CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761278Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

LABELS AND LABELING ASSESSMENT

Date of Assessment:	February 13, 2023
Assessor:	Scott Dallas, RPh Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Asha Hewarathna, PhD Product Quality Assessor OBP/Division of Biotechnology Review and Research 3
Application:	BLA 761278
Applicant:	Chiesi Farmaceutici S.p.A.
Submission Date:	June 17, September 14, 2022, January 11, January 18, January 31, February 6 and February 10, 2023
Product:	Lamzede (velmanase alfa-tycv)
Dosage form:	For injection
Strength and Container-Closure:	10 mg in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for velmanase alfa-tycv seeking approval for the treatment of alpha-mannosidosis. This BLA has been granted Fast Track Designation, Orphan Drug Designation, and Rare Pediatric Disease Designation.
Recommendations:	The prescribing information, container label, and carton labeling are acceptable from an OBP labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices. (see Appendix B)

CONCLUSION

The prescribing information submitted on February 10, 2023, and the container label, and carton labeling submitted on January 31, 2023, were assessed, and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on June 17, 2022)
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- Container Labels (submitted on June 17, 2022)

(b) (4)

- Carton Labeling (submitted on June 17, 2022)

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Appendix B: Evaluation Tables
Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

Comment/Recommendation:

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Confirm there is no text on the ferrule and cap overseal of the vials.

Applicant's Response: The applicant responded "Chiesi confirms that there is not text on the ferrule and cap overseal. The only language that appears on the ferrule and cap is the last 4 digits of the lot number."

The applicant's response is acceptable.

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.

Applicant's Response: The applicant responded "Chiesi confirms that a sufficient area of the container remains uncovered to allow for visual inspection." The applicant also provided a photograph of the vial with a sample label attached to the vial.

The applicant's response is acceptable.

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

NDC numbers **(container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Considered a partial label and there is not enough space to provide this information on the label.

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: There are no misleading statements.

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A

Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: Considered a partial label and there is not enough space to provide this information on the label.

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Comment/Recommendation:

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

USP General Chapters: <7> Labeling	

Comment/Recommendation:

Storage temperature/requirements (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Revise the storage statement to read: "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze."

To applicant: Revise the sentence that reads "If immediate use is not possible, …." To read "If immediate use is not possible, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours inclusive of infusion time. Protect from light during refrigeration. Do not freeze."

Applicant's Response: The applicant revised the storage statements as requested.

The applicant's revisions are acceptable.

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Revise the storage statement to read: "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze."

Applicant's Response: The applicant revised the handling statement as requested.

The applicant's revision is acceptable.

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes

	☐ No ☒ N/A

Comment/Recommendation:

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Applicant: To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, and dibasic sodium phosphate, glycine, mannitol and monobasic sodium phosphate.

(b) (4)

(b) (4) dibasic sodium phosphate (2.47 mg) per the monograph definition.

(b) (4)

(b) (4) monobasic sodium phosphate (0.088 mg) per the monograph definition.

Provide an updated Description and Composition Table in section 3.2.P.1 adding a footnote to Table 1 (b) (4)

(b) (4)

Lastly, inactive ingredients names have been revised to appear in alphabetical order.

Revise the contents statement to read: "Each single-dose vial contains 10 mg of velmanase alfa-tycv and dibasic sodium phosphate (2.47 mg), glycine (10.1 mg), mannitol (227.5 mg) and monobasic sodium phosphate (0.088 mg)."

Applicant's Response: The applicant responded "Chiesi has confirmed the name and milligram quantity revision. This change and the order of the excipients to be alphabetical has been implemented in the carton artwork, as attached. A revised 3.2.P.1 is included with this response reflecting the requested footnote."

Footnotes added to section 3.2.P.1 Description and Composition of Drug Product:

(b) (4)

The applicant's response and revisions to the carton labeling and footnotes to section 3.2.P.1 are acceptable.

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OBP Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for velmanase-alfa products (i.e., there is no specific test method described in regulation for velmanase-alfa products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Lamzede because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

To applicant: Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable.

Applicant's Response: The applicant removed the potency statement.

The applicant's revision is acceptable.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes

	☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Add the resultant concentration (in XX mg/mL) to the instructions for reconstituting the product. The concentration will inform persons responsible for preparing the product the amount of drug contained in each milliliter once reconstituted.

Consider revising the statement to read:

"Reconstitute with 5 mL Sterile Water for Injection, USP prior to use. After reconstitution, the final concentration is 2 mg/mL." or "After reconstitution with 5 mL Sterile Water for Injection, USP the resultant concentration is 2 mg/mL."

Applicant's Response: The applicant revised the statement to read: Reconstitute with 5 mL Sterile Water for Injection, USP prior to use. After reconstitution, the final concentration is 2 mg/mL.

The applicant's revisions are acceptable.

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Consider deleting the NDC and "Rx only" statement from the two side panels that contain information on the contents/manufacturer and dosage/storage information to create more white space.

Applicant's Response: The applicant deleted the NDC and "Rx only" statement from the two side panels.

The applicant's deletions are acceptable.

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes

	☐ No ☒ N/A

Comment/Recommendation:

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)* *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No

	☒ N/A

Comment/Recommendation:

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Other (package labeling)	**Acceptable**
	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Revise the statement: "Allow the reconstituted vials to stand on the table for 5-10 minutes" to read "Allow the reconstituted vials to stand on the table for 5 – 15 minutes." The statement was based upon the OBP quality team review of the applicant's reconstitution time data and release acceptance criteria.

The reconstituted solution identifying characteristics were revised to read "clear to slightly opalescent". The OBP quality team confirmed the reconstituted solution identifying characteristics.

To applicant: Revise the information for the "Storage of the Reconstituted Solution (b) (4)" to read:

"If the reconstituted LAMZEDE is not used immediately, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours inclusive of infusion time. Protect from light during refrigeration. Do not freeze.

Reconstituted LAMZEDE must be infused within 10 hours after removal from the refrigerator, inclusive of total infusion time. Discard if not used within 10 hours.

Infuse reconstituted solution within 24 hours from the time of preparation, which includes the storage time in the refrigerator, the time at room temperature, and the duration of the infusion."

To applicant: Administration Instructions: Include the statement "Do not shake the syringe".

Applicant's Response: The applicant revised and or accepted FDA's proposed revisions to Section 2.

The applicant's revisions are acceptable.

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

To applicant: Revise the dosage forms and strength statement to include the phrase "with a cake-like appearance".

Applicant's Response: The applicant included the phrase "with a cake-like appearance" as requested.

The applicant's revision is acceptable.

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**

Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant:
Revise the first paragraph that describes the drug substance, first sentence to read: "Velmanase alfa-tycv is a lysosomal alpha-mannosidase (b) (4) produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells." In addition, a third sentence was included to indicate velmanase alfa-tycv has a molecular weight of 130kDa.

Revise the second paragraph that describes the drug product, to state the product is sterile, and revise the inactive ingredient names and quantities to reflect their compendial name and associated quantity. Specifically, the ingredients (b) (4) (b) (4) dibasic sodium phosphate and monobasic sodium phosphate, respectively.

(b) (4) dibasic sodium phosphate quantity of 2.47 mg. (b) (4) (b) (4) monobasic sodium phosphate quantity of 0.088 mg.

In addition, the following comments were provided to the applicant:
To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, dibasic sodium phosphate, glycine, mannitol, and monobasic sodium phosphate.

(b) (4)

Provide an updated Description and Composition Table in section 3.2.P.1 adding a footnote to Table 1 (b) (4) (b) (4)

(b) (4)

Lastly, inactive ingredients names have been revised to appear in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients.

Applicant's Response: The applicant revised section 11 as requested.

The applicant's revisions are acceptable.

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant:
The dosage form was corrected (from injection to for injection) and identifying characteristics of the dosage form (white to off-white) were added per 21 CFR 201.57(c)(17).

A "do not freeze" statement is required due to lack of data to support freezing. Revise the storage and handling statement to read: "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze."

Applicant's Response: The applicant revised section 16 as requested.

The applicant's revisions are acceptable.

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
The applicant proposed a 2-line statement that included the qualifiers "Manufactured by", "at" and "for".
To applicant:
Revise the statement to three distinct pieces of information and use the qualifiers, "Manufactured by", "Manufactured at", and "Manufactured for".

Applicant's Response:
The applicant revised the statement to display 3 distinct statements with an appropriate qualifier.

The applicant's revisions are acceptable.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on February 10, 2023)
  \\CDSESUB1\EVSPROD\bla761278\0074\m1\us\1-14-1-3-draft-labeling-text-clean-20230210.docx

- Container Label (submitted on January 31, 2023)

(b) (4)

2 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

Scott Dallas

Digitally signed by Scott Dallas
Date: 2/13/2023 09:08:21PM
GUID: 508da712000294048aa136a18a6af06a

Asha Hewarathna

Digitally signed by Asha Hewarathna
Date: 2/13/2023 09:34:19PM
GUID: 5ea1f7880000b42e55aa569e14a4257d

BLA Executive Summary
Assessment Date: January 13, 2023

1. Application/Product Information

BLA number	761278
Submission Type	Original submission
Regulatory Pathway	NME 351(a); Fast Track, Orphan Drug, and Rare Pediatric Disease
Associated IND(s)/BLA	IND 113186
Review Designation	Priority
Applicant	Chiesi Farmaceutici S.p.A. Authorized U.S. Agent Name: Chiesi USA Inc.
Indication	Alpha-mannosidosis
Rx/OTC dispensed	Rx
Drug Product Name	Lamzede (velmanase alfa-tycv)
	Velmanase alfa; rhLAMAN
	RPROT O00754 (MA2B1_HUMAN) LYSOSOMAL ALPHA-MANNOSIDASE [CHFLMZYMAA1]
Drug Product Description	Lamzede (velmanase alfa-tycv) is supplied as 10 mg lyophilized powder (white to off-white powder) in a 10 mL glass vial, which contains 10 mg velmanase alfa, (b) (4) , 227.5 mg mannitol, and 10.1 mg glycine. Each vial is reconstituted with 5 mL sterile water for injection (WFI) to 2 mg/mL velmanase alfa, (b) (4) , 45.5 mg/mL mannitol, and 2.02 mg/mL glycine, at a pH of (b) (4) for intravenous (IV) infusion.
	Lamzede (velmanase alfa-tycv) is a recombinant human lysosomal alpha-mannosidase (rhLAMAN) developed as an Enzyme Replacement Therapy (ERT) for the treatment of pediatric and adult patients with confirmed diagnosis alpha-mannosidosis (AM). Velmanase alfa drug product (DP) predominantly exists as a homodimer prior to IV infusion (2 × 130 kDa). (b) (4)
Dosage Form	Lyophilized powder for solution for infusion
Strength	10 mg
Route of Administration	Intravenous
Primary container closure system	10 mL glass vial

Device Information	Not applicable		
Co-packaged Product Information	Not applicable		
	Subdiscipline	Primary	Secondary
	Drug substance (DS)	Asha Hewarathna	Ian McWilliams
	Drug product (DP)	Asha Hewarathna	Ian McWilliams
	Immunogenicity Assay	Joao Pedras-Vasconcelos	Ian McWilliams
	Facility	DS: Hamet Toure DP: Candace Gomez-Broughton	Mike Shanks
	Microbiology	DS: Hamet Toure DP: Candace Gomez-Broughton	Virginia Carroll
	RBPM	Melinda Bauerlien	
	ATL	Ian McWilliams	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability:
   The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761278 for Lamzede (velmanase alfa-tycv) manufactured by Chiesi Farmaceutici S.p.A. The data submitted in this application are adequate to support the conclusion that the manufacture of Lamzede (velmanase alfa-tycv) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter
   a. Manufacturing Location:
      i. Drug Substance:
         Rentschler Biopharma SE
         Erwin-Rentschler-Str. 21
         88471 Laupheim
         Germany
         FEI: 1000291122
      ii. Drug Product:
         Patheon Italia S.p.A.
         2° Trav. SX Via Morolense, 5
         03013 Ferentino FR
         Italy
         FEI: 3004110157

b. Fill size and dosage form: 10 mg lyophilized powder in a 10 mL glass vial.

c. Dating Period:
   i. Drug Product: 36 months at 2 to 8°C
   ii. Drug Substance: (b) (4)
   iii. Not packaged.
   iv. Stability Option: We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

4. Exempt from lot release:
   a. Yes
   b. Velmanase alfa is exempted from lot release per FR 95-29960.

5. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if applicable
   a. 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).
   b. Submit the leachables study protocol as well as the time zero (T0) report.
   c. Implement a drug product release specification for deliverable volume (e.g., according to USP <697>)
   d. 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.
   e. Implement a cell-based potency assay in drug product release specifications with pre-defined acceptance criteria.
   f. 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.
   g. 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.

h. 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.
i. Develop and validate a titering anti-drug antibody (TADA) assay as recommended the FDA guidance for industry Immunogenicity Testing for Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection (February 2019). This TADA assay will be used to test available confirmed anti-drug antibody positive samples from studies rhLAMAN-07, rhLAMAN-08, rhLAMAN-09, and rhLAMAN-10 and subsequent phase 4 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.
j. Develop and validate cell-based neutralizing antibody (NADA) assay to test inhibition of velmanase alfa enzyme uptake into target 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, and rhLAMAN-10 and subsequent phase 4 studies. Provide a final validation report detailing the performance of the cell-based NADA assay.

6. Draft Complete Response Comments and Additional Comments, if applicable – Not applicable

7. Basis for Recommendation
   a. Summary:

      Lamzede (velmanase alfa-tycv) is proposed for the treatment of pediatric and adult patients with confirmed diagnosis of AM. AM is characterized by an accumulation of intracellular mannose glycoproteins due to deficiencies in the endogenous hLAMAN enzyme. Lamzede (velmanase alfa-tycv) is an ERT that, after cellular internalization into the lysosomal low pH environment and processing into the mature form, degrades intracellular stored oligomannose.

      Lamzede (velmanase alfa-tycv) potency is controlled via the specific enzymatic activity assay and cell-based biological activity assay. The specific activity assay measures the rate of synthetic mannose substrate conversion under substrate saturating conditions. The cell-based potency assay measures the cellular internalization of Lamzede in an alpha-mannosidosis-patient derived fibroblast cell line (GM00654) and the subsequent clearance of accumulated mannose-rich glycan storage products by HILIC-HPLC. Potency is reported relative to a qualified

reference standard. Additional potency controls will be developed and implemented, via PMC, to control Lamzede enzymatic kinetics.

(b) (4)

Overall, the DS process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process by (b) (4) Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

(b) (4)

The overall velmanase alfa control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of

the DS and DP. The manufacturing processes and overall control strategies for Lamzede (velmanase alfa-tycv) as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Immunogenicity PMCs are included for further immunogenicity assay development.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Rentschler Biopharma SE (FEI: 1000291122) and Patheon Italia S.p.A. (FEI: 3004110157). All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage.

The BLA is recommended for approval from a product quality, facility, microbiology, and sterility assurance perspectives.

b. Subdiscipline Recommendation:

i.	Drug Substance	-	Adequate with PMCs/PMRs
ii.	Drug Product	-	Adequate with PMCs/PMRs
iii.	Immunogenicity Assay	-	Adequate with PMCs/PMRs
iv.	Facilities	-	Adequate
v.	Microbiology	-	Adequate

c. Environmental Assessment (EA): Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling: As an initial matter, we determined that no U.S. standard of potency has been prescribed for velmanase alfa (i.e., there is no specific test method described in regulation for velmanase alfa that establishes an official standard of potency). We next considered whether potency is a factor for velmanase alfa within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if “potency is a factor” and “no U.S. standard of potency has been prescribed.” We have determined that potency is not a factor for Lamzede (velmanase alfa-tycv) for purposes of § 610.61(r) because lot variability is not a concern for Lamzede (velmanase alfa-tycv) as Lamzede (velmanase alfa-tycv) manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

8. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No
b. Drug Substance:
   i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.S.2.3	Qualification of new working cell banks	(b) (4)	Annual report
3.2.S.2.3	Master cell bank and working cell bank retest results		Annual report
3.2.S.2.5	TFF membrane life-time study		Annual report
3.2.S.5	Primary and secondary reference standard qualification protocol		Annual report
3.2.S.5	Primary and secondary reference standard requalification protocol		Annual report
3.2.S.7.2	DS stability updates		Annual report

   ii. Residual risk: None
   iii. Future inspection points to consider: None

c. Drug Product:
   i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.S.7.2	DP stability updates	Annual stability results will be reported.	Annual report

   ii. Residual risk: None
   iii. Future inspection points to consider: None

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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/

IAN L MCWILLIAMS
01/13/2023 05:19:03 PM