BLA 761278

BLA APPROVAL

Chiesi Farmaceutici S.p.A.
% Chiesi USA Inc.
Attention: Veronica Backlund
Senior Regulatory Affairs Manager, Global Rare Diseases
175 Regency Woods Place, Suite 600
Cary, NC 27518

Dear Ms. Backlund:

Please refer to your biologics license application (BLA) dated and received June 17, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Lamzede (velmanase alfa-tycv) injection.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2245 to Chiesi Farmaceutici S.p.A., Parma, Emilia-Romagna, Italy, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Lamzede (velmanase alfa-tycv). Lamzede is indicated for the treatment of the non-central nervous system manifestations of alpha-mannosidosis in adult and pediatric patients.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture velmanase alfa drug substance at Rentschler Biopharma SE, Laupheim, Germany. The final formulated drug product will be manufactured and filled at Patheon Italia S.p.A., Ferentino FR, Italy, and labeled and packaged at Chiesi Farmaceutici S.p.A., Parma, Italy. You may label your product with the proprietary name, Lamzede, and market it in a 10 mg lyophilized powder single-dose vial.

DATING PERIOD

The dating period for Lamzede shall be 36 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) °C.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Lamzede 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 Lamzede, 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 (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 *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed**

[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.

Carton and Container Labeling for approved BLA 761278." Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the Federal Food, Drug, and Cosmetic Act (FDCA). This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 761278. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

- the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
- the estimated demand in the U.S. for the product, and
- the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

ADVISORY COMMITTEE

Your application for Lamzede was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 assess a signal of carcinogenic risk due to the increased alpha-mannosidase exposure.

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

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

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

4397-1 Perform an assessment of the potential effects of increased alpha-mannosidase exposure (and increased MAN2B1 expression) on tumor formation.

The timetable you submitted on February 14, 2023, states that you will conduct this study according to the following schedule:

Interim Report Submission: 02/2024
Final Report Submission: 08/2024

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).**[4]

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 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 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.

[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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4397-2 Perform a bridging pharmacokinetic study in rats to characterize the velmanase alfa-tycv exposure in the reproductive toxicity and pre- and postnatal development studies.

The timetable you submitted on February 14, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 08/2023
Final Protocol Submission: 02/2024
Study Completion: 08/2024
Final Report Submission: 02/2025

4397-3 Conduct a 26-week repeat-dose pharmacodynamic (PD) study in alpha mannosidase-deficient transgenic-knockout mice to evaluate changes in the M2 biomarker and histopathology in response to treatment with velmanase alfa-tycv.

The timetable you submitted on February 14, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 08/2023
Final Protocol Submission: 02/2024
Study Completion: 02/2025
Final Report Submission: 10/2025

Study Protocol Details: Use a validated bioanalytical method to evaluate changes in the M2 biomarker. Perform histopathology on all animals. Perform expanded neuropathology and use an expert neuropathologist to either read the slides or perform a peer review of the brains and spinal cords taken from all animals on this study. Measure oligosaccharide contents of tissues (particularly neural tissues) in the toxicokinetic cohort animals. Characterize the contents of the vacuoles and perform quantitative micrometry of the dose-effect on vacuolar burden in tissues from the study.

4397-4 Evaluate the pharmacodynamics of velmanase alfa-tycv in pediatric patients less than 3 years of age with a confirmed diagnosis of alpha-mannosidosis. If the results suggest inadequate pharmacodynamic response at the currently recommended dose of 1 mg/kg, additional clinical studies may be needed to explore doses higher than 1 mg/kg for patients who cannot achieve an optimal pharmacodynamic response at 1 mg/kg.

The timetable you submitted on February 14, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2023
Final Protocol Submission: 09/2023
Interim Report: 09/2026
Trial Completion: 09/2029
Final Report Submission: 09/2030

4397-5 Develop and validate a titering anti-drug antibody (TADA) assay as recommended in the FDA guidance for industry *Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019). This TADA assay will be used to test available confirmed anti-drug antibody positive samples from studies rhLAMAN-07, rhLAMAN-08, rhLAMAN-09, rhLAMAN-10, and on-going clinical studies to complement and replace the current rabbit anti-velmanase alfa reference standard-based semi-quantitative ADA assay. Provide a final validation report detailing the performance of the TADA assay.

The timetable you submitted on January 6, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2023

4397-6 Develop and validate cell-based neutralizing antibody (NADA) assay to test inhibition of velmanase alfa enzyme uptake into cells. This NADA assay will be used to test available confirmed anti-drug antibody positive samples from clinical studies rhLAMAN-07, rhLAMAN-08, rhLAMAN-09, rhLAMAN-10, and on-going clinical studies. Provide a final validation report detailing the performance of the cell-based NADA assay.

The timetable you submitted on January 6, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2023

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 113186 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:

4397-7 Submit a risk assessment of the extractables identified for the drug substance container closure system (CCS) and drug product CCS, including a risk assessment of the threshold of toxicological concern (TTC), acceptable daily exposure (ADE), and/or permissible daily exposure (PDE).

The timetable you submitted on January 6, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2023

4397-8 Submit a leachables study protocol as well as the time zero (T0) report.

The timetable you submitted on January 6, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2023

4397-9 Implement a drug product release specification for deliverable volume (e.g., according to USP <697>).

The timetable you submitted on January 6, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2023

4397-10 Develop, validate, and implement a test method with justified numerical acceptance criteria to reliably detect and control for the presence of Chinese hamster ovary (CHO) lysosomal enzyme alpha-mannosidase (LAMAN) in the final velmanase alfa drug substance.

The timetable you submitted on January 6, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

4397-11 Implement a cell-based potency assay in drug product release specifications with pre-defined acceptance criteria.

The timetable you submitted on January 6, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

4397-12 Develop, validate, and implement a test method with justified numerical acceptance criteria for (b) (4) during drug product release and stability testing. (b) (4) If applicable, justification and data supporting the use of a synthetic substrate, and its relevance to the natural substrate, will be provided. The method validation report for the (b) (4) assay, the revised drug product release and stability specifications, and all supporting studies and data will be provided in a final study report per 21 CFR 601.12.

The timetable you submitted on January 6, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2025

4397-13 Implement (b) (4) prior to vial fill at (b) (4) mg/mL. Include “gross content of protein content per vial” in the drug product release specification to control the total amount of velmanase alfa in the final vial.

The timetable you submitted on February 14, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2023

4397-14 Conduct a worst-case drug product transport qualification study shipping 10 mg vials of velmanase alfa drug product from Chiesi Farmaceutici S.p.A. in Italy to distribution sites in the USA. Perform product quality testing on the final shipped velmanase alfa drug product to support purity and potency after worst-case shipping conditions.

The timetable you submitted on January 6, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2023

Submit clinical protocols to your IND 113186 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.

[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

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:

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, call Avinash Kalsi, Regulatory Project Manager, at (301) 348-1432.

Sincerely,

{See appended electronic signature page}

Christine P. Nguyen, MD
Deputy Director
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drug
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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