BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

XPHOZAH® (tenapanor) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Xphozah (tenapanor) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of chronic kidney disease (CKD) on dialysis needing **add-on therapy** to reduce serum phosphorus who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy

4. Documentation of **ALL** of the following:

a. Receiving dialysis 3-times per week for at least 3-months
b. Kt/V urea is at least 1.2 (a measure of dialysis adequacy) within 30-days
c. Receiving at least 3-doses per day of a phosphate binder which will be continued
d. Doses of vitamin D and/or calcimimetic have been stable for at least 4-weeks

5. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
    a. Phosphorus level is between 5.5 mg/dL and 10 mg/dL inclusive
    b. Serum calcium
    c. Serum albumin
    d. Intact parathyroid hormone (iPTH)

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Individual has documented failure, contraindication per FDA label, intolerance, or is not a candidate for **TWO** of the following:
    a. Lanthanum (generic or branded Fosrenol)
    b. Sevelamer HCl (generic or branded Renagel)
    c. Sevelamer carbonate (generic or branded Renvela)

8. The individual does **NOT** have the FDA-label contraindication of known or suspected mechanical gastrointestinal obstruction

9. Individual will not use Xphozah (tenapanor) with Ibsrela (tenapanor)

10. Individual does not have any of the following;
    a. Serum parathyroid hormone of more than 1,200 pg/mL
    b. Clinical signs of hypovolemia
    c. History of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome
    d. Scheduled for kidney transplant
    e. Diarrhea or loose stools 3 or more times per day for 2 or more days per week

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Xphozah (tenapanor) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Nephrologist

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
    a. Achieved and maintains a serum phosphorus levels between 3.5-5.5 mg/dL (1.13-1.78 mmol/L)
    b. Achieved and maintains a serum levels of corrected total calcium between 8.4-9.5 mg/dL (2.10-2.37 mmol/L)

c. Achieved and maintains iPTH (second-generation PTH assay) levels between 150-300 pg/mL (or 80-160 pg/mL using the bio-intact PTH assay)

3. Individual has been adherent with the medication and still requires dialysis

4. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Severe diarrhea
   b. Severe dehydration
   c. Severe hyponatremia

6. Individual will not use Xphozah (tenapanor) with Ibsrela (tenapanor)

7. Individual does not have any of the following;
   a. Clinical signs of hypovolemia
   b. History of inflammatory bowel disease or diarrhea predominant irritable bowel syndrome
   c. Scheduled for kidney transplant
   d. Diarrhea or loose stools 3 or more times per day for 2 or more days per week

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Xphozah (tenapanor) 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. Tenapanor 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.

Tenapanor is also marketed as Ibsrela® which is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

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Changes in bone mineral metabolism & deviations in calcium-phosphate balance occur early in CKD. These changes progress as kidney function declines. They are grouped under the term Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) which includes renal osteodystrophy and extra-skeletal (vascular) calcification related to these abnormalities. Renal osteodystrophy includes osteitis fibrosa (hyperparathyroidism), osteomalacia, and adynamic bone disease. Patients with CKD-MBD are at higher risk of death.

CKD leads to hyperphosphatemia and a number of chronic disturbances of calcium-phosphate homeostasis. As kidney function declines, the ability to regulate and eliminate phosphorus declines. There are several complications from hyperphosphatemia: 1) conversion of 24-hydroxyvitamin D to 1, 25-dihydroxyvitamin D (calcitriol) is inhibited; 2) there is a decrease in the intestinal absorption of calcium leading to hypocalcemia; 3) there is development of renal bone loss; and 4) extraosseous calcification of soft tissue and vasculature occurs. Risk for death is increased with hyperphosphatemia > 6.5 mg/dL.

Low levels of calcitriol and low levels of calcium with hyperphosphatemia stimulate the secretion of parathyroid hormone (PTH). Secondary hyperparathyroidism contributes to abnormal bone metabolism in CKD. PTH secretion is regulated by extracellular calcium, extracellular phosphate, calcitriol, and fibroblast growth factor 23. A change in calcium concentration is sensed by a sensitive calcium-sensing receptor (CaSR) on the surface of parathyroid cells. A decrease in serum ionized calcium concentration produces a large increase in serum PTH concentration within minutes.

Management of the bone disorder includes maintain calcium and phosphorus balance and vitamin D supplementation. CKD patients on dialysis should have: a goal serum phosphorus level between 3.5-5.5 mg/dL (1.13-1.78 mmol/L) and a goal total serum calcium level (corrected for serum albumin) of 8.4-9.5 mg/dL (2.10-2.37 mmol/L).

Management of secondary hyperparathyroidism in dialysis patients involves the administration of some combination of: phosphate binders (either calcium-containing or non-calcium-containing binders) such as calcitriol or synthetic vitamin D analogs or calcimimetic (cinacalcet, etelcalcetide). The goal in secondary hyperparathyroidism is either: an intact parathyroid hormone (iPTH; second-generation PTH assay) between 150-300 pg/mL or a biointact PTH assay between 80-160 pg/mL.

The data on phosphate binders are inconclusive as to whether there is a difference in long-term clinical outcome benefit among the phosphate binders (calcium-based phosphate binders compared to non-calcium-based phosphate binders). All available phosphate lowering medications (calcium salts, aluminum salts, magnesium salts, sevelamer and lanthanum carbonate) are effective in lowering serum phosphorus levels.

Calcium-based phosphate binders should not be used in the following: persistent or recurrent hypercalcemia (a corrected calcium of > 10.2 mg/dL), arterial calcification, or adynamic bone disease. They may be used in the following: hypocalcemic patients or normocalcemic patients who have no evidence of vascular calcification or adynamic bone disease.

Aluminum hydroxide should not be used for the long-term, chronic treatment of hyperphosphatemia, because of the risk for aluminum toxicity. Aluminum hydroxide may be used for short-term therapy (a single, four-week course) for severe hyperphosphatemia.

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Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Calculation for corrected calcium:

Corrected calcium = serum calcium + 0.8 (4 – serum albumin)
Ex. For measured calcium 9.9 mg/dl; albumin 3.2 gm/dl
Corrected calcium = 9.9 + 0.8 (4 – 3.2)
Corrected calcium = 10.54 (10.5 mg/dl)

Stages of Chronic Kidney Disease (CKD):

Stage	GFR (mL/min/1.73 m^2)	
G1	≥ 90	Normal kidney or high
G2	60-89	Mildly reduced kidney function
G3 A	45-59	Mild to moderately reduced kidney function
G3 B	30-44	Moderate to severely reduced kidney function
G4	15-29	Severely reduced kidney function
G5	< 15 or on dialysis	End stage kidney failure (sometimes called established renal failure)
In the absence of evidence of kidney damage, neither G1 nor G2 fulfill the criteria for CKD		

Resources:

Xphozah (tenapanor) product information, revised by Ardelyx, Inc. 10-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Quarles LD, Kendrick J. Management of hyperphosphatemia in adults with chronic kidney disease. In: UpToDate, Berns JS, Taylor EN (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2024. Topic last updated September 27, 2024. Accessed January 08, 2025.

Nitta K, Itoyama S, Ikejiri K, et al.: Randomized study of tenapanor added to phosphate binders for patients with refractory hyperphosphatemia. Kidney Int Rep . 2023 Aug 13;8(11):2243-2253. DOI: 10.1016/j.ekir.2023.08.003. Accessed December 02, 2023. Re-evaluated January 08, 2025.

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; 2:1600–1610, 2021. doi: https://doi.org/10.34067/KID.0002002021. Accessed December 02, 2023. Re-evaluated January 08, 2025.

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 June; 32(6):1465–1473. doi: 10.1681/ASN.2020101398. Accessed December 04, 2023. Re-evaluated January 08, 2025.

Shigematsu T, Une Y, Ikejiri K, et al.: Therapeutic effects of add-on tenapanor for hemodialysis patients with refractory hyperphosphatemia. Am J Nephrol. 2021 Aug; 52(6): 496–506. doi: 10.1159/000516156. Accessed December 03, 2023. Re-evaluated January 08, 2025.

Block GA, Rosenbaum, Yan A, Chertow GM. Efficacy and safety of tenapanor in patients with hyperphosphatemia receiving maintenance hemodialysis: A randomized phase 3 trial. J Am Soc Nephrol. 2019 Apr; 30(4): 641–652. DOI: 10.1681/ASN.2018080832. Accessed December 02, 2023. Re-evaluated January 08, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03824587: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy of Tenapanor as Adjunctive Therapy to Phosphate Binder Therapy in End-Stage Renal Disease (ESRD) Subjects With Hyperphosphatemia. Available from: http://clinicaltrials.gov. Last update posted March 06, 2023. Last verified February 2023. Accessed December 02, 2023. Re-evaluated January 08, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT03427125: A 26-Wk, Phase 3, Open Label (OL) Study With a 12-Wk, Placebo-Controlled, Randomized Withdrawal Period and an OL Safety Extension to Evaluate the Safety and Efficacy of Tenapanor to Treat Hyperphosphatemia in CKD Patients on Dialysis. Available from: http://clinicaltrials.gov. Last update posted June 29, 2023. Last verified June 2023. Accessed December 02, 2023. Re-evaluated January 08, 2025.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT02675998: An 8-week, Multicenter, Randomized, Double-Blind, Parallel Group Study With a 4-week, Placebo-Controlled, Randomized Withdrawal Period to Evaluate the Efficacy, Safety, and Tolerability of Tenapanor to Treat Hyperphosphatemia in End-Stage Renal Disease Patients on Hemodialysis (ESRD-HD). Available from: http://clinicaltrials.gov. Last update posted August 10, 2020. Last verified August 2020. Accessed December 02, 2023. Re-evaluated January 08, 2025.