09-J5000-13

Original Effective Date: 04/01/25

Reviewed: 03/12/25

Revised: 00/00/00

Subject: Tenapanor (Xphozah) Tablet

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:

Hyperphosphatemia in chronic kidney disease (CKD) patients is a potentially life altering condition that can lead to cardiovascular calcification, metabolic bone disease (renal osteodystrophy) and the development of secondary hyperparathyroidism (SHPT). In clinical practice, the management of hyperphosphatemia is focused on controlling factors that are responsible for the intake and removal of phosphate from the body. There are three main strategies for correcting hyperphosphatemia: dietary restriction of phosphate intake, removing phosphate with adequate dialysis, and reducing intestinal absorption using phosphate binders. Reducing dietary phosphate intake can be challenging, as it is usually incompatible with the recommended daily protein intake, and diet control alone is insufficient. Currently available dialysis techniques are usually ineffective in normalizing phosphate concentration. Using phosphate binders to assist in the management of hyperphosphatemia in patients undergoing dialysis is common, with more than 95% of patients being prescribed phosphate binders. Tenapanor is a first-in-class, minimally absorbed, small-molecule sodium-hydrogen exchanger 3 (NHE3) inhibitor with a unique mechanism of action that effectively reduces phosphate levels. Inhibition of gastrointestinal NHE3 results in increased sodium and water excretion as well as reduced paracellular permeability to phosphate. This modest intracellular proton retention generated is proposed to modulate tight junction proteins (claudins) resulting in increased transepithelial electrical resistance (TEER) and reducing permeability specific to phosphate, thereby decreasing phosphate absorption through the paracellular pathway.

The ability of tenapanor to lower serum phosphorus in adults with CKD on dialysis was evaluated in 3 trials: TEN-02-201 [NCT02675998], TEN-02-301 [NCT03427125]), and TEN-02-202 [NCT03824587]). 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 1.5 mg/dL (compared to pre-wash out value) and a serum phosphorus level of at least 6 mg/dL and not more than 10 mg/dL.

Study TEN-02-301 (PHREEDOM trial) was a 52-week phase 3 study. It included a 26-week randomized, active-controlled open-label treatment period, in which patients were randomized (3:1) to tenapanor 30 mg twice daily for 26 weeks (treatment period) or sevelamer carbonate (52-week safety period). Patients completing 26 weeks of treatment with tenapanor entered into a blinded placebo-controlled randomized withdrawal period and were rerandomized (1:1) to tenapanor or placebo for 12 weeks. These patients were eligible to enter the 14-week safety extension period. The primary efficacy end point was the difference in the change in serum phosphate from the end of the randomized treatment period to the end of the randomized withdrawal period, among participants who achieved a greater than or equal to 1.2 mg/dL decrease in serum phosphate during the randomized treatment period (efficacy analysis set). Efficacy was also evaluated in the intention-to-treat (ITT) analysis set. In the ITT analysis set, during the randomized withdrawal phase, the phosphorus concentration rose in the placebo group by 0.7 mg/dL (95% CI: (0.2, 1.1), p=0.002) relative to patients who remained on tenapanor. In the efficacy analysis set, the difference in estimated mean change in serum phosphate level between tenapanor and placebo from the beginning to the end of the randomized withdrawal period was -1.4 mg/dL (P<0.0001). Loosened stools were the most frequently reported adverse event.

Study TEN-02-201 included an 8-week randomized, double-blind period that evaluated three dosing regimens of tenapanor (3 mg twice daily, 10 mg twice daily, or a titration regimen). This period was followed by a 4-week placebo-controlled randomized-withdrawal phase, during which patients were rerandomized 1:1 to their current tenapanor treatment or to placebo. During the randomized withdrawal phase, the phosphorus concentration rose in the placebo group by 0.7 mg/dL (95% CI: (0.3, 1.2), p=0.003) relative to patients who remained on tenapanor.

Study TEN-02-202 was a randomized, parallel-group, double-blind, placebo-controlled study that evaluated the effect of tenapanor 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 5.5 mg/dL. During the 4-week period, the serum phosphorus decreased by 0.7 mg/dL (95% CI: (0.3, 1.0), p=0.0004) in the add-on tenapanor group as compared to the add-on placebo group.

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 tenapanor (Xphozah) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “7”):

1. The member has a diagnosis of chronic kidney disease (CKD).
2. The member is on chronic maintenance dialysis.
3. The member has a serum phosphorus level of at least 5.5 mg/dL.
4. **ONE** of the following (“a”, “b”, or “c”):
    a. **ALL** of the following (“i”, “ii”, and “iii”):

i. The member has tried and had an inadequate response to at least **ONE** generic phosphate binder (calcium carbonate, calcium acetate, calcium with magnesium, lanthanum carbonate, sevelamer carbonate, or sevelamer HCl).

ii. The member has tried and had an inadequate response to ferric citrate (Auryxia).

iii. The member will be using tenapanor in combination with phosphate binder therapy [calcium carbonate, calcium acetate, calcium with magnesium, ferric citrate (Auryxia), lanthanum carbonate, sevelamer carbonate, sevelamer HCl, or sucroferric oxyhydroxide (Velphoro)].

b. The member is intolerant or has a hypersensitivity to generic phosphate binder therapy **AND** ferric citrate (Auryxia).

c. The member has an FDA labeled contraindication to **ALL** generic phosphate binders **AND** ferric citrate (Auryxia).

5. The prescriber is a specialist in the area of the member's diagnosis (e.g., nephrologist), or the prescriber has consulted with a specialist in the area of the member's diagnosis.
6. The member does **NOT** have a known or suspected mechanical gastrointestinal obstruction (which is an FDA-labeled contraindication to therapy).
7. The member is 18 years of age or older, **OR** the member's age is within FDA labeling for the requested indication.
8. The dosage does not exceed 30 mg twice daily **OR** 60 tablets per 30 days.

Approval duration: 6 months

Continuation of tenapanor (Xphozah) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

1. An authorization or reauthorization for tenapanor (Xphozah) has been previously approved by Florida Blue or another health plan in the past 2 years for a member with CKD on chronic maintenance dialysis, **OR** the member has previously met **ALL** indication-specific criteria.
2. The member has had clinical benefit with the requested agent (i.e., reduction in serum phosphorus level).
3. **ONE** of the following ("a", "b", or "c"):
   a. The member is using tenapanor in combination with phosphate binder therapy [calcium carbonate, calcium acetate, calcium with magnesium, ferric citrate (Auryxia), lanthanum carbonate, sevelamer carbonate, sevelamer HCl, or sucroferric oxyhydroxide (Velphoro)].
   b. The member is intolerant or has a hypersensitivity to phosphate binder therapy.
   c. The member has an FDA labeled contraindication to **ALL** phosphate binders.
4. Prescriber is a specialist in the area of the member's diagnosis (e.g., nephrologist), or the prescriber has consulted with a specialist in the area of the member's diagnosis.
5. The member does **NOT** have a known or suspected mechanical gastrointestinal obstruction (which is an FDA-labeled contraindication to therapy).
6. The dosage does not exceed 30 mg twice daily **OR** 60 tablets per 30 days.

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 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
- The recommended dosage is 30 mg orally twice daily before the morning and evening meals. Monitor serum phosphorus and adjust the dosage as needed to manage gastrointestinal tolerability. Instruct patients not to take tenapanor right before a hemodialysis session, and instead take right before the next meal following dialysis, as patients may experience diarrhea after taking.

Dose Adjustments

- Dosage may be reduced (e.g., 20 mg BID) based on serum phosphorus and gastrointestinal tolerability.
- Hepatic impairment - no dosage adjustments are needed.
- Renal impairment - no dosage adjustments are needed.

Drug Availability

- 20- and 30-mg oval, biconvex, film-coated tablets supplied in bottles containing 60 or 14 tablets.
- Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). Keep bottle tightly closed to protect from moisture. Store and dispense in original bottle with the desiccant.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- Patients under 6 years of age because of the risk of diarrhea and serious dehydration.
- Patients with known or suspected mechanical gastrointestinal obstruction.

Precautions/Warnings

- **Diarrhea**: Diarrhea was the most common adverse reaction in tenapanor-treated patients with CKD on dialysis. In clinical trials, diarrhea was reported in up to 53% of patients, reported as severe in 5%, and associated with dehydration and hyponatremia in less than 1% of patients. Treatment with Xphozah should be discontinued in patients who develop severe diarrhea.

- **OATP2B1 Substrates**: Tenapanor is an inhibitor of intestinal uptake transporter, OATP2B1. Drugs which are substrates of OATP2B1 (for example, enalapril) may have reduced exposures when concomitantly taken with tenapanor. Monitor for signs related to loss of efficacy and adjust the dose of concomitantly administered drug as needed.
- **Sodium Polystyrene Sulfonate**: Separate administration of tenapanor and sodium polystyrene sulfonate (SPS) by at least 3 hours. SPS binds to many commonly prescribed oral medicines.

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-10 Diagnosis Codes That Support Medical Necessity

E83.39	Other disorders of phosphorus metabolism

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.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Block GA, Bleyer AJ, Silva AL, et al. Safety and Efficacy of Tenapanor for Long-term Serum Phosphate Control in Maintenance Dialysis: A 52-Week Randomized Phase 3 Trial (PHREEDOM). Kidney360. 2021 Aug 27;2(10):1600-1610.
2. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2025. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 02/27/25.
3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011). 2017 Jul;7(1):1-59. Epub 2017 Jun 21. Erratum in: Kidney Int Suppl (2011). 2017 Dec;7(3):e1.
4. Kovesdy CP, Adebiyi A, Rosenbaum D, et al. Novel Treatments from Inhibition of the Intestinal Sodium-Hydrogen Exchanger 3. Int J Nephrol Renovasc Dis. 2021 Dec 1;14: 411-420.
5. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 02/27/25.
6. Pergola PE, Rosenbaum DP, Yang Y, Chertow GM. 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.
7. Scialla JJ, Kendrick J, Uribarri J, et al. State-of-the-Art Management of Hyperphosphatemia in Patients With CKD: An NKF-KDOQI Controversies Perspective. Am J Kidney Dis. 2021 Jan;77(1):132-141.
8. Shaman AM, Kowalski SR. Hyperphosphatemia Management in Patients with Chronic Kidney Disease. Saudi Pharm J. 2016;24(4):494-505.
9. Xphozah (tenapanor tablet, film coated) [package insert]. Ardelyx, Inc. Waltham, MA: October 2023.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/12/25.

GUIDELINE UPDATE INFORMATION:

04/01/25	New Medical Coverage Guideline.