compared with placebo, a significant effect in reducing serum calcium levels at 6 months compared with calcium carbonate, a significant effect in reducing the risk of hypercalcemia compared with calcium carbonate and calcium acetate, and a significant effect for decreasing the risk of constipation compared with calcium acetate and sevelamer hydrochloride.[24] The evidence for sucroferric oxyhydroxide showed a clinically significant effect for increasing the proportion of adults achieving phosphate control compared with placebo and a significant effect in reducing the risk of constipation compared with calcium acetate and sevelamer carbonate, but there was a higher risk of diarrhea compared with sevelamer hydrochloride.[24]

In 4 placebo-controlled RCTs in adults with stage 4 or 5 CKD not on dialysis, the active comparator (calcium carbonate, calcium acetate, ferric citrate, and lanthanum) was more favorable in reducing serum phosphate levels over 2 to 4 months.[24] In the head-to-head comparisons, there was no meaningful difference between phosphate binders in reduction of serum phosphate levels for CKD patients not on dialysis.[24] For adverse effects, there was no difference between lanthanum and ferric citrate in incidence of constipation or diarrhea.[24] However, lanthanum caused more constipation than placebo.[24]

NICE Recommendations:

- Calcium acetate for adults with stage 4 or 5 CKD and hyperphosphatemia to control serum phosphate levels.[1]
- Sevelamer carbonate if calcium acetate is not indicated (e.g., hypercalcemia or low serum PTH levels) or not tolerated.[1]
- If calcium acetate and sevelamer carbonate cannot be used, consider:
    - Sucroferric oxyhydroxide for adults on dialysis if a calcium-based phosphate binder is not needed or
    - Calcium carbonate if a calcium-based phosphate binder is needed.[1]
- Only consider lanthanum carbonate for adults with stage 4 or 5 CKD if other phosphate binders cannot be used.[1]
- If hyperphosphatemia persists in adults with stage 4 or 5 CKD after taking the maximum recommended dose (or the maximum dose they can tolerate) of a calcium-based phosphate binder, check they are taking it as prescribed and
    - consider combining a calcium-based phosphate binder with a non-calcium-based phosphate binder.[1]
- For all adults who are taking more than a single phosphate binder, titrate the dosage to achieve the best possible control of serum phosphate while keeping serum calcium levels below the upper normal limit.[1]

At every routine clinical review for adults, children and young people, assess the person's serum phosphate control, taking into account: diet, whether they are taking the phosphate binders as prescribed and other relevant factors, such as vitamin D levels, serum PTH levels, alkaline phosphatase, serum calcium, and medications that might affect serum phosphate, or dialysis.[1]

Randomized Controlled Trials:

A total of 22 citations were manually reviewed from the initial literature search. After further review, 22 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION: Tenapanor (XPHOZAH)

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Tenapanor oral tablets were initially approved in 2019 for management of constipation-predominant irritable bowel syndrome under the brand name IBSRELA.[25] In October 2023, another tenapanor branded formulation, XPHOZAH, received FDA approval for reduction of serum phosphate in adults with CKD on dialysis as add-on therapy in patients who have had an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.[2] Tenapanor is a locally acting inhibitor of the sodium-hydrogen exchanger-3 (NHE3) in the small intestine and colon.[2] Inhibition of NHE3 reduces paracellular phosphate transport by blocking phosphate intestinal absorption.[2] Tenapanor is unique because it does not bind phosphate in the GI tract; instead, it reduces intestinal phosphate absorption. The recommended dose is 30 mg orally twice daily before the morning and evening meals.[2]

The safety and efficacy of tenapanor to lower serum phosphate in adults with CKD on dialysis was evaluated in three phase 3 RCTs.[2] Across these trials, the mean age of tenapanor-treated patients was 56 years (range 24 to 88 years), 61% were males, 44% were White, 49% were Black/African American, 3% were Asian, and 3% were American Indian or Alaska Native.[2]

The first RCT was conducted in 2 phases: an 8-week dose-finding phase followed by a 4-week placebo-controlled phase.[3] The trial was originally designed as a double-blind, dose-ranging phase 2 study with the primary end point the change in serum phosphate from baseline to the end of the 8-week randomized treatment period.[3] After trial initiation, FDA informed the sponsor that a previous phase 2 study was sufficient for dose-range finding and proposed conversion to a phase 3 trial incorporating a 4-week, double-blind, placebo-controlled, randomized withdrawal period.[3] The primary end point was amended to the between-groups (pooled tenapanor versus placebo) difference in the mean change in serum phosphate from the end of the randomized treatment period to the end of the randomized withdrawal period.[3]

In the first 8 weeks, 3 oral dosing regimens of tenapanor were evaluated (3 mg twice daily, 10 mg twice daily, or 30 mg twice daily) in 219 adults with hyperphosphatemia (serum phosphate 6.0 to 10 mg/dL).[3] Enrolled participants were receiving maintenance hemodialysis and taking at least 3 doses of a phosphate binder per day.[3] The types of phosphate binders were not described in the study summary. Of the 219 patients included in the trial, 164 patients completed the 8-week dose-finding treatment period and were re-randomized 1:1 to receive tenapanor or placebo in the next 4-week phase of the trial.[3] At the end of 4-week withdrawal phase, the difference in serum phosphorous change between the tenapanor group (n=82) and the placebo group (n=82) was statistically significant (mean ± SD increase of 0.85 ± 1.68 mg/dL with placebo versus mean ± SD 0.02 ± 1.63 mg/dL with tenapanor; LSMD, −0.72 mg/dL; 95% CI, −1.19 to −0.25 mg/dL; p=0.003).[3]

The second RCT (AMPLIFY) was a parallel-group, double-blind, placebo-controlled study that evaluated the effect of tenapanor on the change in serum phosphate when used as add-on therapy in adults maintained on hemodialysis or peritoneal dialysis and stable phosphate-binder therapy with serum phosphate greater than or equal to 5.5 mg/dL.[4] Most patients were receiving sevelamer (49%) as the phosphate binder.[4] Other phosphate binders included: calcium acetate (20%), calcium carbonate (2%), ferric citrate (9%), lanthanum (2%), sucroferric oxyhydroxide (9%) and a combination of non-sevelamer products (8%).[4] A total of 236 patients were randomized to receive oral tenapanor 30 mg twice daily (n=117) or placebo twice daily (n=119) for 4 weeks.[4] The primary efficacy end point was the change in serum phosphate from baseline to week 4.[4] Patients treated with tenapanor plus phosphate binder achieved a larger mean change in serum phosphate concentration from baseline to week 4 compared with placebo plus binder (−0.84 vs. −0.19 mg/dL; LSMD, -0.65; 95% CI -1.01 to -0.29; p<0.001).[4]

A 52-week phase 3 RCT (PHREEDOM) had a complex study design as it was conducted in 3 separate periods: a 26-week open-label randomized treatment period, a 12-week double-blind, placebo-controlled, randomized withdrawal period, and a 14-week open-label safety extension period.[5] Patients with a serum phosphate 4.0–8.0 mg/dL at the screening visit were eligible to enter the phosphate binder washout period of 1 to 4 weeks in duration.[5] Patients whose serum phosphate had increased by 1.5 mg/dL or more during this period, and who had a measured serum phosphate 6.0 mg/dL or higher and less than 10.0 mg/dL at the end of the washout period, were randomly assigned (3:1) to receive either tenapanor at a starting dose of 30 mg orally, twice daily for 26 weeks (randomized treatment period), or sevelamer carbonate (on the basis of standard of care) for 52 weeks.[5] At the end of the randomized treatment period, participants were re-randomized (1:1) to either continue to receive tenapanor treatment at the same dose, or switch to placebo for 12 weeks (randomized withdrawal period).[5] On completion of, or discontinuation from, the randomized withdrawal period, all re-randomized participants were eligible to enter a 14-week safety extension period for tenapanor treatment.[5] To compare the rates of serious adverse events (SAEs) among the high-risk population enrolled in the study, participants taking open-label sevelamer for the 52-week study were followed as a control group for safety comparison only.[5] Efficacy data are not presented for this group,

because these participants received sevelamer as "standard of care."[5] The use of phosphate binders to treat hyperphosphatemia (other than sevelamer used in the safety control group) was prohibited.[5]

The primary efficacy end point was the difference in the change in serum phosphate from period-specific baseline to the end of the 12-week randomized withdrawal period between the pooled tenapanor group and placebo group.[5] A total of 310 participants completed the 12-week randomized withdrawal period (83% of the 372 participants who entered the period): 112 (96%) participants in the sevelamer group, 99 (78%) participants in the placebo group, and 99 (77%) participants in the tenapanor group.[5] For the efficacy analysis set, the fixed tenapanor dose administered during the randomized withdrawal period (and the final tenapanor dose of the randomized treatment period) was 30 mg twice daily for 75 (57%) participants, 20 mg twice daily for 39 (30%) participants, and 10 mg twice daily for 17 (13%) participants, with a mean value of 24.4 mg twice daily.[5] In the efficacy analysis set (n=131), the least squares mean change in serum phosphate from period-specific baseline to the end of the randomized withdrawal period was 0.4 mg/dL for the tenapanor group and 1.8 mg/dL for the placebo group (LSMD −1.37; 95% CI -1.92 to -0.82 mg/dL; p<0.001).[5]

Additional study details are described and evaluated below in **Table 5.** In 3 RCTs conducted over 4 to 12 weeks, tenapanor combined with a phosphate binder was efficacious in reducing serum phosphate compared with placebo. However, these relatively short-term trials do not provide evidence for the long-term safety and efficacy of tenapanor. A long-term RCT would provide additional evidence on the impact of tenapanor on CV events and fractures. Tenapanor was always studied in combination with phosphate binders. Currently, there is insufficient comparative evidence between tenapanor and phosphate binders on relevant outcomes such as serum phosphate reduction, mortality, bone metabolism, and CV events.

The 52-week phase 3 PHREEDOM trial randomized enrolled participants to sevelamer only for safety analysis; an active comparator efficacy assessment was not conducted. The trial was largely open-label (40 weeks), and only 12 weeks were conducted in double-blind, randomized fashion. Participants who discontinued tenapanor during the randomized treatment period were not included in subsequent study periods; thus, the randomized withdrawal and safety extension periods may have been enriched for individuals who were better able to tolerate tenapanor.[5] Another limitation was that insufficient data were collected on the change in dose of concomitant medications that are known to affect serum phosphate (e.g., active vitamin D analogs, calcimimetics).[5]

Clinical Safety:

In clinical trials, the most common AE was diarrhea, reported by 43% to 53% of patients.[2] Most diarrhea events were reported to be mild-to-moderate in severity and resolved over time or with dose reduction.[2] Severe diarrhea was reported in 5% of tenapanor-treated patients.[24] Tenapanor is contraindicated in patients with a known or suspected mechanical GI obstruction.[24] The safety and effectiveness of tenapanor in pediatric patients has not been established.[3]

Look-alike / Sound-alike Error Risk Potential: Tenapanor (IBSRELA) – FDA-approved for treat of adults with irritable bowel syndrome with constipation[25]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Surrogate endpoint: serum phosphate concentration
2) Serum calcium concentration
3) Overall mortality
4) Mortality related to cardiovascular events
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Serum phosphate concentration

Table 4. Pharmacology and Pharmacokinetic Properties.[2]

Parameter	
Mechanism of Action	Sodium hydrogen exchanger 3 (NHE3) inhibitor
Oral Bioavailability	Minimal systemic absorption
Distribution and Protein Binding	Plasma protein binding: 99%
Elimination	Primarily in feces 70-79% as unchanged drug; 9% renal excretion as metabolites
Half-Life	Not determined due to minimal systemic absorption
Metabolism	Metabolized by the CYP3A4/5 primarily to an inactive metabolite, M1

Table 5. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Block GA, et al.[3] MC, DB, PC, Phase 3 RCT 8-week dose finding period followed by 4-week placebo-controlled withdrawal phase	1. Tenapanor 3 mg PO BID 2. Tenapanor 10 mg PO BID 3. Tenapanor 30 mg PO BID 4. Placebo PO BID	Demographics: -Mean age: 56 y -Male: 58% -Race White: 40% Black: 57% Asian: 2% -Baseline serum phosphate: 7.4 mg/dL Key Inclusion Criteria: -Age 18-80 y -ESRD on HD -3 doses PB daily -Serum phosphate 6 to 10 mg/dL Key Exclusion Criteria: - Serum PTH > 1200 pg/mL - Serum phosphate >10 mg/dL -History of IBD or IBS with diarrhea - Diarrhea/loose stool ≥3 stools/day	ITT: 1. 25 2. 23 3. 34 4. 82 PP: 1. 24 2. 22 3. 32 4. 74 Attrition: 1. 1 (4%) 2. 1 (4%) 3. 2 (6%) 4. 8 (10%)	Primary Endpoint: LSMD change in serum phosphate over 4 weeks. (Pooled 1+2+3): 0.02 ± 1.63 mg/dL 4. Placebo: 0.85 ± 1.68 mg/dL LSMD: -0.72 mg/dL 95% CI -1.19 to -0.25 mg/dL P=0.003 Secondary Endpoint: Percent of Patients Achieving serum phosphorus < 5.5 mg/dL at 8 weeks. 1. 24/70 (34.3%) 2. 22/69 (31.9%) 3. 18/65 (27.7%) 4. Not Assessed	NA	AEs after placebo-controlled 4-week phase 1. 4 (16%) 2. 7 (30%) 3. 12 (35%) 4. 21 (26%) Treatment-related AE after initial 8-week phase 1. 24 (32%) 2. 38 (52%) 3. 33 (47%) 4. Not Applicable Diarrhea after initial 8-week phase 1. 24 (32%) 2. 35 (48%) 3. 40 (56%) 4. Not Applicable 95% CI and p-values NR	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1 to tenapanor (3 separate dosing regimens) or placebo using a computer-generated schedule. Baseline characteristics similar in all groups. Performance Bias: Unclear. Study staff and patients blinded to treatment assignment. Method of blinding not described. Adverse effect of diarrhea may have resulted in unblinding. Patients recorded daily bowel habits in an electronic diary every day. Elevated phosphate levels in placebo arm could also lead to unblinding. All tenapanor doses looked alike. No details provided regarding appearance of placebo tablets. Detection Bias: Low. Patients and investigators masked to treatment assignment. Attrition Bias: Low. Attrition rates were similar in all 4 arms. Reporting Bias: Unclear. Protocol available online. Study design and primary efficacy outcome modified twice as study progressed based on FDA feedback. Other Bias: High. Manufacturer funded the trial. Several investigators received financial support from the manufacturer. **Applicability**: Patient: Only adults with ESRD on dialysis were enrolled this study. Cannot extrapolate data to patients not receiving dialysis or children. Renal disease impacts a large proportion of Black patients and a higher percentage of Black patients over White patients were enrolled in this trial. Intervention: Tenapanor formulation and doses are approved by FDA and available in U.S. Comparator: Placebo is appropriate to assess efficacy as an add-on therapy. Outcomes: Reduction in serum phosphate is surrogate outcome for an inhibitor of phosphate absorption. Trial was not long enough to evaluate cardiovascular and mortality outcomes. Setting: 41 sites in the U.S.

2. Pergola PE, et al.[4] AMPLIFY DB, MC, Phase 3 RCT Conducted over a 4-week treatment period while continuing to receive daily PB	1. Tenapanor 30 mg PO BID 2. Placebo PO BID	Demographics: -Mean age: 54 y -Male: 59% -Race White: 50% Black: 43% Asian: 2.5% Other: 4.5% -Baseline serum phosphate: 6.8 mg/dL -Concomitant PB Sevelamer: 49% Non-sevelamer: 51% Key Inclusion Criteria: -Adults undergoing HD or PD -Hyperphosphatemia (5.5-10 mg/dL) despite taking 3 doses of a PB daily Key Exclusion Criteria: - Serum PTH > 1200 pg/mL - Serum phosphate > 10 mg/dL -History of IBD or IBS with diarrhea	ITT: 1. 117 2. 119 PP: 1. 112 2. 116 Attrition: 1. 5 (4%) 2. 3 (3%)	Primary Endpoint: LSMD change in serum phosphorous over 4 weeks. 1. -0.84 2. -0.19 LSMD: -0.65 95% CI -1.01 to -0.29 P<0.001 Secondary Endpoint: Percent of Patients Achieving serum phosphorus < 5.5 mg/dL at 4 weeks. 1.43 (37.1%) 2.26 (21.8%) OR 2.1; P=0.0097	 NA NA	AEs: 1. 60 (51%) 2. 33 (28%) Treatment-related AEs: 1 .51 (44%) 2. 15 (13%) SAE: 1. 3 (2.6%) 2. 5 (4.2%) Diarrhea: 1.50(43%) 2.8 (7%) Nausea: 1. 6 (5%) 2. 3 (2.5%) 95% CI and p-values NR	 NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized via IRT 1:1 to active drug or placebo. Stratified by type of PB (sevelamer, non-sevelamer) and baseline serum phosphorus (< 7.5 or ≥ 7.5 mg/dL). Baseline demographics balanced between groups. Performance Bias: Unclear. Study described as double-blind. Blinding methods not described. Not clear how placebo and tenapanor tablets were formulated to minimize unblinding. Detection Bias: Low. Patients and investigators masked to treatment assignment. Attrition Bias: Low. Attrition rates similar in both arms. Reporting Bias: Low. Protocol available online. All outcomes reported as prespecified. Other Bias: High. Manufacturer funded the trial. Several investigators received financial support from the manufacturer. **Applicability**: Patient: Only adults with ESRD on dialysis were enrolled this study. Cannot extrapolate data to patients not receiving dialysis or children. Intervention: Tenapanor formulation and doses are approved by FDA and available in U.S. However, short study duration limits applicability. Comparator: Placebo is appropriate to establish efficacy as an add-on therapy. Additional comparative evidence with other PBs would be useful. Outcomes: Reduction in serum phosphate is surrogate outcome for an inhibitor of phosphate absorption. Trial was not long enough to evaluate cardiovascular and mortality outcomes. Setting: 46 sites in the U.S.

3. Block G, et al.[5] PHREEDOM MC, Phase 3 RCT 52-week study design: a. 26-weeks OL b. 12 weeks DB, PC , randomized withdrawal period. c. 14 weeks OL safety extension period	1. Tenapanor 30 mg PO BID 2. Placebo PO BID	Demographics: -Mean age: 58 y -Male: 65% -Race White: 48% Black: 45% Other: 6% -Baseline serum phosphate: 7.3 mg/dL Key Inclusion Criteria: -Adults -HD -3 doses of PB daily -Serum phosphate 6-10 mg/dL Key Exclusion Criteria: Serum PTH > 1200 pg/mL - Serum phosphate > 10 mg/dL -History of IBD or IBS with diarrhea	12-week period ITT: 1. 128 2. 127 12-week period PP: 1. 99 2. 99 Attrition: 1. 29 (23%) 2. 28 (22%)	Primary Endpoint: LSMD change in serum phosphorous over 12 weeks: 1. 0.4 mg/dL 2. 1.8 mg/dL LMSD: -1.37 mg/dL 95% CI -1.92 to -0.82 P<0.001	NA	AEs after 12-week phase 1.58 (46%) 2.70 (56%) AEs leading to drug discontinuation during 12-week phase 1.11 (9%) 2.17 (13%) Diarrhea during 12 week-phase 1. 5 (4%) 2. 2 (2%) 95% CI and p-values NR		**Risk of Bias (low/high/unclear)**: Selection Bias: High. Patients randomized 1:1 to tenapanor or placebo. Method of randomization not described. Baseline characteristics balanced between groups. Performance Bias: Unclear. Study described as double-blind for 12 weeks during placebo-controlled phase. Blinding methods not described. Not clear how placebo and tenapanor tablets were formulated to minimize unblinding. Detection Bias: Unclear. 40 weeks of this study were open label. Attrition Bias: High. Extensive attrition in both arms. Reporting Bias: Low. Protocol available online. All outcomes reported as prespecified. Other Bias: High. Manufacturer funded the trial. Several investigators received financial support from the manufacturer. **Applicability**: Patient: Only adults with ESRD on dialysis were enrolled this study. Cannot extrapolate data to patients not receiving dialysis or children. Intervention: Tenapanor formulation and doses are approved by FDA and available in U.S. Comparator: Placebo is an appropriate to establish efficacy. Additional comparative evidence with other PBs would be useful. Sevelamer included as safety control only, comparative efficacy not evaluated. Outcomes: Reduction in serum phosphate is surrogate outcome for an inhibitor of phosphate absorption. Trial was not long enough to evaluate cardiovascular and mortality outcomes. Setting: 104 sites in the U.S.

Abbreviations: AE = adverse effect; ARR = absolute risk reduction; BID = twice daily; CI = confidence interval; CKD = chronic kidney disease; DB = double-blind; dL = deciliter; ESRD = end stage renal disease; FDA = Food and Drug Administration; HD = hemodialysis; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; IRT = interactive response technology; ITT = intention to treat; mg = milligram; MC = multi-center; LSMD = least squares mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OL = open label; PB = phosphate binder; PC = placebo-controlled; PD = peritoneal dialysis; pg = picograms; PO = oral; PP = per protocol; PTH = parathyroid hormone; RCT = randomized controlled trial; SAE = serious adverse effect; U.S.=United States; y = years.

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Appendix 1: Current Preferred Drug List

Generic	Brand	Route	Form	PDL
calcium acetate	CALCIUM ACETATE	ORAL	CAPSULE	Y
calcium acetate	CALCIUM ACETATE	ORAL	TABLET	Y
calcium acetate	ACETICAL 170	ORAL	TABLET	Y
calcium acetate	CALCIUM ACETATE	ORAL	TABLET	Y
calcium acetate	CALPHRON	ORAL	TABLET	Y
sevelamer carbonate	RENVELA	ORAL	TABLET	Y
sevelamer carbonate	SEVELAMER CARBONATE	ORAL	TABLET	Y
sevelamer HCl	RENAGEL	ORAL	TABLET	Y
sevelamer HCl	SEVELAMER HCL	ORAL	TABLET	Y
calcium acetate	CALCIUM ACETATE	ORAL	TABLET	N
calcium carbonate/mag carb	MAGNEBIND 300	ORAL	TABLET	N
calcium carbonate/mag carb	MAGNEBIND 400	ORAL	TABLET	N
ferric citrate	AURYXIA	ORAL	TABLET	N
lanthanum carbonate	FOSRENOL	ORAL	POWD PACK	N
lanthanum carbonate	FOSRENOL	ORAL	TAB CHEW	N
lanthanum carbonate	LANTHANUM CARBONATE	ORAL	TAB CHEW	N
sevelamer carbonate	RENVELA	ORAL	POWD PACK	N
sevelamer carbonate	SEVELAMER CARBONATE	ORAL	POWD PACK	N
sucroferric oxyhydroxide	VELPHORO	ORAL	TAB CHEW	N
tenapanor HCl	XPHOZAH	ORAL	TABLET	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) 1996 to January Week 2 2024; Ovid MEDLINE(R) In-Process & In-Data-Review Citations 1946 to January 18, 2024

1	calcium acetate.mp.	397
2	exp Sevelamer/	707
3	sucroferric oxyhydroxide.mp.	90
4	ferric citrate.mp.	977
5	Lanthanum/	2807
6	tenapanor.mp.	72
7	Phosphorus Metabolism Disorders/ or Kidney Failure, Chronic/ or Hyperphosphatemia/	70875
8	1 or 2 or 3 or 4 or 5 or 6	4754
9	7 and 8	782
10	limit 9 to (humans and yr="2021 -Current" and (clinical trial, all or clinical trial, phase iii or comparative study or consensus development conference or consensus development conference, nih or controlled clinical trial or evaluation study or guideline or meta-analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review"))	22

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XPHOZAH® safely and effectively. See full prescribing information for XPHOZAH.

XPHOZAH (tenapanor) tablets, for oral use
Initial U.S. Approval: 2019

----------INDICATIONS AND USAGE----------
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 (1).

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage: 30 mg orally twice daily before the morning and evening meals (2.1).
- Manage serum phosphorus levels and tolerability with dosage adjustments (2.1).
- Take just prior to the first and last meals of the day (2.2).
- Instruct patients not to take right before a hemodialysis session, and instead take right before the next meal following dialysis (2.2).

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 10 mg, 20 mg, 30 mg (3).

----------CONTRAINDICATIONS----------
Pediatric patients under 6 years of age (4).
Patients with known or suspected mechanical gastrointestinal obstruction (4).

----------WARNINGS AND PRECAUTIONS----------
Patients may experience severe diarrhea (5.1).

----------ADVERSE REACTIONS----------
Most common adverse reaction in the combined clinical trials was diarrhea, reported by 43-53% of patients (6).

----------DRUG INTERACTIONS----------
- OATP2B1 Substrates: Potential for reduced exposure of the concomitant drug (e.g., enalapril). Monitor for signs related to loss of efficacy and adjust the dosage of the concomitantly administered drug as needed (7.1).
- Sodium Polystyrene Sulfonate (SPS): Separate administration by at least three hours (7.2).

To report SUSPECTED ADVERSE REACTIONS, contact Ardelyx at 1-844-974-6924 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2023

Phosphate Binders and Absorption Inhibitors

Goal(s):
- Promote use of preferred drugs for OHP-funded diagnoses.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:
- Up to 12 months

Requires PA:
- Non-preferred phosphate binders

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Is this an OHP-funded diagnosis?	**Yes:** Go to #3	**No:** Go to #7
3. Is the request for an FDA-approved indication?	**Yes:** Go to #4	**No:** Go to #7
4. Is the request for tenapanor?	**Yes:** Go to #5	**No:** Go to #6
5. Is the request to use tenapanor as add-on therapy to a phosphate binder in an adult with chronic kidney disease receiving dialysis who has had an inadequate response to phosphate binders or who is intolerant of any dose of a phosphate binder?	**Yes:** Approve for 1 year	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Has the patient tried or have contraindications to a preferred phosphate binder (i.e., calcium acetate, sevelamer carbonate)?	**Yes:** Approve for 1 year	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred phosphate binder product.

7.

- RPh only: All other indications need to be evaluated as to whether use is for an OHP-funded diagnosis.
- If funded and clinic provides supporting literature, approve for up to 12 months.
- If not funded:
  - If current age < 21 years; Is there documentation that the condition is of sufficient severity that it impacts the patient's health (e.g., quality of life, function, growth, development, ability to participate in school, perform activities of daily living, etc)? AND
  - Is the request for a preferred product OR has the patient failed to have benefit with, or have contraindications or intolerance to, at least 2 preferred products?
    - Is yes, may approve for up to 12 months.
    - If No, Deny (medical appropriateness)
- If current age ≥ 21 years, Deny; not funded by the OHP.

P&T Review: *4/24 (DM); 8/21 (DM); 1/16 (AG); 11/12; 9/12; 9/10*
Implementation: *TBD; 5/1/16; 2/21/13*