CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761161Orig1s000

OTHER ACTION LETTERS

BLA 761161

COMPLETE RESPONSE

Chiesi USA
Attention: Matt Medlin, PhD, RAC
Sr. Manager, US Regulatory Affairs R&D
175 Regency Woods Place, Suite 600
Cary, NC 27518

Dear Dr. Medlin:

Please refer to your biologics license application (BLA) dated and received May 27, 2020, and your amendments, under section 351(a) of the Public Health Service Act for PRX-102.

We acknowledge receipt of your major amendment dated November 4, 2020, 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.

DEFICIENCES AND INFORMATION NEEDED TO RESOLVE THE DEFICIENCIES

1. Facilities

During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, we communicated issues with the (b) (4) manufacturing facility named in your application. Satisfactory resolution of the remaining issues is required before this application may be approved. We will communicate the outstanding issues to the facility no later than 10 business days after issuing this complete response letter. Contact the (b) (4) manufacturing facility for additional information.

2. Use of the Accelerated Approval Pathway When There is Available Therapy

You requested accelerated approval of PRX-102 based on a reduction in renal peritubular capillary globotriaosylceramide (Gb3) inclusions. As previously communicated on March 15, 2021, with the full approval of Fabrazyme

(agalsidase beta) on March 11, 2021, Fabrazyme is now available therapy[1,2] for Fabry disease. Your product will no longer qualify for accelerated approval if it does not provide a therapeutic advantage over available therapy. We acknowledge your response dated March 26, 2021. Given the late timing of this development in the review cycle we have not completed our review of that amendment.

Prior to your resubmission, we recommend an End-of-Review meeting to discuss whether accelerated approval remains an appropriate pathway for your product. That discussion should also include a status update on your ongoing intended confirmatory postmarketing trial, and your assessment of the likelihood that this trial will be able to show superiority of your product to Fabrazyme on eGFR based on what is known with regard to the effects of these products on renal Gb3 inclusions, and your plans should that trial fail to show superiority of PRX-102 over Fabrazyme.

An alternative approach to seeking accelerated approval may be to establish that the reduction in renal Gb3 inclusions with PRX-102 predicts clinical benefit, allowing for full approval of your product. Data to support such an approach should show that:

- Gb3 is toxic to tissues when it accumulates
- Gb3 accumulates in all tissues where Fabry disease causes structural damage and functional loss
- The degree of Gb3 accumulation is correlated with the degree of tissue damage
- A reduction in Gb3 is associated with normalization of structure and function
- PRX-102 sufficiently removes Gb3 from Fabry target tissues, including in women.

We recommend also discussing whether full approval may be a possible path forward for your product at the End-of-Review meeting.

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

PRESCRIBING INFORMATION

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format as described at FDA.gov.[5]

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

PROPRIETARY NAME

Refer to correspondence dated, February 17, 2021, which addresses the proposed proprietary name, Elfabrio. This name was found acceptable pending approval of the

[3] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[4] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[5] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

application in the current review cycle. 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 product 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 product. Include an updated estimate of use for product marketed in other countries.

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

ADDITIONAL INFORMATION

1. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response.

   An inspection of the Protalix Ltd. (FEI# 3008289067), Carmiel, Israel manufacturing facility is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are assessed with regard to your application. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

   For more information, see the FDA guidances related to COVID 19.[6]

2. Infusion-Related Reactions

   It is unclear why you chose a window of only 2 hours after PRX-102 administration for defining an infusion-related reaction. You also have not provided sufficient reasoning for excluding adverse events that you considered related to the infusion procedure rather than PRX-102. You have also not provided a clear narrative regarding premedication that was given in your safety database. Therefore, in the next review cycle include:

   - A dataset and assessment of all infusion-related reactions that occurred within 24 hours of PRX-102 administration.

   - Provide additional details on each of the excluded events that you attributed to the infusion procedure, including the investigator verbatim term, any additional clinical details, and your basis for determining that they were related to the infusion procedure and not PRX-102.

   - Patient narratives on every subject in the safety database who required premedication (specifically what medications were given) with an explanation of why they were given premedication.

[6] https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). 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 601.3(c). 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, call Michael G. White, PhD, Chief, Project Management Staff, at 240-402-6149.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
Director
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Center for Drug Evaluation and Research

ENCLOSURE:

- Labeling

17 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

HYLTON V JOFFE
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