

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761161Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary

Assessment Date: May 5, 2023

1. Application/Product Information

BLA number	761161
Submission Type	Resubmission
Regulatory Pathway	NME 351(a)
Associated IND/BLA	IND 110161
Review Designation	Standard Review
Applicant	Chiesi Farmaceutici S.p.A.
Indication	For the treatment of adults with confirmed Fabry disease.
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: ELFABRIO
	Non-proprietary Name/Code Name: pegunigalsidase alfa-iwxj, PRX-102
	OBP Naming: None
Drug Product Description	Pegunigalsidase alfa-iwxj injection is a sterile, preservative-free, 20 mg/10 mL (2 mg/mL) solution in a single-dose vial for intravenous infusion. Each mL contains 2 mg of pegunigalsidase alfa-iwxj, and anhydrous citric acid (0.2 mg), sodium chloride (7.06 mg), sodium citrate (6.73 mg), and Water for Injection, USP. The pH is approximately 5.9 to 6.4. Pegunigalsidase alfa-iwxj, a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme, is a PEGylated, covalently crosslinked, chemically modified, recombinant human alpha-galactosidase A (alpha-Gal A) enzyme produced by genetically modified Bright Yellow 2 (<i>Nicotiana tabacum</i>) plant cells. Pegunigalsidase alfa-iwxj is a homodimeric glycoprotein with an average of nine 2.3 kD PEG per dimer. The total molecular weight of the cross-linked dimer is approximately 116 kDa. Pegunigalsidase alfa-iwxj has specific activity of approximately 35-62 U/mg (one enzyme unit is defined as the amount of enzyme which catalyzes the hydrolysis of one micromole of synthetic substrate, p-nitrophenyl-α-D-galactopyranoside per minute at 37°C).
Dosage Form	Liquid
Strength	20 mg/10 mL (2 mg/mL)

Route of Administration	Intravenous infusion		
Primary Container Closure System	Clear glass vial		
Device Information	N/A		
Co-packaged Product Information	N/A		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Ying-Xin Fan	Kelley Burrridge
	Drug product		
	Immunogenicity Assay		
	Facility	DS: Charles Yuan-Chia Kuo	Zhong Li
	Microbiology	DP: Jeanne Fringer	Maxwell Van Tassell
	RBPM	Erica Keafer	
	ATL	Kelley Burrridge	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761161 for ELFABRIO manufactured by Chiesi Farmaceutici S.p.A. The data submitted in this application are adequate to support the conclusion that the manufacture of ELFABRIO 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:

- **Drug Substance:** Protalix Ltd., 2 Snunit St., Science Park, Carmiel 2161401 Israel; FEI: 3008289067
- **Drug Product:** Chiesi Farmaceutici S.p.A., 96 via S. Leonardo, 41322 Parma, Italy; FEI: 3002806655

b. Fill size and dosage form: ELFABRIO is supplied as a 20 mg/10 mL (2 mg/mL) solution in a single-dose glass vial.

c. Dating Period:

- **Drug Product:** 48 months at 2 to 8°C
- **Drug Substance:** (b) (4) months at (b) (4)°C
- **Intermediate Substance** (b) (4)

- **For packaged products:** Not co-packaged
- d. Exempt from lot release:**
- Yes
 - Rationale, if exempted: ELFABRIO is exempted from lot release per FR 95-29960.

4. Basis for Recommendation

a. Summary:

Pegunigalsidase alfa is a PEGylated, crosslinked, chemically modified, recombinant human alpha-galactosidase A enzyme. The DS is a homodimeric glycoprotein covalently crosslinked with an average of nine 2.3 kD PEG per dimer. The total molecular weight of the cross-linked dimer is approximately 116 kDa. The major form of pegunigalsidase DS is a homodimer covalently cross-linked by PEG chains. Some PEG chains are bound to one protein monomer only. Pegunigalsidase alfa also contains noncovalently bound homodimers when no crosslinking occurs between protein subunits (quantified as subunits by denatured SE-HPLC). In addition, biologically active tetramers (two homodimers) are also found.

(b) (4)



(b) (4)

the human alpha GAL-A sequence of 398 amino acids, and an endoplasmic reticulum retention sequence of 6 amino acids at the C-terminus. (b) (4)

(b) (4)

Because prh-alpha-GAL-A is expressed in plant cells, it has typical plant glycosylation at Asn-109, Asn-162, and Asn-185. The prh-alpha-GAL-A sequence contains 5 disulfide bonds and two unpaired cysteines. The disulfide bonds in prh-alpha-GAL-A are formed with cystine pairs C22–C64, C26–C33, C112–C142, C172–C193, and C348–C352.

Pegunigalsidase alfa drug product is an enzyme replacement therapy (ERT) designed to treat Fabry disease. Patients with Fabry disease have elevated plasma Lyso-Gb3 levels due to low or absent enzyme activity of the lysosomal enzyme alpha-Gal A. Pegunigalsidase alfa-iwxj provides an exogenous source of alpha-Gal A. Pegunigalsidase alfa-iwxj is internalized and transported into lysosomes where it exerts its enzymatic activity on globotriaosylceramide (Gb3). The enzyme is PEGylated and crosslinked to increase stability, resulting in more enzyme entering the target cells before undergoing degradation.

To fulfill its biological function, the enzyme needs to be active and internalized into target cells. Potency is measured through two assays to assess enzyme kinetics and cellular uptake. The Michaelis Menten enzyme kinetics assay measures specific activity, Michaelis constant (Km), and turnover number (Kcat). The enzymatic assay uses the synthetic substrate p-nitrophenyl- α -D-galactopyranoside (pNP-G). The cell-based uptake assay quantitatively measures the internalization of pegunigalsidase alfa into a NR8383 macrophage cell line. The assay measures the ability of the enzyme to be internalized by cell surface mannose receptors as demonstrated by inhibition of cell uptake while using mannan. Relative potency is calculated as the ratio between the EC50 values of the reference standard and the tested samples, multiplied by 100.

The enzyme is produced by

(b) (4)

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

Assessment of method validation concluded that the peptide map purity method required additional consideration of oxidized product-related substances to establish quantitative correlations between the levels of the peaks and the levels of the impurities. PMC number 11 will address this analytical method issue and confirm that the method is suitable for its intended purpose.

The potential impact of the drug product shipping and handling process on product quality has not been directly evaluated. Evaluating the shipping impact is important because pegunigalsidase alfa drug product is shipped in liquid form. The sponsor plans to perform a real-time shipping validation study using the first three commercial drug product batches. The confirmatory shipping study in PMC number 10 includes tests to compare critical quality attributes before and after shipping.

Four PMRs, numbers 3 through 6, relate to immunogenicity assay development and improvement. These PMRs were developed collaboratively with Clinical Pharmacology Reviewers Dr. Jack (Jie) Wang and Dr. Michelle (Xiaohui) Li. The neutralizing antibody assay will be used to assess banked clinical samples from studies PB-102-F01/02, PB-102-F03, and PB-102-F20, which will be recommended as separate PMR study number 7.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate with PMCs/PMRs
Drug Product	-	Adequate with PMCs/PMRs
Immunogenicity Assay	-	Adequate with PMCs/PMRs
Facilities	-	Adequate
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 ELFABRIO (i.e., there is no specific test method described in regulation for ELFABRIO that establishes an official standard of potency). We next considered whether potency is a factor for ELFABRIO 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 ELFABRIO for purposes of § 610.61(r) because lot variability is not a concern for ELFABRIO as ELFABRIO’s manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No



ii. Residual risk:

1. Oxidized Species: Improve and revalidate the analytical method for quantifying oxidized species and update the DS and DP specifications under PMC.

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocol approved:

1. Annual Stability Protocol

ii. Residual risk:

1. Oxidized Species: Improve and revalidate the analytical method for quantifying oxidized species and update the DS and DP specifications under PMC.
2. Shipping: Conduct a DP shipping validation study on first three commercial shipments that includes product quality testing before and after under PMC.
3. Immunogenicity: Four PMRs to improve and validate the following assays: detection of neutralizing antibodies that inhibit cellular uptake, anti-PEG IgE antibody, anti-pegunigalsidase IgG antibody assay or new assay to improve drug tolerance, and anti-pegunigalsidase IgM antibody.

iii. Future inspection points to consider: OPMA will request a post approval inspection of the drug product manufacturing facility, Chiesi Farmaceutici, to be conducted by ORA in order to verify adequate completion of corrective actions from the Form 483 Observations.

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/

KELLEY A BURRIDGE
05/08/2023 11:59:48 AM

Recommendation: Complete Response

BLA Number: 761161
Assessment Number: 1
Assessment Date: April 26, 2021

Drug Name/Dosage Form	ELFABRIO (pegunigalsidase alfa-iwxj) injection, for intravenous use
Strength/Potency	20 mg/10 mL (2 mg/mL)
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	For the treatment of adults with confirmed Fabry disease. This indication is approved under accelerated approval based on reduction of globotriaosylceramide (Gb3) inclusion bodies in renal peritubular capillary cells. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.
Applicant/Sponsor	Chiesi USA
US agent, if applicable	N/A

Product Overview:

Pegunigalsidase alfa-iwxj, a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme, is a PEGylated, crosslinked, chemically modified, recombinant human alpha-galactosidase A (alpha-Gal A) enzyme that is produced by genetically modified Bright Yellow 2 (*Nicotiana tabacum*) plant cells. Pegunigalsidase alfa-iwxj is a homodimeric glycoprotein covalently crosslinked with an average of nine 2.3 kD PEG per dimer. The total molecular weight of the cross-linked dimer is approximately 116 kDa. Pegunigalsidase alfa-iwxj has specific activity of approximately 36-60 U/mg (one enzyme unit is defined as the amount of enzyme which catalyzes the hydrolysis of one micromole of synthetic substrate, p-nitrophenyl- α -D-galactopyranoside per minute at 37°C).

Pegunigalsidase alfa-iwxj provides an exogenous source of alpha-Gal A. Pegunigalsidase alfa-iwxj is internalized and transported into lysosomes where it exerts its enzymatic activity on globotriaosylceramide (Gb3). Pegunigalsidase alfa-iwxj injection is a sterile, preservative-free, 20 mg/10 mL (2 mg/mL) solution in a single-dose vial for intravenous infusion. Each mL contains 2 mg of pegunigalsidase alfa-iwxj, and citric acid (0.2 mg), sodium chloride (7.06 mg), sodium citrate (b) (4) (b) (4) mg), and Water for Injection, USP. The pH is approximately 5.9 to 6.4.

Quality Assessment Team:

Discipline	Assessor	Team Leader	Branch/Division
Drug Substance	Ying-Xin Fan	Kelley Burridge	CDER/OPQ/OBP/DBRRIV
Drug Product	Leiyun (Janney) Boone		
Analytical Methods	Sivakoteswara Rao Mandadapu		
Immunogenicity	Ying-Xin Fan		
Labeling	Vicky Borders-Hemphill		CDER/OPQ/OBP
Facility	Jeanne Fringer	Thuy Thanh Nguyen	CDER/OPQ/OPMA/DBM/BMB1
Microbiology-Drug Substance	Zhong Li	Maxwell Van Tassell	
Microbiology-Drug Product	Jeanne Fringer		
Application Team Lead	Kelley Burridge		CDER/OPQ/OBP/DBRRIV
RBPM	Andrew Shiber		CDER/OPQ/OPRO/DRBPMI/RBPMB1

Multidisciplinary Assessment Team:

Discipline	Assessor	Team Lead	Office/Division
RPM	Michael G. White, Nicolas Kong		CDER/OND/ORO/DRORDPURM
Cross-disciplinary Team Lead	Patroula Smpokou		CDER/OND/ORDPURM/DRDMG
Medical Officer	Anita Zaidi	Patroula Smpokou	CDER/OND/ORDPURM/DRDMG
Pharmacology/Toxicology	Jackye Peretz	Mukesh Summan	CDER/OND/OII/DPTII
Clinical Pharmacology	Xiaohui (Michelle) Li	Jie (Jack) Wang	CDER/OTS/OCP/DTPM
Statistics	Yared Gurmu	Yan Wang	CDER/OTS/OB/DBIV
Pharmacometrics	Hongshan Li	Lian Ma	CDER/OTS/OCP/DPM

1. Names:

- a. Proprietary Name: ELFABRIO
- b. Trade Name: ELFABRIO
- c. Non-Proprietary Name/USAN: pegunigalsidase alfa-iwxj
- d. CAS Name: 1644392-61-9
- e. Common Name: PRX-102
- f. INN Name: pegunigalsidase alfa-iwxj
- g. OBP systematic name: none

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 761161/0001 - New/BLA	May 27, 2020
STN 761161/0002 - Labeling/Package Insert Draft	June 5, 2020
STN 761161/0004 - Quality/Response To Information Request	July 13, 2020
STN 761161/0006 - Quality/Response To Information Request	July 17, 2020
STN 761161/0011 - Quality/Response To Information Request	August 19, 2020
STN 761161/0019 - Quality/Response To Information Request	October 14, 2020
STN 761161/0020 - Meeting/Meeting Request; Meeting/Meeting Package	October 20, 2020
STN 761161/0023 - Quality/Response To Information Request	October 30, 2020
STN 761161/0024 - Labeling/Container-Carton Draft	November 3, 2020
STN 761161/0027 - Quality/Response To Information Request	November 13, 2020
STN 761161/0031 - Quality/Response To Information Request	December 9, 2020
STN 761161/0032 - Meeting/Meeting Request; Meeting/Meeting Package	December 21, 2020
STN 761161/0034 - Quality/Response To Information Request	January 22, 2021
STN 761161/0036 - Quality/Response To Information Request	February 19, 2021
STN 761161/0039 - Labeling/Container-Carton Draft	March 17, 2021
STN 761161/0040 - Labeling/Package Insert Draft	March 25, 2021
STN 761161/0043 - Labeling/Container-Carton Draft	March 31, 2021
STN 761161/0044 - PMR/PMC/General Correspondence	April 1, 2021
STN 761161/0047 - PMR/PMC/General Correspondence	April 12, 2021

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	3	N/A	N/A	LOA October 13, 2020
	III			3	N/A	N/A	

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows:
2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed).

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	110161	Investigation of the use of PRX-102 for the treatment of patients with Fabry disease. Initially submitted on October 7, 2010.

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion: Acceptable per 21 CFR 25.31(b) and 21 CFR 25.31(c)

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of STN 761161 for ELFABRIO (pegunigalsidase alfa-iwxj) manufactured by Chiesi USA. The data submitted in this application are not sufficient to support a conclusion that the manufacture of ELFABRIO is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Chiesi USA to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues: (Action Letter Language)

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.

FACILITIES

During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, the FDA 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. The FDA will communicate the outstanding issues to the facility no later than 10 business days from issuing this complete response letter. Please contact (b) (4) manufacturing facility for additional information.

OTHER

FACILITY INSPECTIONS

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, please see the FDA guidances related to COVID 19.

C. Approval Action Letter Language: CR (see items listed above)

D. Benefit/Risk Considerations:

Pegunigalsidase alfa drug product is an enzyme replacement therapy (ERT) designed to treat Fabry disease. Patients with Fabry disease have elevated plasma Lyso-Gb3 levels due to low or absent enzyme activity of the lysosomal enzyme alpha-Gal A. Treatment with ELFABRIO reduced plasma lyso-Gb3 levels in patients with Fabry disease in both ERT-naïve and ERT-experienced patients.

Due to the COVID-19 pandemic, we were unable to perform pre-license inspections on the DS manufacturing site Protalix in Israel and the DP manufacturing site (b) (4). This BLA cannot be approved before the DP manufacturer (b) (4) provides satisfactory resolution of the issues from the 704(a)(4) records review communicated to the firm in an Assessment Issues Letter (AIL) and the FDA conducts an inspection of the DS site Protalix. Post-marketing requirements (PMRs) and post-marketing commitments (PMCs) were agreed upon by the sponsor prior to the CR as the facility recommendation occurred late in the cycle due to pandemic-related logistical issues.

Five PMRs, numbers 4 through 8, relate to immunogenicity assay development and improvement. These PMRs were developed collaboratively with Clinical Pharmacology Reviewers Dr. Jack (Jie) Wang and Dr. Michelle (Xiaohui) Li. The neutralizing antibody assay will be used to assess banked clinical samples from studies PB-102-F01/02, PB-102-F03, and PB-102-F30, which will be recommended as separate PMR study number 9.

Currently, microbial (bioburden and endotoxin) testing data from (b) (4)

The potential impact of the shipping and handling process on product quality has not been directly evaluated. Because pegunigalsidase alfa drug product is shipped in liquid form, it is important to evaluate the shipping impact. The sponsor plans to perform the real-time shipping validation study using the first three commercial drug product batches. PMC number 14 is a confirmatory shipping study that will include tests to compare critical quality attributes before and after shipping.

Assessment of method validation concluded that the peptide map purity method required additional consideration of oxidized product-related substances to establish quantitative correlations between the levels of the peaks and the levels of the impurities. Also, (b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

PMR XXXX-4

PMR Description

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

PMR Schedule Milestones

Study/Trial Completion: 07/2023
Final Report Submission: 01/2024

PMR XXXX-5

PMR Description

Develop and validate an anti-PEG IgE antibody assay.

PMR Schedule Milestones

Study/Trial Completion: 08/2023
Final Report Submission: 02/2024

PMR XXXX-6

PMR Description

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

PMR Schedule Milestones

Study/Trial Completion: 05/2022
Final Report Submission: 08/2022

PMR XXXX-7

PMR Description

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.

PMR Schedule Milestones

Study/Trial Completion: 05/2022
Final Report Submission: 08/2022

PMC XXXX-14

PMC Description

Conduct a drug product (DP) shipping validation study using

(b) (4)

the first three commercial shipments of 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.

PMC Schedule Milestones

Final Report Submission: 12/2021

PMC XXXX-15

PMC Description

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.

PMC Schedule Milestones

Final Report Submission: 12/2022



(b) (4)

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

Type of CQA	Quality Attribute	Risk	Origin	Control Strategy
Appearance	Clarity	Stability	Formulation	(b) (4)
	Color		Formulation. Potentially from process or environment.	
	Visible Particles			
Strength	Protein Concentration and Batch Homogeneity	Biological Activity, Safety	Formulation	
Potency	- Enzymatic Activity (b) (4), DS, and DP) - Enzyme Kinetics (DS and DP)	Stability, Biological Activity	Intrinsic to molecule, in-process and on stability	

Type of COA	Quality Attribute	Risk	Origin	Control Strategy
Product-related Impurities	(b) (4)	Stability, Biological Activity, Safety	(b) (4)	(b) (4)
	HMMS species	Stability, biological activity, PK/PD, immunogenicity, safety Tetramer and isoforms identified by HIC have same enzymatic activity and cellular uptake activity as the main forms.	Protein isoforms. Potentially impacted by in-process conditions, formulation, and on stability. Tetramers are active in the cellular uptake and enzymatic activity potency assays.	(b) (4)
	Oxidation	Stability, biological activity, PK/PD, immunogenicity	Protein isoforms. Potentially impacted by in-process conditions and on stability.	(b) (4)

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- Description:

(b) (4)

[REDACTED] the human alpha GAL-A sequence of 398 amino acids, and an endoplasmic reticulum retention sequence of 6 amino acids at the C-terminus. [REDACTED]

(b) (4)

[REDACTED]. Because prh-alpha-GAL-A is expressed in plant cells, it has typical plant glycosylation at Asn-109, Asn-162, and Asn-185. The prh-alpha-GAL-A sequence contains 5 disulfide bonds and two unpaired cysteines. The disulfide bonds in prh-alpha-GAL-A are formed with cystine pairs C22–C64, C26–C33, C112–C142, C172–C193, and C348–C352.

- Potency Assay: Michaelis Menten assay measuring specific activity. The enzymatic assay uses the synthetic substrate p-nitrophenyl- α -D-galactopyranoside (pNP-G) because the native substrate has very low solubility making detection problematic.

- Reference Materials:

(b) (4)

- Critical starting materials or intermediates:

(b) (4)

[Redacted content] (b) (4)

- Manufacturing process summary: [Redacted content] (b) (4)

- Container closure: [Redacted content] (b) (4)
- Dating period and storage conditions: [Redacted content] (b) (4)

C. Drug Substance [pegunigalsidase alfa-iwxj] Quality Summary

Table 3: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

Type of CQA	Quality Attribute	Risk	Origin	Control Strategy
Identity	Identity by: 1) Peptide Map 2) SDS-PAGE/Western Blot 3) Molecular Weight	Control of batch-to-batch variability, biological activity, safety	Intrinsic to molecule	[Redacted content] (b) (4)

Type of CQA	Quality Attribute	Risk	Origin	Control Strategy
Potency	Cellular Uptake	Stability, biological activity, PK/PD	Intrinsic to molecule, in-process and on stability	(b) (4)
Extent of Crosslinking	Total PEG Content	Biological activity, PK/PD, Immunogenicity	PEGylation and crosslinking reaction performed (b) (4)	
Physicochemical Properties	pH	Stability	Formulation. Potentially impacted by in-process conditions and on stability.	
Microbiological Contaminants	Bacterial Endotoxins	Safety, purity	Process, raw materials	
	Bioburden (total aerobic count)	Safety, purity Efficacy due to degradation or modification of the product by microbial contamination.		

- Description:** Pegunigalsidase alfa is a PEGylated, crosslinked, chemically modified, recombinant human alpha-galactosidase A enzyme. The DS is a homodimeric glycoprotein covalently crosslinked with an average of nine 2.3 kD PEG per dimer. The total molecular weight of the cross-linked dimer is approximately 116 kDa. The major form of pegunigalsidase DS is a homodimer covalently cross-linked by PEG chains. Some PEG chains are bound to one protein monomer only. Pegunigalsidase alfa also contains noncovalently bound homodimers when no crosslinking occurs between protein subunits (quantified as subunits by denatured SE-HPLC). In addition, biologically active tetramers (two homodimers) are also found.
- Mechanism of Action (MoA):** Pegunigalsidase alfa is an enzyme replacement therapy for Fabry disease that provides an exogenous source of alpha-Gal A. Pegunigalsidase alfa is internalized and transported into lysosomes where it exerts its enzymatic activity on globotriaosylceramide (Gb3). The enzyme is PEGylated and crosslinked to increase stability, resulting in more enzyme entering the target cells before undergoing degradation.

D. Drug Product [ELFABRIO] Quality Summary:

Table 4: Drug Product CQA Identification, Risk, and Lifecycle Management

Type of CQA	Quality Attribute	Risk	Origin	Control Strategy ^{(b) (4)}
Identity	Identity by: 1) Peptide Map 2) Molecular Weight	Control of batch-to-batch variability, biological activity, safety	Intrinsic to molecule	
Potency	Cellular Uptake	Stability, biological activity, PK/PD	Intrinsic to molecule, in-process and on stability	
Extent of Crosslinking	Total PEG Content	Biological activity, PK/PD, Immunogenicity	PEGylation and crosslinking reaction performed ^{(b) (4)}	
Particles	Subvisible Particles ^{(b) (4)}	Stability, safety	Formulation, protein precipitation	
Physicochemical Properties	pH	Stability	Formulation. Potentially impacted by in-process conditions and on stability.	
	Osmolality	Stability, safety	Formulation	
Microbiological Contaminants and Sterility Assurance	Bacterial Endotoxins	Safety, purity	Process, raw materials	
	Sterility	Safety, purity Efficacy due to degradation or modification of the product by microbial contamination.	Process, failure of container closure integrity, breach during manufacture or storage.	

Type of CQA	Quality Attribute	Risk	Origin	Control Strategy (b) (4)

- Potency and Strength: 20 mg/10 mL (2 mg/mL) solution of pegunigalsidase alfa in a single-dose vial
- Summary of Product Design: Sterile, preservative-free, clear, colorless solution that is diluted in 0.9% Sodium Chloride Injection, USP before intravenous infusion to deliver the recommended dosage of 1 mg/kg.
- List of Excipients: citric acid (0.2 mg), sodium chloride (7.06 mg), sodium citrate (b) (4) (b) (4) mg), and Water for Injection, USP
- Reference Materials: (b) (4)
- Manufacturing process summary: (b) (4)
- Container closure: clear, (b) (4) type (b) (4) glass vial closed with (b) (4) 20 mm, (b) (4) rubber stopper and aluminum crimp seal with (b) (4) flip off cap
- Dating period and storage conditions: 48 months at 2 to 8°C
- List of co-package components, if applicable: N/A

E. Novel Approaches/Precedents:

Due to the COVID-19 pandemic, we were unable to perform pre-license inspections on the DS manufacturing site Protalix in Israel or the DP manufacturing site (b) (4). Peter Qiu from OPMA, Ying-Xin Fan and Kelley Burrige from OBP, and Thomas Arista and Simone Pitts from ORA remotely observed an GMP inspection of the Protalix site conducted by the (b) (4). Because this is the first manufacturing process at Protalix using BY2 cells and performing PEGylation, an FDA inspection is required for approval of this BLA. Maxwell Van Tassell, Jeanne Fringer, Wayne Seifert, Zhong Li, and Peter Qiu from OPMA plus Leiyun Boone and Kelley Burrige from OBP

completed a joint OPQ-OMQ 704(a)(4) records review for the DP manufacturing facility (b) (4). An Assessment Issues Letter (AIL) with eight issues was sent to (b) (4) on April 13, 2021. The manufacturer was unable to provide satisfactory resolution of the AIL observations, which was required for approval of this BLA.

F. Any Special Product Quality Labeling Recommendations:

- Store in a refrigerator at 2 to 8°C.
- Do not freeze.
- Do not shake.
- Store reconstituted solutions of ELFABRIO for up to 24 hours at 2°C to 8°C (36°F to 46°F) or up to 8 hours at room temperature at 20°C to 25°C (68°F to 77°F).

G. Establishment Information:

Overall Recommendation: Withhold					
DRUG SUBSTANCE					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Storage of MCB/WCB; Manufacture of DS; Release and stability	Protalix Ltd Carmiel, Israel	3008289067	Pre-license inspection requested	N/A	Deferred – Travel Restrictions-COVID
(b) (4)			Acceptable based on previous history	N/A	Approve
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary

(b) (4)					
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
			No evaluation necessary	N/A	No evaluation necessary
DRUG PRODUCT					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
(b) (4)			Section 704 Assessment	8 AIL Issues Communicated	Withhold
			Acceptable based on previous history	N/A	Approve
DP Secondary Packaging (Including Labelling); Batch release	Chiesi Farmaceutici S.p.A. Parma, Italy	3002806655	No evaluation necessary	N/A	No evaluation necessary
Drug product final release	Chiesi USA, Inc. Cary, North Carolina, USA	3006389494	No evaluation necessary	N/A	No evaluation necessary
(b) (4)			No evaluation necessary	N/A	No evaluation necessary
			Acceptable based on previous history	N/A	Approve

(b) (4)	Acceptable based on previous history	N/A	Approve
	No evaluation necessary	N/A	No evaluation necessary
	Acceptable based on previous history	N/A	Approve
	No evaluation necessary	N/A	No evaluation necessary
	No evaluation necessary	N/A	No evaluation necessary
	Acceptable based on previous history	N/A	Approve
	No evaluation necessary	N/A	No evaluation necessary

H. Facilities:

A pre-license inspection of the DS manufacturer, Protalix, in Israel (FEI: 3008289067) is recommended based on the firm’s inexperience with the manufacturing requirements for BLA products. (b) (4)

In addition, there are deficiencies in the sponsor’s application about process control and quality systems at Protalix, and the firm’s production system was not covered during the last surveillance inspection.

Due to COVID restrictions, the inspection of Protalix was initially postponed. FDA remotely observed the PRX-102 manufacturing process at the Protalix facility during an (b) (4) inspection conducted in March 2021. The preliminary findings from the (b) (4) inspection were reviewed and have not changed the FDA’s recommendation of a PLI for Protalix due to the number of GMP concerns cited. The recommendation for this facility is deferred due to the COVID travel restrictions.

A withhold is recommended for this application based on the outcome of the Section 704(a)(4) records review of the DP manufacturer, (b) (4)

The 704(a)(4) records request was initiated for (b) (4) based on the firm’s most recent acceptable inspection history: an inspection by FDA from (b) (4) resulted in (b) (4). The pre-inspection audit documents submitted by (b) (4) were assessed, and an AIL containing 8 issues was sent to the firm on April 13, 2021. The issues described inadequacies in the following: (b) (4)

(b) (4) The response from the firm was received on April 23rd, 2021 and deemed inadequate. The firm referenced ongoing investigations into the issues cited in the AIL letter; however, as the outcome of those investigations are still pending, a withhold recommendation from FDA is warranted.

I. Lifecycle Knowledge Management:

a. (b) (4) Drug Substance:

- i. Protocols approved: None
- ii. Outstanding assessment issues/residual risk: See inspection points below plus the DS and DS microbiology reviews for items to be followed up on during the pre-license inspection.
 - 1. Follow-up on stability testing of WCB during storage.
- iii. Future inspection points to consider: Pre-license inspection not yet conducted.

b. Drug Product

- i. Protocols approved: None
- ii. Outstanding assessment issues/residual risk: See inspection points below plus the DP and DP microbiology reviews for items to be followed up on.

(b) (4)

- iii. Future inspection points to consider: 704(a)(4) records review completed; site's response to Assessment Issues Letter not satisfactory

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/

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04/26/2021 06:05:54 PM

CHRISTOPHER D DOWNEY
04/26/2021 08:02:52 PM