CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213931Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	213931
PDUFA Goal Date	October 17, 2023
Nexus TTT #	2023-4877
Reviewer Name(s)	Courtney Cunningham, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Deputy Director	Laura Zendel, PharmD
Review Completion Date	October 17, 2023
Subject	REMS Memo
Established Name	Tenapanor hydrochloride
Trade Name	Xphozah
Name of Applicant	Ardelyx, Inc.
Therapeutic Class	Sodium/hydrogen exchanger 3 (NHE3) inhibitor
Formulation(s)	10 mg, 20 mg, and 30 mg oral tablets
Dosing Regimen	30 mg by mouth twice daily

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1. Introduction and Background

This memo by the Division of Risk Management (DRM) documents DRM's assessment of the need for a REMS for a non-new molecular entity (NME) for Xphozah (tenapanor). Ardelyx, Inc submitted a New Drug Application (NDA) 213931 with the proposed indication for the control of serum phosphorus in adult patients with chronic kidney disease (CKD) on dialysis who have had an inadequate response or intolerance to a phosphate binder therapy.[1] This application is under review in the Division of Cardiology and Nephrology. If approved, the indication will be 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.[2] The applicant did not submit a proposed REMS or risk management plan with this application.

NDA 213931 was initially submitted on June 29, 2020. The application received a Complete Response (CR) on July 28, 2021, due to concerns that the magnitude of treatment effect was small and unclear in clinical significance. The CR letter stated that while there was a precedent that serum phosphorus levels are an accepted surrogate endpoint and basis for approval, there was no precedent to accept the treatment effects of the magnitude demonstrated in the tenapanor development program.[3] On December 3, 2021, the Applicant submitted a request for formal dispute resolution to the Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN) which was denied, and a second dispute resolution was submitted to the Director of the Office of New Drugs (OND) on February 18, 2022. The Director granted an interim appeal and directed the Division to present the application at a Cardiovascular and Renal Advisory Committee (CRDAC) and gave the Applicant the option to either present at the Advisory Committee or conduct the additional analyses listed in the CR Letter. The Applicant chose to present at the Advisory Committee meeting that occurred on November 16, 2022.[4] CRDAC voted nine to four that the benefits outweighed the risks for the control of serum phosphate in CKD patients on dialysis when administered as monotherapy, and voted ten to two, with one abstention, that the benefits outweighed the risks for the control of serum phosphate in CKD patients on dialysis when administered with a phosphate binder.[5] Following the meeting, the Director of OND granted the appeal, noting that "the benefit risk assessment for tenapanor is not favorable as initial therapy but favorable when prescribed dialytic, nutritional, and maximally tolerated pharmacological therapy does not provide adequate phosphate-lowering. I direct the Division to work with you to develop a label with this indication."[4] The Applicant resubmitted the NDA for review on April 17, 2023.

Hyperphosphatemia is common in patients with CKD on dialysis and is defined as elevated phosphorous levels in the blood (normal range is 2.5-4.5 mg/dL). Hyperphosphatemia is associated with the risk of vascular, valvular, and soft tissue calcification, cardiovascular disease, and secondary

hyperparathyroidism in patients with CKD.[a] In patients on dialysis with hyperphosphatemia, there is an increase in mortality risk.[b]

Current therapies for hyperphosphatemia in CKD patients include 4 classes of phosphate binders: calcium-based binders, sevelamer-based products, lanthanum carbonate, and iron-binding agents. Common adverse events of all products are gastrointestinal adverse events, and pill-burden can be significant leading to compliance issues with the current therapies. Calcium-based products can lead to hypercalcemia and vascular calcification due to calcium accumulation. All currently approved products for hyperphosphatemia act by binding phosphate in the gastrointestinal tract.

Tenapanor is proposed as a 10, 20, and 30 mg oral tablet, with an optional dose of 30 mg twice daily for chronic therapy.[c] It is proposed as a locally acting inhibitor of sodium/hydrogen exchanger 3 (NHE3), which is located on the apical surface of the small intestine and colon epithelium. This inhibition of NHE3 reduces sodium and phosphate absorption by the reduction of phosphate permeability through the paracellular pathway.[4]

Tenapanor has been approved since September 12, 2019, with the tradename Ibsrela (NDA 211801) for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults. A risk evaluation and mitigation strategy (REMS) was not required for the approved indication to ensure the benefits outweigh its risks; a Medication Guide and labeling are used to inform healthcare providers and patients of the risk of diarrhea with use of Ibsrela. [6,7]

2. Benefit Assessment

To support monotherapy for reducing serum phosphorus in patients with chronic kidney disease on dialysis, the Applicant submitted two randomized, multicenter trials, TEN-02-201 (NCT02675998) and TEN-02-301 (NCT03427125). The Applicant submitted a randomized, double-blind, placebo-controlled third trial, TEN-02-202 (NCT03824587) to support the use of tenapanor in combination with existing phosphate binder therapy. In the resubmission, the Division also reviewed the data in a long-term, open label trial TEN-02-401 (NCT03988920), and TEN-02-402 (NCT04549597), two studies supporting efficacy that had not been completed in the first review cycle.[8]

Both monotherapy trials included an initial treatment period followed by a randomized, double-blind, placebo-controlled withdrawal. In trial TEN-02-201, different dosages of tenapanor were compared by randomizing 164 subjects to tenapanor 3 mg BID, 10 mg BID, a tenapanor dose titration, or placebo for an 8-week double blind, randomized treatment period that preceded a 4-week withdrawal phase. The

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[b] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

change in serum phosphorus from the end of the 8-week treatment period to the end of the 4-week withdrawal period in the efficacy analysis set, which included all subjects who completed the 8-week treatment period and achieved at least a 1.2 mg/dL reduction in phosphate levels from baseline to the end of the 8-week In the open-label, randomized trial TEN-02-301, 423 subjects were randomized to tenapanor and 126 subjects randomized to sevelamer carbonate for 26 weeks of treatment prior to the 12-week withdrawal phase. The primary efficacy endpoint was the change in serum phosphorus from the end of the treatment period to the end of the withdrawal period or the endpoint visit for this period in the responder population , which included all subjects who had at least 1 dose of tenapanor, completed the 26-week treatment period, and achieved a reduction of >1.2 mg/dL in serum phosphorus from baseline to the end of the 26-week treatment. These subjects made up the efficacy analysis set.

In trial TEN-02-201, the least squares (LS) mean change in serum phosphorus was 1.38 mg/dL in the placebo group and 0.56 mg/dL in the tenapanor group, which is a LS mean treatment difference of -0.82 mg/dL (p=0.01). In trial TEN-02-301, the least square (LS) mean change in serum potassium from baseline to the end of the 12-week randomized withdrawal period the least squares (LS) mean change in serum phosphorus was 1.80 mg/dL in the placebo group and 0.43 mg/dL in the tenapanor group, which is a LS mean treatment difference of -1.37mg/dL for the tenapanor group (p<0.0001). [d,8]

Trial TEN-02-401 was an open-label, long-term trial that assessed the efficacy of tenapanor as monotherapy or with sevelamer to achieve a serum phosphorus level of 2.5 mg/dL to 4.5 mg/dL and the ability to reduce sevelamer dose. Results showed the addition of tenapanor to sevelamer reduced phosphorus levels in a magnitude consistent with results in trial TEN-02202, and the average pill number was unchanged from baseline.

Trial TEN-02-402 was a randomized, open-label trial that evaluated the use of tenapanor as therapy, with use of sevelamer if needed, for hyperphosphatemia. Results showed a mean reduction in phosphate similar to TEN-02-301, while the mean daily pill number decreased by 2-4 pills.[4]

3. Risk Assessment & Safe-Use Conditions

A limitation of the original submission's safety database is the lack of double-blind, placebo-controlled initial treatment periods with tenapanor monotherapy. The safety review focused primarily on trial TEN-02-301, which had the longest (52 week) exposure of monotherapy, used the dosage proposed in labeling, and included the longest (26 weeks with an active comparator) duration of controlled safety data. For any adverse event of special interest or warranted evaluation, analysis from trials TEN-02-201 and TEN-02-202 were performed.[8]

Several deaths occurred during the open-label treatment period in trial TEN-02-301 (1.7% in the tenapanor arm and 2.2% in the phosphate-binder arm). Most deaths were due to cardiovascular disease

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

or sepsis, both risks of patients with CKD on dialysis. There were no reports of diarrhea in subjects who died during the trial.

Diarrhea is the most common, serious adverse event associated with tenapanor.[3]

3.1. Diarrhea

In trial TEN-02-301, 54% of subjects treated with tenapanor experienced diarrhea, as opposed to 8% in the placebo group. Thirty-six percent of tenapanor treated subjects had at least one episode of moderate diarrhea, and 6% had at least one episode of severe diarrhea. In the majority of cases, diarrhea occurred soon after treatment initiation, and resolved despite continued treatment. However, 16% of tenapanor-treated diarrhea cases required discontinuation and 32% required a dose reduction, compared with 1 discontinuation and no dose reductions in subjects with diarrhea in the placebo arm.[e]

In trial TEN-02-202, which assessed tenapanor use with a phosphate binder, 3% of tenapanor treated subjects discontinued due to diarrhea, while 2% of placebo patients discontinued due to diarrhea. Dose reductions occurred in 27% of subjects in the tenapanor arm, and in 4% of patients in the placebo arm.[8]

Trials TEN-02-401 and TEN-02-402 produced the expected adverse events of diarrhea. One subject in trial TEN-02-401 reported colitis as an adverse event, which required a hospital stay of several days and an interruption of tenapanor. The subject resumed therapy and completed the trial. Several patients experienced dehydration and 1 who also had a concomitant small bowel obstruction experienced hyponatremia. Most patients resumed therapy and completed the study. Three of the 4 cases of GI bleeding were in the tenapanor arm, and 2 cases were temporarily related to diarrhea. One patient was on concomitant warfarin therapy, and both patients resumed tenapanor and completed the study.[4]

The clinical reviewer noted that labeling would be sufficient to mitigate the risk in the first review of this product.[8]

4. Expected Postmarket Use

Xphozah is expected to be prescribed primarily by nephrologists, who are expected to be familiar with the management of diarrhea in CKD patients on dialysis and monitor appropriately. These practitioners are also expected to meet regularly with these patients. Xphozah will be taken as an outpatient oral medication by patients.

[e] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

5. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Xphozah on the basis of the efficacy and safety information currently available, "assuming agreement can be reached on labeling," which at the time of this review, is possible.[4]

No safety concerns for risk mitigation beyond labeling for diarrhea were expressed by the review team during review of the initial submission, nor was there any discussion of the need for addition risk mitigation beyond labeling during the CRDAC. Patients who have CKD and are on dialysis are seen regularly by their nephrologist and at the dialysis center, and their blood chemistry is monitored frequently. Prescribers are expected to be familiar with complications and management of diarrhea in these patients. As such, no risk management beyond labeling is required for the risk of diarrhea associated with Xphozah.

Ibsrela, the tenapanor product used for irritable bowel syndrome, has a boxed warning regarding the contraindication in patients under 6 years old and avoiding the use of Ibsrela in patients ages 6-12 due to the risk for severe dehydration.[9] As the CKD on dialysis patient population is different, has blood chemistry closely monitored and see their providers frequently, a boxed warning is not necessary for Xphozah.

Since the initial review, postmarket safety surveillance of Ibsrela has identified a potential safety signal of hypersensitivity. This is currently under evaluation. As for this NDA, no signal was detected for hypersensitivity in the Phase 2 and 3 trials.[4]

6. Conclusion & Recommendations

Based on available data, DRM and DCN agree that a REMS is not necessary to ensure the benefits of Xphozah outweigh the risks, which can be managed via labeling. Should DCN have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

7. Appendices

7.1. References

1. Ardelyx, Inc., Xphozah draft labeling, October 3, 2023.
2. Ardelyx, Inc., Draft labeling for Xphozah, October 12, 2023.
3. Soukehal, S., Complete Response Letter for tenapanor (NDA 213931), July 28, 2021, DARRTS ID 4833092.
4. Ongoing DCN review of (b) (4) (NDA 213931) resubmission, October 12, 2023.
5. Ardelyx, Inc., Clinical Overview of Xphozah, April 17, 2023.
6. Crentsil, V., Unireview of Ibsrela (Tenapanor, NDA 211801), September 12, 2019, DARRTS ID 4490899.
7. Abou-Sayed, Y. Division of RIsk Management Determination of the Need for a REMS Review for Ibsrela NDA 211801, Septemeber 9, 2019, DARRTS ID 4488935.
8. Soukehal, S., Integrated Review of Tenapanor, July 28, 2021, DARRTS ID 4833062.
9. Ardelyx, Inc, Ibsrela Prescribing Information, revised May, 2021.

APPEARS THIS WAY ON ORIGINAL

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