Tenapanor (XPHOZAH) in Hyperphosphatemia in End-Stage Renal disease
National Drug Mini-monograph
August 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

NOTE: Tenapanor was previously approved under brand name IBSRELA for constipation predominant IBS

FDA APPROVAL INFORMATION

Description / MOA	Sodium/hydrogen 3 exchange (NHE3) inhibitor
Indication Under Review[1]	Hyperphosphatemia in end-stage CKD
Dosage Regimen	30mg twice daily
Dosage Forms Under Review	Tenapanor 20mg and 30mg Oral Tablets

EFFICACY CONSIDERATIONS

Trial	**TEN-02-0201**	**TEN-02-301 (PHREEDOM)**
Design	Initially a phase 2 dose ranging study where after 1-3 week washout patients with phosphate levels >6 to <10 mg/dL were randomized to tenapanor 3mg, 10mg, or 30mg bid. FDA allowed conversion to a phase 3 double blinded randomized withdrawal assessment (e.g. continue tenapanor vs. convert to placebo)	After 4 week washout pts with Phosphate levels >6-10mg/dL randomized 3:1 to tenapanor or sevelamer titrated to effect. After that, the study population was a re-randomization of the tenapanor arm 1:1 to wither stay on tenapanor or switch to placebo (e.g. cessation trial) and primary endpoint was difference in change from baseline in tenapanor and placebo arms at 12 weeks
Population	Adults with stable hyperphosphatemia (4-8mg/Dl) on maintenance hemodialysis (HD) or peritoneal dialysis (PD) dialysis with at least a 1.5g/dL increase in phosphate level after phosphate binder cessation. Exclusions included: Phosphate>10mg/dL, intact PTH > 1200pg/mL, hypovolemia, IBD/IBS diarrhea	Adults with stable hyperphosphatemia (4-8mg/Dl) on maintenance hemodialysis (HD) or peritoneal dialysis (PD) dialysis with at least a 1.5g/dL increase in phosphate level after phosphate binder cessation. Exclusions included: Phosphate>10mg/dL, intact PTH > 1200pg/mL, hypovolemia, IBD/IBS diarrhea
Intervention	Initiation of tenapanor 3mg, 10mg, or 30mg bid followed by continuation of active treatment vs. conversion to matching placebo	Continuation of tenapanor 30mg bid (or tolerated dose)
Comparator	Bassline phosphate levels (phase 2 outcome) and change in phosphate after cessation vs. placebo (phase 3 outcome)	Tenapanor cessation via transition to placebo
Results	Tenapanor reduced phosphate levels approximately 1 mg/dl (1.00, 1.02, and 1.19 for 3,10,30mg bid doses respectively). Phosphate levels increased after placebo or active treatment cessation by a difference of 0.82mg/dL in the withdrawal phase.	Efficacy analysis cohort (n=131 of tenapanor "responders") achieved 1.4mg/dL reduction vs. placebo. Notably, the full ITT analysis group (n=407 on tenapanor) had less robust reductions (0.66 mg/dL reduction vs placebo). Statistical analysis was not conducted on the sevelamer arm. However, observed phosphate levels at all timepoints were near identical in the sevelamer vs. tenapanor arms
Trial	**TEN-02-202 (AMPLIFY)**	

	Design	4 week trial of tenapanor + baseline phosphate binder therapy vs. placebo+baseline phosphate binder therapy. Primary endpoint difference in change from baseline in phosphate levels
	Population	Patients receiving maintenance dialysis (HD or PD) and phosphate levels >5.5 mg/dL despite phosphate binder therapy (primarily sevelamer)
	Intervention	Tenapanor 30mg bid added to baseline phosphate binder
	Comparator	Placebo added to phosphate binder therapy
	Results	Intervention arm experienced a 0.65 mg/dL greater change from baseline than placebo arm.

SAFETY CONSIDERATIONS	**Boxed Warnings**	None
	Contraindications	Pediatric patients under 6 years of age. Patients with known or suspected mechanical obstruction.
	Other Warnings	Patients may experience severe diarrhea
	Top 5 AEs	Diarrhea (approximately 50%) – in clinical trials reviewed was reported as mild-to-moderate and transient or responding to dose reduction.
	Drug Interactions	Enalapril – tenapanor interferes with oral absorption of OATP2B1 substrates Sodium polystyrene sulfonate - recommend separate administration by 3 hours

PLACE IN THERAPY

DRUG	VANF	CFU	FDA	GUIDELINES
Calcium Acetate	Yes	No	Yes	N/A
Sevelamer carbonate	Yes	No	Yes	N/A
Lanthanum carbonate	PA-F	Yes	Yes	Lanthanum Carbonate Chewable Tablets Criteria Jun 2023.pdf
Tenapanor	TBD	TBD	Yes	TBD

VHA PLACE IN THERAPY	**Summary and Issues for Consideration**	1. Tenapanor reduces phosphate levels in degree similar to sevelamer. It does have a different mechanism of action and can be used in addition to traditional intraluminal phosphate binding agents, albeit the overall result may be less than fully additive (e.g. < 1mg/dL reduction in the ITT population tenapanor+binder vs. placebo+binder arms) 2. Tenapanor is significantly more costly than formulary phosphate reducing agents 3. Most significant clinical difference is that intraluminal phosphate biding agents tend to be constipating, whereas diarrhea was a common side effect with tenapanor. 4. Phosphate reduction is a surrogate endpoint and it is unknown if this correlates to clinically important endpoints

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References

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3. 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 Apr;30(4):641-652
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