tenapanor (Ibsrela®, Xphozah®)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO170

Description

Tenapanor (e.g., Ibsrela, Xphozah) is an orally administered sodium/hydrogen exchange 3 (NHE3) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
tenapanor (Ibsrela)	Irritable bowel syndrome with constipation (IBS-C)	50 mg tablets	60 tablets/30 days
tenapanor (Xphozah)	Reduction of 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	10 mg tablets	60 tablets/30 days
		20 mg tablets	
		30 mg tablets	

Irritable bowel syndrome with constipation (IBS-C)

Initial Evaluation

I. **Tenapanor (Ibsrela)** may be considered medically necessary when the following criteria below are met:
   A. The member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
   C. A diagnosis of **irritable bowel syndrome with constipation (IBS-C)** when the following are met:
      1. The member has had an inadequate response, or intolerance to, all of the following, unless all are contraindicated (*Please note: These agents may be subject to additional prior authorization review):
         i. Dietary and lifestyle modifications (e.g., removal of offending foods, increased fiber intake) and increased physical activity; **AND**
         ii. At least one osmotic laxative (e.g., polyethylene glycol); **AND**
         iii. Plecanatide (Trulance); **AND**
         iv. Lubiprostone or Amitiza*; **AND**

v. Linaclotide (Linzess)*

II. Tenapanor (Ibsrela) is considered investigational when used for all other conditions, including but not limited to:
   A. Hyperphosphatemia
   B. Chronic kidney disease
   C. Irritable bowel syndrome with diarrhea
   D. Mixed irritable bowel syndrome
   E. Chronic idiopathic constipation
   F. Opioid-induced constipation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has a diagnosis of irritable bowel syndrome with constipation (IBS-C); **AND**
IV. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in complete spontaneous bowel movements per week from baseline, reduction in abdominal pain)

Supporting Evidence

I. Tenapanor (Ibsrela) is approved by the US Food and Drug Administration (US-FDA) for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.
II. Given the complexities involved in diagnosis and management of IBS-C, as well as required monitoring for adverse events and therapy response, therapy decisions regarding initiation of tenapanor (Ibsrela) must be made by, or under the supervision of, a specialist practicing in this setting (e.g., gastroenterologist).
III. Tenapanor (Ibsrela) is a sodium/hydrogen exchange 3 (NHE3) inhibitor acting specifically in the GI tract, with minimal systemic availability following oral administration. Inhibition of NHE3 leads to a reduction in dietary sodium absorption and an increase in intracellular protons across membranes in the GI tract, which results in reduction of phosphate absorption from the small intestine and colon. Additionally, consequent increase in sodium and phosphorus content in the stool, decreased urinary sodium and phosphorus excretion, and increased water secretion into the intestinal lumen and the increased stool water content leads to loosened stool consistency and increased bowel movement frequency.
IV. Tenapanor (Ibsrela) has a Black Box Warning for serious dehydration in pediatric patients and has not been evaluated in any pediatric population to date. It is contraindicated in those less

than six years of age and comes with a recommendation to avoid use in those less than 12 years of age due to animal studies showing cause of death to be dehydration in young juvenile rats. Additionally, tenapanor (Ibsrela) is also contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.

V. **Irritable Bowel Syndrome with Constipation (IBS-C):** Tenapanor (Ibsrela) was evaluated in two double-blind, placebo-controlled, randomized trials in adult patients –T3MPO-2 and T3MPO-1. The majority of subjects were female (83%), white, and all met Rome III criteria for IBS-C. This requires a pain score of at least three on a 0-10 scale, less than three complete spontaneous bowel movements (CSBMs) per week, and less than five spontaneous bowel movements (SBMs) per week.
    - The primary outcome was proportion of responders, defined as achieving both of the following for at least six of the first 12 weeks of the trials: an increase of at least one CSBM per week on average and a reduction of 30% in weekly average abdominal pain score compared to baseline.
    - T3MPO-2: 620 subjects were evaluated for 26 weeks of treatment. Responders active vs. placebo: 37% vs. 24% (CI 6-20%). Difference from placebo 13%.
    - T3MPO-1: 606 subjects were evaluated for 12 weeks and then were re-randomized to active drug or placebo for a 4-week withdrawal period. Responders active vs. placebo: 27% vs. 19% (CI: 2-15%). Difference from placebo 8%.

VI. The quality of the evidence is considered low given the invalidated subjective endpoints used to determine efficacy and the short duration of therapy evaluated for safety and efficacy.

VII. First-line treatment options for the treatment of IBS-C include dietary modifications, increased fiber intake, and physical activity. Adjunctive pharmacotherapy includes over-the-counter osmotic laxatives. When lifestyle modifications and osmotic laxatives fail to produce sufficient relief of constipation, further pharmacological interventions are indicated. The 2021 American College of Gastroenterology (ACG) clinical guidelines for management of IBS-C recommend use of guanylate cyclase activators (e.g., linaclotide [Linzess], plecanatide [Trulance]) and chloride channel activator (e.g., lubiprostone [Amitiza]) as recommended therapeutic options based on high and moderate quality of clinical evidence, respectively. As of March 2022, the ACG guidelines do not include tenapanor (Ibsrela) as a recommended agent for the treatment of IBS-C. Based on the clinical evidence showing limited treatment effect and lack of place in therapy information, usability of tenapanor (Ibsrela) is uncertain at this time. Thus, use of non-pharmacologic agents and other established therapies are warranted prior to payment consideration for tenapanor (Ibsrela).

References:

1. Ibsrela [Prescribing Information]. Ardelyx, Inc. Fremont, CA. 2019.
2. Zelnorm [Prescribing Information]. Sloan Pharma/WorldMeds LLC. Louisville, KY. 2019.
3. Moayyedi P, Mearin F, Azpiroz F, et al. Irritable bowel syndrome diagnosis and management: A simplified algorithm for clinical practice. United European Gastroenterol J. 2017;5(6):773-788.

4. Chey WD, Lembo AJ, Rosenbaum DP. Efficacy of Tenapanor in Treating Patients With Irritable Bowel Syndrome With Constipation: A 12-Week, Placebo-Controlled Phase 3 Trial (T3MPO-1). Am J Gastroenterol. 2020 Feb;115(2):281-293.
5. Chey WD, Lembo AJ, Yang Y, Rosenbaum DP. Efficacy of Tenapanor in Treating Patients With Irritable Bowel Syndrome With Constipation: A 26-Week, Placebo-Controlled Phase 3 Trial (T3MPO-2). Am J Gastroenterol. 2021 Jun 1;116(6):1294-1303.
6. Weinberg D.S., Smalley W. Heidelbaugh J.J., et al. American Gastroenterological Association institute guidelines on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014;144: 1146-1148.
7. Lacy BE, Pimentel M, Brenner DM, Chey WD, Keefer LA, Long MD, Moshiree B. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021 Jan 1;116(1):17-44.

Hyperphosphatemia in Chronic Kidney Disease (CKD)

Initial Evaluation

I. **Tenapanor (Xphozah)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. The medication is prescribed by, or in consultation with, a nephrologist; **AND**
   C. A diagnosis of **hyperphosphatemia in Chronic Kidney Disease (CKD); AND**
      1. Member is currently receiving and has been stable on maintenance hemodialysis or peritoneal dialysis for 3 months; **AND**
      2. Presence of hyperphosphatemia, defined as serum phosphate levels >5.5mg/dL within the past 3 months; **AND**
      3. Provider attestation that hyperphosphatemia is not due to a reversible/untreated secondary cause (e.g., hypoparathyroidism, high phosphate containing medications/formulations); **AND**
   D. The member has had an inadequate response, contraindication, or intolerance to, all of the following:
      1. Dietary and lifestyle modifications (e.g., low phosphorus diet); **AND**
      2. Three of the following phosphate binders:
         i. Sevelamer hydrochloride or sevelamer carbonate*
         ii. Lanthanum carbonate*
         iii. Sucroferric oxyhydroxide (Velphoro)*
         iv. Ferric Citrate (Auryxia)*

II. Tenapanor (Xphozah) is considered investigational when used for all other conditions, including but not limited to:
   A. Non-dialysis dependent hyperphosphatemia in chronic kidney disease
   B. Irritable bowel syndrome with diarrhea
   C. Mixed irritable bowel syndrome
   D. Chronic idiopathic constipation
   E. Opioid-induced constipation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member has a diagnosis of hyperphosphatemia in chronic kidney disease (CKD); **AND**
IV. Member is currently receiving and has been stable on maintenance hemodialysis or peritoneal dialysis for 3 months; **AND**
V. Member has exhibited improvement or stability of disease symptoms (e.g., reduction of serum phosphate from baseline or maintenance of serum phosphorus levels within normal range <5.5mg/dL)

Supporting Evidence

I. Excess serum phosphate levels promote vascular calcification and induces endothelial dysfunction leading to cardiovascular toxicity and disease. If left untreated, hyperphosphatemia is correlated with vascular and tissue calcifications, bone pain/fractures, and worsening secondary hyperparathyroidism.
II. The diagnosis and management of chronic kidney disease (CKD) in patients on dialysis requires detailed clinical examination, frequent monitoring of labs, and highly individualized treatment regimens. Given the complexities of treatment of hyperphosphatemia in this patient population, supervision or consultation with a nephrologist is required.
III. CKD is defined as abnormalities of kidney structure or function present for greater than 3 months. Estimated Glomerular filtration rate (eGFR) category (G1-G5) is used to categorize CKD. An eGFR ≥90 mL/min/1.73m^2 (G1) is normal or high, eGFR between 60-89 mL/min/1.73m^2 (G2) is considered mildly decreased, 45-59 mL/min/1.73m^2 (G3a) is mildly to moderately decreased, 30-44 mL/min/1.73m^2 (G3b) is moderately to severely decreased, 15-29 mL/min/1.73m^2 (G4) is severely decreased, and <15 ml/min/1.73m^2 (G5) or requiring dialysis is considered kidney failure. Within clinical guidelines, recommendations for treatment of hyperphosphatemia applies to patients in categories G3a-G5d (i.e., GFR <60 mL/min).
IV. Tenapanor (Xphozah) was studied in patients with CKD requiring dialysis, therefore, the safety, efficacy, and utility of tenapanor (Xphozah) in patients without CKD or in those not requiring dialysis has not been established. Patients with CKD requiring dialysis are at greater risk of developing hyperphosphatemia and at higher risk of CKD related morbidity and mortality. Within all Phase III clinical trials, patients were required to be on chronic maintenance hemodialysis for at least 3 months prior to study enrollment.
V. The safety and efficacy of tenapanor (Xphozah) was evaluated in three Phase III trials (AMPLIFY, PHREEDOM, ESRD-HD), and one Phase IV open-label extension trial (NORMALIZE).
    - AMPLIFY was a Phase III, double-blind, multicenter, placebo-controlled trial enrolling 236 patients undergoing maintenance dialysis with hyperphosphatemia despite receiving phosphate binder therapy (including sevelamer, non-sevelamer,

sevelamer plus non-sevelamer, or multiple non-sevelamer binders). Patients were randomized to receive oral tenapanor (Xphozah) 30 mg twice daily plus phosphate binder or placebo plus phosphate binder for 4 weeks. The primary efficacy endpoint was change in serum phosphorus concentration from baseline to week 4, and key secondary endpoints were proportion of patients with serum phosphorus levels < 5.5mg/dL at weeks 1-4. At week 4, patients receiving tenapanor (Xphozah) plus phosphate binder had a significantly larger least squares mean change in serum phosphorus concentration from baseline when compared to placebo plus phosphate binder (-0.84 vs -0.19 mg/dL, p<0.001). At week 1, 49.1% of patients in the tenapanor (Xphozah) + binder arm achieved serum phosphorus <5.5 mg/dL versus 21.0% of patients for the placebo + binder arm (p<0.001). This effect was sustained through week 2 (41.4% vs 23.5%, p=0.003), week 3 (47.3% vs 17.6%, p <0.001), and week 4 (37.1% vs 21.8%, p=0.01), respectively.

- PHREEDOM was a 564 patient, 52-week, Phase III, multicenter trial consisting of three parts, a 26-week open-label randomized treatment period (RTP), a 12-week double-blind placebo-controlled randomized withdrawal period (RWP), and a 14-week open-label safety extension period (SEP). After a washout period, patients were randomized 3:1 to either tenapanor (Xphozah) for 26 weeks or sevelamer for 52 weeks. Patients in the tenapanor (Xphozah) arm were randomized into a withdrawal period to be continued on tenapanor (Xphozah) or placebo for 12 weeks, followed by an optional 14-week safety extension period. The primary end point was the change in serum phosphorous from the end of the RTP to the end of the RWP, among participants who achieved ≥1.2 mg/dl decrease in serum phosphate during the RTP (efficacy analysis set). In the ITT population, there was a mean difference of 1.4 mg/dL between baseline phosphate and phosphate at 26 weeks for the tenapanor (Xphozah) arm during the 26-week RTP, and a -0.66 mg/dL difference between tenapanor (Xphozah) and placebo in the 12-week RWP (p=0.002). During the RTP, 53% of patients who received tenapanor (Xphozah) experienced diarrhea as an adverse event vs 7% for sevelamer. Twenty four percent of patients discontinued tenapanor versus 1% in the sevelamer arm during the RTP. Adverse events during the 12-week RWP were similar between placebo and tenapanor. Rates of diarrhea were significantly lower during the 14-week safety extension trial for tenapanor, at 7%.
- ESRD-HD was a 219-patient, Phase III randomized, double-blind trial with two periods following a washout of phosphate binders. Patients were randomized 1:1:1 to tenapanor (Xphozah) 3 mg twice daily, tenapanor 10mg twice daily, or tenapanor 30mg twice daily during the 8-week randomized treatment period (RTP), followed by re-randomization to either placebo or their previous dose of tenapanor (Xphozah) during the 4-week randomized withdrawal period. The primary end point was mean change in serum phosphate over the 4-week withdrawal period for the tenapanor (Xphozah) group (using pooled data) versus the placebo group. In the ITT analysis set, there was a statically significant difference in the primary endpoint

between the pool tenapanor group and placebo, mean difference of -0.72 mg/dl (0.07 vs 0.79, p=0.003 for tenapanor (Xphozah) and placebo, respectively). Any adverse events were slightly higher in the 30 mg tenapanor (Xphozah) group when compared to placebo in the RWP, 35.3% vs 25.6%, but serious adverse events were higher in the placebo arm, 4.9% vs 0% for all pooled tenapanor (Xphozah).

- NORMALIZE was an open-label 18-month extension study. Patients entering the study from the tenapanor (Xphozah) arm with serum phosphate levels in the normal range were followed with no medication changes. Patients entering the study from the tenapanor (Xphozah) arm with serum phosphate greater than 4.5 mg/dL had sevelamer tablets added incrementally to achieve normal serum phosphate levels. Patients entering the study from the sevelamer safety control arm had tenapanor (Xphozah) tablets added to their treatment regimen while reducing sevelamer tablets based on their serum phosphate value to achieve normal serum phosphate levels. The primary objective of the study was to evaluate the ability of tenapanor (Xphozah) alone or in combination with sevelamer to achieve serum phosphate levels within the normal range (2.5 to 4.5 mg/dL) in patients with CKD on maintenance dialysis whose serum phosphate levels were greater than 6.0 mg/dL at baseline.
- OPTIMIZE was a 26-week, randomized, open label study, which included 330 patients with CKD on maintenance dialysis with hyperphosphatemia evaluating treatment of hyperphosphatemia in adult patients with CKD on maintenance dialysis, with tenapanor (Xphozah) alone or in combination with phosphate binders, to achieve target serum phosphate ≤5.5 mg/dL. The study randomized patients on a stable dose of phosphate binder treatment with serum phosphate >5.5mg/dL and ≤10.0 mg/dL in a 1:1 ratio to two different treatment cohorts, as well as patients who were phosphate binder naïve with serum phosphate > 4.5 and ≤10.0 mg/dL in a third cohort.
- Results from NORMALIZE and OPTIMIZE are not yet published at this time.

VI. There are two commonly cited clinical practice guidelines for the management of CKD with threshold and guidance on target ranges for serum phosphate levels. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) 2003 practice guidelines recommend that pharmacological and non-pharmacological approaches be implemented to reduce serum phosphate levels below 5.5mg/dL in patients with CKD Stage 5 requiring dialysis. Within this clinical practice guideline, serum phosphate of >5.5 mg/dL is consistent with hyperphosphatemia. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD (2017) recommend to lower elevated serum phosphate levels "toward the normal range" defined as a more stringent 2.5-4.5mg/dL in patients with CKD stages G3a to G5 to. This reference range is cited in part due to the observation that patients with serum phosphate levels close to 4.4 mg/dL had the best survival in observational/epidemiologic studies. The risk of mortality increases in a U-shape pattern from this point, as demonstrated in Block GA et al. (2004) with subsequent observational studies replicating similar findings.

- Block GA et Al. (2004) included 40,538 hemodialysis patients in an observational study which analyzed the relationship between serum phosphorus levels and risk of death. Patients were stratified into serum phosphorous categories of <3 mg/dL, increasing by 1mg/dl groups until > 9mg/dl. The study showed an increasing risk of death and hospitalization with each 1mg/dl increase in serum phosphorus above 5mg/dL. The RR were 1.10 (1.02 to 1.17) and 1.25 (1.18 to 1.33) for serum phosphorus concentrations 5.0 to 5.5 mg/dl and 5.5 to 6.0 mg/dl, respectively, and high serum phosphorus concentrations (≥11.0 mg/dl) were associated with even larger increases in RR (2.47; 95% CI, 1.90 to 3.19).
- A systematic review and meta-analysis by Palmer et al. consisting of 115,552 patients from 16 cohort studies between 1947 and 2010, evaluated the association between levels of serum phosphorus and risks of all-cause and cardiovascular mortality in patients with CKD. Thirteen studies assessed the relationship between serum phosphorus levels and all-cause mortality and 3 studies assessed serum phosphorus levels and CV mortality. The trial noted for every 1 mg/dL increase in serum phosphorus, the risk of mortality increased by 35% (RR 1.35; 95% CI, 1.16-1.57) in adequately adjusted studies, and by 18% (RR 1.18, 95% CI, 1.12-1.25) in the available 13 studies. The risk of CV mortality increased by 10% per 1 mg/dL increase in serum phosphorus (RR, 1.10; 95% CI, 1.06-1.13) in the 3 studies assessing CV mortality.

VII. The quality of evidence is considered low-moderate due to use of study outcomes that have not been directly correlated with improvements in clinically meaningful outcomes such as morbidity, mortality, symptom relief, health-related quality of life, or mental, physical, and emotional functioning. Nevertheless, reduction of phosphate levels in patients with hyperphosphatemia in CKD is an established goal of treatment and is accepted by the FDA as a validated surrogate endpoint based on observational studies that link high phosphate levels to increased risk of death due to cardiovascular causes. It is not known whether tenapanor (Xphozah) improves morbidity or mortality at this time, however, as demonstrated in the AMPLIFY trial, it lowers phosphate to normal levels (sP<5.5mg/dL) in 37.1% of patients at week 4 and provides consistent reduction in phosphate levels compared to placebo as demonstrated in PHREEDOM and ESRD-HD clinical trials.

VIII. In addition to pharmacotherapy, clinical guidelines recommend limiting dietary phosphorus intake in the treatment of hyperphosphatemia, and it is reasonable to consider phosphorus sources (e.g., animal, vegetable, additives).

IX. There are currently no head-to-head trials comparing the efficacy of tenapanor (Xphozah) to available phosphate binders on the market, and indirect comparison is confounded by different patient populations, study designs, and study parameters. Currently available phosphate lowering agents lower serum phosphate levels by roughly 1.5-2.2 mg/dL and remain the standard of care in patients with CKD undergoing dialysis treatment who require serum phosphate lowering. There are four major classes of agents that have been approved in the US to control serum phosphate levels in adults with CKD on dialysis, including calcium-based

binders, sevelamer-based products, lanthanum carbonate, and iron-based binders. Although available phosphate binders have similar phosphorus lowering potential, treatment effect and tolerability can vary in the real-world setting. Due to established safety and efficacy of these agents as well as cost-effectiveness, trial of three phosphate binders is required prior to treatment with tenapanor (Xphozah), unless previously not tolerated, ineffective, or contraindicated. Calcium-based binders are generally not recommended as a first line treatment option due to higher risk of mortality compared to non-calcium-based binders and risks associated with calcium accumulation. Sevelamer and lanthanum carry a contraindication in bowel obstruction and should be used with caution in patients with gastrointestinal (G) disease or with major GI surgery. Sucroferric oxyhydroxide (Velphoro) and ferric citrate (Auryxia) are iron-based binders. There are no contraindications to treatment with sucroferric oxyhydroxide (Velphoro); however, ferric citrate (Auryxia) is contraindicated in iron overload syndromes. Sucroferric oxyhydroxide (Velphoro) is not systemically absorbed, therefore, iron-absorption is minimal. Ferric citrate (Auryxia) may increase serum iron, ferritin, and transferrin saturation (TSAT), which may lead to excessive elevations in iron stores. Serum iron, ferritin, and transferrin saturation (TSAT) should be monitored.

X. Initial authorization is limited to 3 months of therapy as treatment response (e.g., sP lowering) is expected to occur as early as week 1 as shown from the data in AMPLIFY trials. Delayed treatment response beyond 3 months was not shown within the clinical program given the short trial duration of ESRD-HD (12 weeks) and AMPLIFY (4 weeks).

Investigational or Not Medically Necessary Uses

I. Safety and efficacy have not yet been sufficiently established and/or clinical trials are currently underway for the following indications:
   A. Non-dialysis dependent hyperphosphatemia in chronic kidney disease
   B. Irritable bowel syndrome with diarrhea
   C. Mixed irritable bowel syndrome
   D. Chronic idiopathic constipation
   E. Opioid-induced constipation

References

1. 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) [published correction appears in Kidney Int Suppl (2011). 2017 Dec;7(3):e1]. *Kidney Int Suppl (2011)*. 2017;7(1):1-59. doi:10.1016/j.kisu.2017.04.001
2. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(4 Suppl 3):S1-S201.
3. Palmer SC, Hayen A, Macaskill P, et al. Serum Levels of Phosphorus, Parathyroid Hormone, and Calcium and Risks of Death and Cardiovascular Disease in Individuals With Chronic Kidney Disease: A Systematic Review and Meta-analysis. *JAMA.* 2011;305(11):1119–1127. doi:10.1001/jama.2011.308
4. 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. doi:10.1681/ASN.2020101398

5. 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(10):1600-1610. Published 2021 Aug 27. doi:10.34067/KID.0002002021
6. Block GA, Rosenbaum DP, 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;30(4):641-652. doi:10.1681/ASN.2018080832
7. Askar AM. Hyperphosphatemia. The hidden killer in chronic kidney disease. *Saudi Med J*. 2015;36(1):13-19. doi:10.15537/smj.2015.1.9843
8. Doshi SM, Wish JB. Past, Present, and Future of Phosphate Management. *Kidney Int Rep*. 2022;7(4):688-698. Published 2022 Feb 1. doi:10.1016/j.ekir.2022.01.1055
9. Bilezikian JP, Brandi ML, Cusano NE, et al. Management of Hypoparathyroidism: Present and Future. *J Clin Endocrinol Metab*. 2016;101(6):2313-2324. doi:10.1210/jc.2015-3910Fishbane SN, Nigwekar S. Phosphate Absorption and Hyperphosphatemia Management in Kidney Disease: A Physiology-Based Review. *Kidney Med*. 2021;3(6):1057-1064. Published 2021 Aug 27. doi:10.1016/j.xkme.2021.07.003
10. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15(8):2208-2218. doi:10.1097/01.ASN.0000133041.27682.A2
11. Fernández-Martín JL, Carrero JJ, Benedik M, et al. COSMOS: the dialysis scenario of CKD-MBD in Europe. *Nephrol Dial Transplant*. 2013;28(7):1922-1935. doi:10.1093/ndt/gfs418

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Tegaserod (Zelnorm) Policy	Irritable bowel syndrome with constipation (IBS-C)
Opioid-Induced Constipation Agents Policy	Opioid-induced constipation

Policy Implementation/Update:

Action and Summary of Changes	Date
Changed step therapy requirement for tenapanor (Xphozah) to require trial of three phosphate binders.	12/2023
Added tenapanor (Xphozah), indication for hyperphosphatemia in patients with CKD, and supporting evidence. Remove CKD and hyperphosphatemia from E/I section. Updated alternative requirements for IBS indication to include generic lubiprostone.	6/2023
Policy updated to include pre-requisites of trial of current formulary and preferred agents; removed criteria requiring documentation of pain scores and stool frequency; updated supporting evidence	03/2022
Policy created	02/2020