BLA 761161

BLA APPROVAL

Chiesi Farmaceutici S.p.A.
Attention: Matt Medlin, PhD, RAC
Head of US Regulatory Affairs, Global Rare Diseases
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, submitted under section 351(a) of the Public Health Service Act for Elfabrio (pegunigalsidase alfa-iwxj) injection.

We acknowledge receipt of your amendment dated November 9, 2022, which constituted a complete response to our April 27, 2021, action letter.

LICENSING

We have approved your BLA for Elfabrio (pegunigalsidase alfa-iwxj) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Elfabrio under your existing Department of Health and Human Services U.S. License No. 2245. Elfabrio is indicated for the treatment of adults with confirmed Fabry disease.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture pegunigalsidase alfa-iwxj drug substance at Protalix Ltd. in Carmiel, Israel. The final formulated drug product will be manufactured, filled, labeled, and packaged at Chiesi Farmaceutici S.p.A., Parma, Italy. You may label your product with the proprietary name, Elfabrio, and market it as a 20 mg/10 mL solution for infusion in a sterile, single-dose vial.

DATING PERIOD

The dating period for Elfabrio shall be 48 months from the date of manufacture when stored at 2 to 8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4) (b) (4) (b) (4).

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Elfabrio to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Elfabrio, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761161**." Approval of this submission by FDA is not required before the labeling is used.

[1] See http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

ADVISORY COMMITTEE

Your application for Elfabrio was not referred to an FDA advisory committee because this biologic is not the first in its class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 23 months (inclusive) because necessary studies are impossible or highly impracticable. This is because patients with Fabry disease in this age group are asymptomatic, thus clinical trials in this age group would not be informative and would be highly impractical.

We are deferring submission of your pediatric study for ages 2 to <18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

3972-1 Clinical trial to evaluate the safety, efficacy, pharmacokinetics, and pharmacodynamic effects of pegunigalsidase alfa-iwxj in pediatric patients aged 2 to <18 years with confirmed Fabry disease. The trial will evaluate patients over at least 1 year from the time of enrollment and will include assessments of immunogenicity and correlative analyses between antibody formation (and titers if appropriate) and safety, efficacy, pharmacokinetics, and pharmacodynamics in treated patients.

Draft Protocol Submission: 11/2023
Final Protocol Submission: 04/2024
Study/Trial Completion: 07/2026
Final Report Submission: 01/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol to your IND 110161, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant.

Furthermore, the active postmarket risk identification and analysis system, as available under section 505(k)(3) of the FDCA, will not be sufficient to identify unexpected serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3972-2 Conduct a worldwide descriptive study that collects prospective and retrospective data in women and their offspring exposed to ELFABRIO (pegunigalsidase alfa-iwxj) during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The timetable you submitted on May 8, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	11/2023
Final Protocol Submission:	06/2024
Interim study report:	12/2026
Interim study report:	12/2028
Interim study report:	12/2030
Interim study report:	12/2032
Interim study report:	12/2034
Study/Trial Completion:	12/2034
Final Report Submission:	12/2035

3972-3 Develop and validate an assay for detection of neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa-iwxj.

The timetable you submitted on May 8, 2023, states that you will conduct this study according to the following schedule:

Study/Trial Completion:	01/2024
Final Report Submission:	05/2024

3972-4 Develop and validate an anti-PEG IgE antibody assay.

The timetable you submitted on May 8, 2023, states that you will conduct this study according to the following schedule:

Study/Trial Completion:	01/2024
Final Report Submission:	05/2024

3972-5 Improve the current anti-pegunigalsidase alfa-iwxj IgG antibody assay or develop a new assay to improve the drug tolerance. Validate the assay.

The timetable you submitted on May 8, 2023, states that you will conduct this study according to the following schedule:

Study/Trial Completion:	05/2023
Final Report Submission:	08/2023

3972-6 Revise and re-validate the anti-pegunigalsidase alfa-iwxj IgM antibody assay with anti-pegunigalsidase alfa-iwxj IgM antibodies to be used as positive controls.

The timetable you submitted on May 8, 2023, states that you will conduct this study according to the following schedule:

Study/Trial Completion:	01/2024
Final Report Submission:	06/2024

3972-7 Evaluate neutralizing antibodies that inhibit the cellular uptake of pegunigalsidase alfa-iwxj in clinical samples from studies PB-102-F01/02, PB-102-F03, and PB-102-F20 using the assay developed and validated under PMR 3972-3. Assess the impact of cellular uptake neutralizing antibodies on the pharmacokinetics, pharmacodynamics, efficacy, and safety of pegunigalsidase alfa-iwxj.

The timetable you submitted on May 8, 2023, states that you will conduct this study according to the following schedule:

Study/Trial Completion:	03/2025
Final Report Submission:	09/2025

3972-8 A pre- and postnatal development study in rats treated with pegunigalsidase alfa-iwxj.

The timetable you submitted on May 8, 2023, states that you will conduct this study according to the following schedule:

Final study protocol:	03/2024
Study completion:	03/2025
Final report:	12/2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 110161 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3972-9 Conduct a 13-week repeat-dose pharmacokinetic and pharmacodynamic (PK/PD) study in α-galactosidase deficient (αGAL KO) mice to evaluate changes in the GL3 biomarker in plasma and in the kidney, skin, heart, brain, spleen, and liver in relation to treatment with pegunigalsidase alfa. Correlate reductions in GL3 with pharmacokinetic exposures to pegunigalsidase alfa in this study.

The timetable you submitted on May 8, 2023, states that you will conduct this study according to the following schedule:

Draft protocol submission:	12/2023
Final protocol submission:	06/2024
Study Completion:	06/2025
Final report submission:	12/2025

Study Protocol Details: Use a validated bioanalytical method to evaluate changes in the GL3 in response to treatment with pegunigalsidase alfa. Comparison of bioanalytical method used in this study with the method employed in your clinical trials. Perfuse animals prior to collection of tissues to ensure that measurement of tissue enzyme levels is not confounded by levels in residual blood.

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 110161 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3972-10 Conduct a drug product (DP) shipping validation study using the first three commercial shipments of final, finished DP vials from Chiesi Farmaceutici (Parma, Italy) to Chiesi USA (Cary, NC, USA). Include at minimum the following testing on DP samples at release and post-shipping: appearance by visual inspection, particulate matter, non-denatured and denatured SE-HPLC, peptide map purity assay, enzyme kinetics assay, protein content and container closure integrity.

The timetable you submitted on May 8, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2024

3972-11 Improve and revalidate the peptide mapping purity method for the drug substance and drug product to quantify the relative concentrations of product-related substances. Characterize oxidized product-related substances and identify those that may be critical quality attributes or stability-indicating; update the drug substance and drug product specifications accordingly with quantitative acceptance criteria for the relevant substances.

The timetable you submitted on May 8, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

Submit clinical protocols to your IND 110161 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

POST APPROVAL FEEDBACK MEETING

New biological products qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Diego Diaz, Regulatory Project Manager, via email at Diego.Diaz@fda.hhs.gov or at (301) 796-7182.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, MD
Deputy Director
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:
- Content of Labeling
  - Prescribing Information
- Carton and Container Labeling

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/

CHRISTINE P NGUYEN
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