CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213931Orig1s000

OTHER ACTION LETTERS

NDA 213931

COMPLETE RESPONSE

Ardelyx, Inc.
Attention: Robert C. Blanks, MS, RAC
Chief Regulatory and Quality Officer
34175 Ardenwood Blvd.
Fremont, CA 94555

Dear Mr. Blanks:

Please refer to your new drug application (NDA) dated June 26, 2020, received June 29, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tenapanor hydrochloride 10 mg, 20 mg, and 30 mg tablets.

We acknowledge receipt of your major amendment dated April 28, 2021, which extended the goal date by three months.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

To support efficacy as monotherapy for reducing serum phosphorus in patients with chronic kidney disease (CKD) on dialysis, you submitted the results of two randomized, multi-center trials (TEN-02-201 and TEN-02-301). You also submitted the results of a third trial ─ a randomized, double-blind, placebo-controlled trial (TEN-02-202), to support use in combination with existing phosphate binder treatment. All three studies evaluated tenapanor's efficacy in reducing serum phosphorus levels.

In epidemiologic studies, elevated serum phosphorus levels have been associated with an increased risk of secondary hyperparathyroidism, vascular, valvular, and other soft tissue calcification and cardiovascular disease in patients with CKD. In patients on dialysis, higher serum phosphorus levels have also been associated with increased mortality. To date, however, there are no data from outcome studies demonstrating that a treatment's effect on serum phosphorus levels predicts its effect on clinical outcomes such as cardiovascular events or mortality. Nevertheless, the Division of Cardiology and Nephology, following the precedent set by the former Division of Metabolism and Endocrinology Products, treats serum phosphorus reduction as a valid surrogate in patients with CKD on dialysis. All currently marketed products for the control of serum

phosphorus in patients with CKD on dialysis were approved based on effects on serum phosphorus levels. In the trials conducted to support approval, these therapies lowered serum phosphorus levels by ~1.5 – 2.2 mg/dL.

In both monotherapy trials, tenapanor's efficacy in reducing serum phosphorus levels was assessed in a randomized, double-blind, placebo-controlled withdrawal period. In Study TEN-02-201, which compared different dosing strategies, an 8-week double-blind randomized treatment period preceded the randomized withdrawal phase; in Study TEN-02-301, which included an active comparator, a 26-week open-label, randomized treatment period preceded this phase. In both studies, the primary efficacy analysis during the randomized withdrawal period was to be based on the Efficacy Analysis Set, a subset of the intent-to-treat (ITT) population, which was intended to enrich for a responder population. Specifically, the Efficacy Analysis Set limited the primary efficacy analysis to patients who achieved a reduction of ≥ 1.2 mg/dL in serum phosphorus level in the treatment period prior to randomized withdrawal.

Among the patients randomized to tenapanor in the 26-week open-label treatment period of Study TEN-02-301, approximately 60% finished the 26-week treatment period and were re-randomized to receive tenapanor or placebo during the 12-week randomized withdrawal phase. Of the 219 patients who were randomized into the 8-week treatment period of Study TEN-02-201, approximately 75% completed the 8-week treatment period and entered the 4-week randomized withdrawal phase. Of those who entered the randomized withdrawal period, approximately half were excluded from the Efficacy Analysis Set used for the primary analysis in Studies TEN-02-301 and TEN-02-201.

Among the trials, the largest treatment effect was observed in the Efficacy Analysis Set of Study TEN-02-301. In Study TEN-02-301, the point estimate of the treatment difference in the LS mean change in serum phosphorus from baseline to the end of the 12-week randomized withdrawal period was 1.37 mg/dL based on the Efficacy Analysis Set. However, the clinical relevance of this estimand is unclear given that it was derived from a subset of the trial population. Analyses based on the ITT population of the randomized withdrawal periods in Study TEN-02-201 and Study TEN-02-301 provide perhaps the best estimate of the average treatment effect in the subset of patients who are likely to tolerate tenapanor and remain on therapy. The sizes of the treatment effects in this subset were small─ 0.72 mg/dL and 0.66 mg/dL, respectively.

We further note that subgroup analyses and analyses of the distribution of the responses did not suggest a "responder" population with a substantially larger response to treatment. In exploratory analyses of the 26-week active controlled treatment period of Study TEN-02-301, tenapanor's effect size appeared to be larger in patients with more marked elevations at baseline; however, the effect size still appeared to be smaller than that observed with the active control, and, absent a placebo control, the results of these analyses are challenging to interpret. In Study TEN-02-202, which evaluated tenapanor use in combination with existing phosphate binder treatment, the

size of the treatment effect was similar to that observed in the monotherapy trials─ 0.65 mg/dL.

Although we agree that the submitted data provide substantial evidence that tenapanor is effective in reducing serum phosphorus in CKD patients on dialysis, the magnitude of the treatment effect is small and of unclear clinical significance. In some diseases, we have data from interventional trials that can be used to understand the quantitative relationship between treatment-induced changes in a surrogate and changes in clinical outcomes. In this disease state, we do not have such data. And, while there is well-established precedent for accepting serum phosphorus as a surrogate endpoint and basis for approval in this therapeutic area, there is no precedent for accepting treatment effects of the magnitude seen in this development program.

For this application to be approved, you will need to conduct an additional adequate and well-controlled trial demonstrating a clinically relevant treatment effect on serum phosphorus or an effect on a clinical outcome thought to be caused by hyperphosphatemia in CKD patients on dialysis. We note that, in principle, it may be possible to individualize treatment based on a patient's early response to a drug that lowers serum phosphorus levels (i.e., assess for a response at some early time point and only continue treatment in patients who have a clinically relevant response); however, such a strategy would need to be prospectively tested and would also likely need to be based on multiple measurements of serum phosphorus over time to distinguish the treatment effect from intrasubject variability.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, November 23, 2020 which addresses the proposed proprietary name, Xphozah. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, MD, MS
Deputy Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALIZA M THOMPSON
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