CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761161Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 8, 2023

To: Diego Diaz, Regulatory Project Manager
Division of Rare Diseases and Medical Genetics (DRDMG)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for ELFABRIO® (pegunigalsidase alfa-iwxj) injection, for intravenous use

BLA: 761161

Background:
In response to DRDMG's consult request dated November 28, 2022, OPDP has reviewed the proposed Prescribing Information (PI) and carton and container labeling for the original BLA submission for ELFABRIO® (pegunigalsidase alfa-iwxj) injection, for intravenous use.

PI:
OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on May 4, 2023, and we do not have any comments at this time.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on May 3, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at carrie.newcomer@fda.hhs.gov.

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

---

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/

CARRIE A NEWCOMER
05/08/2023 11:55:03 AM

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: Expedited ARIA Sufficiency Determination for Pregnancy Safety Concerns
Version: 2018-01-24

Date:	May 8, 2023
Reviewer:	Joel L. Weissfeld, MD MPH Division of Epidemiology 1
Team Leader:	Benjamin J. Booth, PhD MS Division of Epidemiology 1
Division Director:	Wei Hua, MD PhD MS MHS Division of Epidemiology 1
Subject:	ARIA Sufficiency Memo
Drug Name(s):	Pegunigalsidase alfa (ELFABRIO)
Application Type/Number:	BLA 761161
Submission Number:	0058
Applicant:	Chiesi USA
OSE TTT #:	2023-4078

1. BACKGROUND INFORMATION

1.1. Medical Product

Pegunigalsidase alfa (ELFABRIO) is PEGylated recombinant human alpha-galactosidase A (GLA) enzyme replacement therapy (ERT) for Fabry disease, a low prevalence X-linked inherited disease caused by deficient GLA activity. Fabry disease classically presents with symptoms in childhood, proteinuria in early adulthood, and premature death from renal failure, heart failure, cardiac arrhythmia, or stroke.

The Applicant (Chiesi USA) resubmitted its BLA for ELFABRIO on November 9, 2022, to address deficiencies identified in an original application submitted on May 27, 2020, and amended on November 4, 2020.[a]

Prescribing Information (PI) for ELFABRIO recommends dosing at 1 mg/kg body weight every other week by intravenous (IV) infusion. The PI presents the mean elimination half-life at (1) 79 hours for the first dose in adults without any ERT in the previous 26 weeks and (2) 121 hours in adults after 52 weeks of ERT with pegunigalsidase alfa.

1.2. Describe the Safety Concern

An October 2020 review by the Division of Pediatric and Maternal Health (DPMH) described one clinical trial participant who became pregnant during ERT with pegunigalsidase alfa.[b] This participant electively terminated pregnancy (for personal reasons) one week after normal fetal ultrasound at 13 weeks.

The PI presents results from non-clinical embryofetal studies, which showed:

- No maternal or fetal adverse effects in rats at exposures 3.6-fold greater than the equivalent human dose of 1 mg/kg every two weeks.
- Maternal toxicity (e.g., mortality) and embryofetal effects (e.g., abortion) in rabbits at exposures as low as 3.2-fold greater than the equivalent human dose of 1 mg/kg every two weeks.

DPMH recommended a pregnancy safety study as a postmarketing requirement (PMR) because "[t]here are no data on the use of pegunigalsidase alfa in pregnancy."

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

[a] Complete Response, filed under BLA 761161 on April 27, 2021 (DARRTS Reference ID: 4786555).

[b] Sun W, C Ceresa, and LP Yao, Division of Pediatric and Maternal Health Review: [redacted] (b) (4) (pegunigalsidase alfa) injection, for intravenous use, filed under BLA 761161 on October 6, 2020 (DARRTS Reference ID: 4681128).

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of child bearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)

☐ Electronic database study with chart review

☐ Electronic database study without chart review

☒ Other, please specify: A protocol-driven single-arm observational study of pegunigalsidase alfa safety during pregnancy. This study should prospectively or retrospectively collect detailed clinical information to enable complete case narratives of maternal and fetal outcomes after pregnancy exposures to pegunigalsidase alfa. A comparative study with pre-specified sample size is not feasible because of the low population prevalence of Fabry disease.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population

☐ Exposures

☒ Outcomes

☐ Covariates

☐ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: The requested single-arm observational study requires targeted questionnaires that collect detailed information about the timing of pegunigalsidase alfa exposures in relation to

well-characterized pregnancy outcomes. A series of well-documented case narratives that present detailed clinical information acquired directly from primary sources (e.g., medical records) might permit credible assessment of the causal significance of adverse events associated with pegunigalsidase alfa exposures during pregnancy. (b) (4)

2.5. Please include the proposed PMR language in the approval letter.

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

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/

JOEL L WEISSFELD
05/08/2023 08:54:30 AM

BENJAMIN J BOOTH
05/08/2023 08:58:42 AM

WEI HUA
05/08/2023 09:48:32 AM

JUDITH W ZANDER
05/08/2023 10:34:15 AM

PATRICIA L BRIGHT
05/08/2023 11:17:36 AM

ROBERT BALL
05/08/2023 11:20:28 AM

Division of Cardiology and Nephrology Consult

Date: April 24, 2023
BLA number and product name: BLA 761161 PRX-102
From: Yaa Oppong, Medical Officer, Division of Cardiology and Nephrology
Through: Rekha Kambhampati, Team Leader, Division of Cardiology and Nephrology
Aliza Thompson, Deputy Director, Division of Cardiology and Nephrology
To: Diego Diaz, Regulatory Project Manager, Division of Rare Diseases and Medical Genetics
Mehul Desai, Medical Officer, Division of Rare Diseases and Medical Genetics
Subject: Input on eGFR as a clinical endpoint to support approval and appropriateness of the non-inferiority margin versus Fabrazyme

---

Background

PRX-102 (pegunigalsidase alfa) is a PEGylated, plant cell expressed, recombinant human protein α-galactosidase A protein that is being developed as long-term enzyme replacement therapy (ERT) in patients with Fabry disease (FD). Fabry disease is a lysosomal storage disease that results from an X-linked mutation in the GLA gene causing a deficiency of the enzyme α-galactosidase A. In Fabry disease, Globotriaosylceramide (Gb3) accumulates in cardiovascular, nervous system, and renal tissues leading to a variety of clinical manifestations including progressive renal impairment.

On November 9, 2022, the Division of Rare Diseases and Medical Genetics (DRDMG) received a class 2 BLA submission for pegunigalsidase alfa (PRX-102) for the proposed indication of "treatment of adults with confirmed Fabry disease." In support of the resubmission, the Applicant submitted trial PB-102-F20 which compared PRX-102 to the approved ERT agalsidase beta (Fabrazyme) in FD patients. On November 28, 2022, the Division of Rare Diseases and Medical Genetics (DRDMG) asked the Division of Cardiology and Nephrology (DCN) to assist in evaluating the data on change in eGFR slope as relates to clinical benefit and the non-inferiority margin (NI) used in study PB-102-F20. In an email dated December 14, 2022, DRDMG also asked DCN to comment on the strength and quality of the available external clinical data (e.g., published studies) supporting the Applicant's proposed NI margin, and also on any additional data such as biomarkers or secondary clinical endpoints that showed a favorable signal for renal benefit.

Regulatory History

On May 27, 2020, the Applicant (Chiesi) initially submitted a BLA (761161) to DRDMG seeking approval under the provisions of 21 CFR Part 601 Subpart E (i.e., accelerated approval pathway), utilizing a reduction in renal peritubular capillary Gb3 inclusions as a reasonably likely surrogate endpoint. To support approval, the Applicant submitted the results of Study PB-102-F01/F02 which was an open label study that evaluated reductions of Gb3 inclusions in the renal peritubular capillary at different PRX-102 dose levels (0.2mg/kg, 1.0mg/kg and 2.0mg/kg) in FD patients. On April 27, 2021, DRDMG issued a Complete Response Letter (CRL), which stated the following: 1) "Satisfactory resolution of the remaining [manufacturing facility] issues is required before this application may be approved," and 2) "…with the full approval of Fabrazyme (agalsidase beta) on March 11, 2021, Fabrazyme is now available therapy for Fabry disease. Your product will no longer qualify for accelerated approval if it does not provide a therapeutic advantage over available therapy." Subsequently, the Applicant revised the protocol of their ongoing phase 3 study (PB-102-F20) from an evaluation of superiority comparing eGFR slope at 2 years

between PRX-102 and Fabrazyme to a non-inferiority evaluation. During the End-of-Review meeting on September 9, 2021, the Agency agreed that a non-inferiority analysis plan may be a reasonable approach to address the deficiency cited in the CRL, "provided adequate justification and strong evidence to support such a statistical approach" was presented.

During a Type C meeting on January 21, 2022, the Agency did not agree with the Applicant's proposed non-inferiority margin of -3 mL/min/1.73 m^2/year. The Agency noted that an appropriate noninferiority margin should adequately reflect an anticipated treatment effect of Fabrazyme (over placebo), and the data submitted (i.e., interim analysis of Study PB-102-F20) by the Applicant and available data for Fabrazyme during its approval did not justify the selected NI margin. The Agency also recommended that the Applicant provide an additional analysis of the treatment benefit on the primary efficacy endpoint for patients in the phase 3 trial treated with PRX-102 compared to an (external) untreated cohort of FD patients in their BLA resubmission. In the BLA resubmission, the Applicant indicated that a real-world untreated cohort that was comparable to patients in their study (PB-102-F20) could not be "constituted" for the statistical analysis due to the small number of patients fitting the requirements.

Of note, on March 8, 2022, the Medical Policy & Program Review Council (MPPRC) discussed the data submitted under BLA 761161 (PRX-102) and whether it is sufficient to support substantial evidence of effectiveness. See the official meeting minutes (once available) for details.

Materials reviewed

- Clinical Study Report for Study PB-102-F20 version 1.0, July 22, 2022
- BLA 103979/S-5309 (Fabrazyme) Multi-disciplinary Review and Evaluation, March 11, 2021
- Applicant's response to DRDMG's Information Requests (IRs), January 13, 2023

Consult Questions

Question 1

Please comment on whether there is precedence for using changes in eGFR slope as a clinical endpoint to support a new drug approval.

DCN Response to Question 1

Assuming the endpoint is appropriately defined and analyzed, we accept eGFR slope as a surrogate endpoint for a treatment's effect on progression to kidney failure in patients who are at high life-time risk of progressing to kidney failure. Analyses, including meta-analyses of observational studies, meta-analyses of clinical trials, and simulations of trial designs, support the use of eGFR slopes calculated over a sufficient period of time (the workgroup focused on eGFR slopes assessed over 3 years) as a surrogate endpoint[1]. To support approval, we have generally required that development programs demonstrate that the effect continues to accrue over time and across the various stages of disease so as to provide reassurance that the treatment effect, which is expected to be small in absolute terms, is likely to translate into a clinically relevant benefit on progression to kidney failure. To address whether the

[1] Change in Albuminuria and GFR as End Points for Clinical Trials in Early Stages of CKD: A Scientific Workshop …: American Journal of kidney diseases (ajkd.com)

treatment effect continues to accrue over time, we have generally required at least 2 years of eGFR data; to address whether efficacy accrues across the various stages of disease, we have generally advised sponsors to ensure adequate representation of patients across the full spectrum of eGFR.

With regard to specific precedents:

In 2018, DCN approved JYNARQUE (tolvaptan) to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease based on evidence that the drug slowed the loss of kidney function in earlier and later stages of disease and that the benefit accrued over time (1 to 3 years). Based on such data, DCN concluded that the drug, when used chronically, would have a meaningful impact on the risk of progression to kidney failure (JYNARQUE 2009; FDA 2018). There are also ongoing trials in our division using eGFR (slope) at 2 years as (1) the endpoint that will support traditional approval or (2) the endpoint that will be used to verify the clinical benefit of a product approved under the accelerated approval pathway.

Question 2

Please comment on the sponsor's justification/rationale for the proposed NI margin. Please see page 62 of F20 CSR.

DCN Response to Question 2

The Applicant's NI margin of -3 mL/min/1.73 m^2/year for their 2-year NI analysis was based on the following: (1) data on the natural history of FD which suggests that eGFR declines by -4 to -12 ml/min/1.73 m^2/year in untreated male FD patients and (2) the European Expert Consensus Statement on Therapeutic Goals in Fabry Disease, which defines "stabilization of function" for FD patients as an eGFR slope loss of ≤1-3 mL/min/1.73 m^2/year (Wanner 2018). The Applicant also notes that this NI margin was also used for the 12-month NI interim analysis in Study F20 (based on a similar logic).

In response to an Information Request by DRDMG regarding the rationale for the NI margin, the Applicant also cited studies that showed a mean decline in eGFR in FD patients treated with Fabrazyme of -0.39 to -6.82 mL/min/1.73 m^2/year, and noted that an NI margin of -3 mL/min/1.73 m^2/year falls within this observed range. The Applicant also noted that a more stringent and/or robust NI margin would require a larger sample size which would not be feasible for this rare disease.

While we acknowledge the Applicant's rationale for the proposed NI margin, we do not find it to be compelling. For a NI study to be interpretable, there must be reliable information about the effect size of the active control drug and there should be reason to believe the effect the active control drug has in the current NI study is similar to the effect observed in past studies. We do not think the cited data is sufficient to determine the likely effect size of Fabrazyme on eGFR in the study population. If anything, the analyses highlight the heterogeneity in rates of disease progression and challenges associated with using such data to determine the effect (and effect size) of Fabrazyme on the rate of kidney function decline in patients with FD.

Question 3

Please comment on the strength and quality of clinical data (e.g. controlled clinical trials, registry, natural history, other) that are available in the published Fabry's literature to support establishing a NI margin on eGFR slope. If data are available, are the population(s) in those studies comparable to the population enrolled in the F20 study?

DCN Response to Question 3

See our response above regarding the challenges associated with using observational data to obtain a reliable estimate of the effect of Fabrazyme on the rate of loss of kidney function in patients with FD. To obtain such an estimate, we believe one would need data from a randomized placebo-controlled trial of Fabrazyme that demonstrated an effect on the rate of loss of kidney function in a population comparable to the population enrolled in the F20 study. To our knowledge, such data are not available.

Question 4

Please comment on the data on changes in eGFR slope from pre-study to post-study to establish evidence of clinical benefit. Please see Table 11.3 and 11.9 in F20 CSR.

DCN Response to Question 4

To be eligible for the study, patients had to be treated with Fabrazyme for at least one year with stable doses for six months or more and have a baseline eGFR slope less than -2 mL/min/1.73 m^2/year. At baseline, eGFR slopes (based on serum creatinine values from screening, Day 1 and up to 18 months prior to study) were - 8.03 mL/min/1.73 m2/year for the PRX-102 arm and -8.25 mL/min/1.73 m2/year for the Fabrazyme arm. The mean duration of Fabrazyme treatment prior to study entry was 5.4 years for the PRX-102 arm and 6.4 years for the Fabrazyme arm. After two years in the study (on treatment), the eGFR slopes improved to -2.38 mL/min/1.73 m2/year and -2.31 mL/min/1.73 m2/year in the PRX-102 and Fabrazyme arms, respectively.

As we understand, in general, on an individual level, previous eGFR slope may not be a reliable predicter of future eGFR slope[2]. We further note that there appeared to be a drastic improvement in eGFR for the patients who remained on the same dose of fabrazyme during the treatment period as they were on prior to study entry, which would also suggest that the calculated pre-baseline eGFR slopes may not be reliable.

Additional Comment:

In their response to Information Requests (IRs) from the primary review team inquiring about the observed eGFR trajectory on January 13, 2023, the Applicant noted that the baseline eGFR slopes were captured from historical data in patient files, which may have been derived from different laboratories resulting in variability. They also noted differences in the number of creatinine assessments and spacing over time for the baseline eGFR slope compared to the methodology used for the post-treatment eGFR slope (i.e., central laboratory, frequent timepoints for measuring creatinine). The Applicant also noted that potentially improved care and adherence to therapies including adjunctive therapies (such as ACEi/ARBs) during the study may have contributed to the observed improved eGFR slopes during the study. The Applicant also pointed to the "Hawthorne effect" as a possible explanation (i.e., phenomenon whereby participants in a clinical study tend to modify or improve aspects of their behavior simply in response to their awareness of being evaluated or studied). In theory, a combination of these factors could have contributed to the observed differences between the pre and post-study values. Regardless, we believe the data are challenging to interpret.

[2] The Kidney Failure Risk Equation: Evaluation of Novel Input... : Journal of the American Society of Nephrology (lww.com)

Question 5

What additional data (e.g. biomarkers, clinical endpoints, etc.) collected by the sponsor convince you of a favorable signal for clinical(renal) benefit? (Please see Section 11.4.2 of the F20 CSR)

DCN Response to Question 5

The secondary renal efficacy endpoints evaluated by the Applicant include: (1) change in UPCR category, (2) achievement of Fabry kidney disease therapeutic goals (which compared a patient's kidney disease status at baseline [stable, progressing, or fast progressing] to post-baseline), (3) change in biomarkers of Fabry disease (plasma lyso-Gb3, urine lyso-Gb3, plasma Gb3), and (4) incidence of Fabry clinical events (FCEs) (defined as the incidence of pre-defined renal, cardiac, cerebrovascular, and non-cardiac-related death events).

In brief, the following were reported:

- There was an improvement in baseline UPCR category for four patients (8%) in the PRX-102 arm (three improved from baseline moderate proteinuria [0.5 < UPCR < 1 g/g] to mild [UPCR ≤ 0.5 g/g] by the end of treatment, and one improved from severe proteinuria [UPCR ≥ 1 g/g] at baseline to moderate at the end of treatment). There was no improvement in UPCR categories for any patients in the Fabrazyme arm.
- Regarding the achievement of kidney function therapeutic goals, most patients at baseline were categorized as fast progressing (i.e., eGFR slope < -5 mL/min/1.73 m^2/year) in both arms (84% for Fabrazyme and 85% for PRX-102). The proportion of patients that achieved the defined goals (improved eGFR slope category or maintained the stable category) by the end of study (Year 2) was similar in both treatment arms (80% for PRX-102 and 80% for Fabrazyme).
- For the PRX-102 group, the mean plasma concentration of lyso-Gb3 increased by 3 nM (percent change of +10%) at Year 2 compared to baseline. For the fabrazyme group, the mean decreased by 9 nM (percent change of -13%) compared to baseline. Similar trends were observed for urine lyso-Gb3 and plasma Gb3. Of note, the Applicant does not consider any of these changes to be clinically significant.
- The incidence of FCEs was higher in the PRX-102 arm, with nine patients (17%) experiencing a total of 11 events (seven cardiac, three cerebrovascular, and one renal) compared to two patients (8%) with two events (both cardiac) in the Fabrazyme arm. The Applicant observed that many of the patients who experienced an FCE event had "pre-existing Fabry cardiomyopathy or other related co-morbidities" at baseline.

With regard to these specific findings, we note the following:

1) UPCR and eGFR are continuous variables, and the interpretation/clinical significance of an "improvement" from one (somewhat arbitrary) category to the subsequent category for each of these endpoints is not clear.
2) Treatment effects on an improvement in kidney function therapeutic goals is based on an improvement compared to the baseline eGFR slope. As noted in our response to question 4, we find these data challenging to interpret.

3) The numerical imbalance for FCEs favored the Fabrazyme arm; however, given the size of the trial and duration of treatment/follow-up (i.e., the ability of the trial, as designed, to resolve such issues), we think it is challenging to draw firm conclusions from these data.

We defer to the review team regarding the clinical significance of the change in levels of plasma lyso-Gb3, urine lyso-Gb3, and plasma Gb3.

Question 6

The lower bound of 95% CI of the difference in slopes was -2.4. Is a 2.4 mL/min/year decline in eGFR in Fabry's patients clinically meaningful?

DCN Response to Question 6

We do not understand your question. If you are asking whether slowing the rate of loss of kidney function over time by 2.4 mL/min/1.73 m^2/year would be clinically meaningful in a population at high risk of progressing to kidney failure, then the answer is yes. Assuming the treatment effect accrues over time and across the various stages of disease, such an effect would be expected to translate into a meaningful effect on progression to kidney failure. See also our response to question 1.

Appendix

Overview of study PB-102-F20

Study PB-102-F20 was a randomized, double-blind, active control study examining the safety and efficacy of PRX-102 compared to agalsidase beta (Fabrazyme) in patients with symptomatic Fabry Disease (FD) previously treated with agalsidase beta. The study enrolled adult patients aged 18-60 years who were on agalsidase beta for at least one year with stable doses for at least six months, screening eGFR 40 to 120 mL/min/1.73 m^2 and linear eGFR slope less than -2 mL/min/1.73 m^2 per year (based on at least 3 creatinine values up to 18 months prior to the study including screening values). Patients with a urine protein creatinine ratio (UPCR) >0.5 g/g and those not treated with an ACEi/ARB were excluded.

Patients were randomized 2:1 to PRX-102 or agalsidase beta (intravenous infusion every two weeks at a dose of 1 mg/kg for both therapies) for 24 months. Randomization was stratified by UPCR less than or greater than 1 g/g. Renal function was monitored every two or four weeks during the study (total of 30 assessments) and eGFR was calculated using the CKD-EPI (2009) equation. UPCR was measured every three months during study. The primary endpoint was annualized change (slope) in eGFR between the two treatment arms at Week 104. For Study F20, the Applicant proposed a NI analysis using an NI margin of -3 mL/min/1.73 m^2/yr.

Patients who completed Study F20 were eligible to enter a long-term open extension study (PB-102-F60) where all patients received PRX-102.

Baseline characteristics

Overall, 78 patients were enrolled, 53 to the PRX-102 arm and 25 to the agalsidase beta arm. One PRX-102 patient withdrew before receiving study product and the Applicant did not include the patient in the "ITT set." The overall mean duration of treatment with agalsidase beta prior to enrollment in study F20 was 5.4 years for the PRX-102 group and 6.4 years for the agalsidase beta group. At baseline, the mean eGFR was 73 mL/min/1.73 m^2 in the PRX-102 arm and 74 mL/min/1.73 in the agalsidase beta arm. The mean baseline eGFR slopes were -8.03 mL/min/1.73/year in the PRX-102 arm and -8.23 mL/min/1.73/year in the agalsidase beta arm. A total of 16 (50%) patients in PRX-102 arm were on treatment with an ACEi/ARB compared to 16 (64%) patients in the agalsidase beta arm. Overall, 66.2% of the study population were from the United States (see table below).

Key Baseline Demographics and Clinical Characteristics, Study F20

	PRX – 102 N = 52	**Agalsidase Beta N = 25**
Age (years)		
Mean (standard error)	43.9 (1.4)	45.2 (1.9)
Minimum, Maximum	20, 60	18, 58
Gender: n (%)		
Male	29 (55.8)	18 (72.0)
Female	23 (44.2)	7 (28.0)
Race: n (%)		

Asian	2 (3.8)	0
Black or African American	1 (1.9)	2 (8.0)
White	49 (94.2)	23 (92.0)
eGFR (mL/min/1.73 m2)		
Mean (SD)	73.46 (20.21)	74.16 (20.97)
Median (Min, Max)	73.45 (30.2; 125.9)	74.85 (34.1; 107.6)
eGFR Category (mL/min/1.73 m2), n (%)		
≤ 60	13 (25.0%)	8 (32.0%)
60 < and ≤ 90	28 (53.8%)	11 (44.0%)
>90	11 (21.2%)	6 (24.0%)
eGFR slope at baseline (mL/min/1.73 m2/year)[2]		
Mean (SD)	-8.03 (6.60)	-8.25 (4.27)
Median (Min, Max)	-6.70 (-30.5; 6.3)	-7.84 (-20.3; -2.8)
UPCR stratification (at screening), n (%)		
< 1 gr/gr	41 (78.8%)	21 (84.0%)
≥ 1 gr/gr	11 (21.2%)	4 (16.0%)
Treatment with ACEi or ARBs, n (%)		
Yes	26 (50.0%)	16 (64.0%)
No	26 (50.0%)	9 (36.0%)
Duration of the last continuous agalsidase-beta treatment (months)[3]		
Mean (SD)	65.03 (47.98)	77.34 (41.25)
Median (Min, Max)	51.53 (12.6; 236.9)	67.84 (27.6; 168.3)
Type of Fabry disease, n (%)		
Classic	27 (51.9%)	14 (56.0%)
Non-classic	25 (48.1%)	11 (44.0%)

ADA = anti-drug antibodies.

1 eGFR slope at screening was based on historical serum creatinine and screening serum creatinine.

2 eGFR slope at baseline was based on historical, screening, and baseline serum creatinine.

3 “Last” treatment refers to patients who had several periods of treatment with agalsidase beta in the past.

Source: Tables 11.2, 11.3 and 11.4 of Clinical Study Report for Study F20 version 1.0 (dated July 22, 2022)

Primary Efficacy Results

Table 11.9 Summary of eGFR slopes (first stage of 2-stage ANCOVA and of 2-stage with quantile regression)

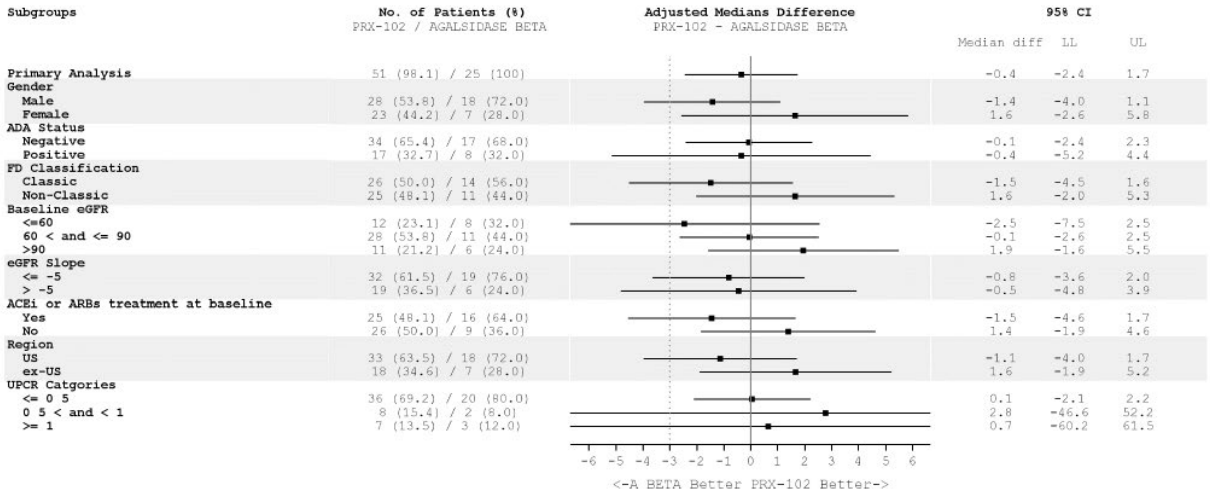
	ITT set		PP set	
	PRX-102 N=52	Agalsidase beta N=25	PRX-102 N=48	Agalsidase beta N=24
eGFR slopes (mL/min/1.73 m^2/year)				
n	51	25	48	24
Mean (SE)	-2.38 (1.25)	-2.31 (0.71)	-2.32 (0.69)	-2.35 (0.74)
SD	8.90	3.56	4.75	3.63
Median (Q1; Q3)	-2.51 (-4.8; 0.8)	-2.16 (-4.6; -0.5)	-2.52 (-4.7; 0.5)	-2.47 (-4.7, -0.4)
Min; Max	-45.3; 28.9	-10.1; 8.1	-16.2; 9.9	-10.1; 8.1

Q1 – 25th percentile; Q3 – 75th percentile

Note: The individual annualized mean change (slope) in eGFR is estimated for each patient with at least 4 eGFR observations using a linear regression model.

Source: Clinical Study Report for Study F20 version 1.0 (dated July 22, 2022)

Figure 11.4 Forest plot of eGFR difference in slopes – subgroups within ITT set



FD = Fabry Disease; UPCR = Urinary protein to creatinine ratio; ACEi = Angiotensin converting enzyme inhibitors; ARBs = Angiotensin receptor blocker; LL= Lower Limit; UL= Upper Limit, ADA = Anti-drug antibody, eGRF = Estimated glomerular filtration rate

Note: Vertical dotted line drawn at the prespecified non-inferiority margin of -3.0 ml/min/1.73 m^2/year

Source: Clinical Study Report for Study F20 version 1.0 (dated July 22, 2022)

Secondary efficacy analysis

Urine protein creatinine ratio

Table 11.13 Shift from baseline to Week 104 in UPCR categories - ITT set

Post base-line UPCR categories	Baseline UPCR categories							
	UPCR ≤ 0.5 gr/gr n (%)		0.5 < UPCR < 1 gr/gr n (%)		UPCR ≥ 1 gr/gr n (%)		Overall n (%)	
PRX-102 (N = 52)								
UPCR ≤ 0.5 gr/gr	31	(86.1%)	3	(33.3%)	0		34	(65.4%)
0.5 < UPCR < 1 gr/gr	1	(2.8%)	3	(33.3%)	1	(14.3%)	5	(9.6%)
UPCR ≥ 1 gr/gr	0		1	(11.1%)	5	(71.4%)	6	(11.5%)
Missing	4	(11.1%)	2	(22.2%)	1	(14.3%)	7	(13.5%)
Overall	36	(100.0%)	9	(100.0%)	7	(100.0%)	52	(100.0%)
Agalsidase beta (N = 25)								
UPCR ≤ 0.5 gr/gr	18	(90.0%)	0		0		18	(72.0%)
0.5 < UPCR < 1 gr/gr	1	(5.0%)	1	(50.0%)	0		2	(8.0%)
UPCR ≥ 1 gr/gr	0		1	(50.0%)	3	(100.0%)	4	(16.0%)
Missing	1	(5.0%)	0		0		1	(4.0%)
Overall	20	(100.0%)	2	(100.0%)	3	(100.0%)	25	(100.0%)

Source: Clinical Study Report for Study F20 version 1.0 (dated July 22, 2022)

Incidence of Fabry Clinical events (FCEs)

The incidence of Fabry Clinical Events (FCEs) evaluated clinical outcomes based on reported AEs and clinical information from the study database. The renal events included were initiation of dialysis and kidney transplantation.

Table 11.24 Number of patients with Fabry clinical events - ITT set

	PRX-102		Agalsidase beta	
Fabry clinical events categories	Number (%) of Patients N=52	Number of Events (Rate)	Number (%) of Patients N=25	Number of Events (Rate)
Overall	9 (17.3%)	11 (11.2)	2 (8.0%)	2 (4.0)
Cardiac events	6 (11.5%)	7 (7.1)	2 (8.0%)	2 (4.0)
Cerebrovascular events	3 (5.8%)	3 (3.1)	0	0
Renal events	1 (1.9%)	1 (1.0)	0	0
Non-cardiac related death	0	0	0	0

[1] Rate of events adjusted to 100 years of exposure

Source: Clinical Study Report for Study F20 version 1.0 (dated July 22, 2022)

Achievement of Fabry Kidney Disease Therapeutic Goals

At baseline, patients' severity of kidney disease was categorized as follows:

Stable	Pre-treatment eGFR slope $\leq$ -3 mL/min/1.73 m^2/year
Progressing	Pre-treatment eGFR slope $\geq$ -5 but < -3 mL/min/1.73 m^2/year
Fast progressing	Pre-treatment eGFR slope < -5 mL/min/1.73 m^2/year

Achievement of the therapeutic goal was dependent on the patient's pre-treatment status:

Stable	Post-treatment eGFR slope $\geq$ -3 mL /min/1.73 m^2/year
Progressing	Post-treatment eGFR slope $\geq$ - 3 mL /min/1.73 m^2/year
Fast progressing	Post-treatment eGFR slope $\geq$ -5 mL /min/1.73m^2/year **or** > 50% decrease in progression: i.e., (pre-treatment eGFR slope – post-treatment eGFR slope) / pre-treatment eGFR slope > 50%

Source: Clinical Study Report for Study F20 version 1.0 (dated July 22, 2022)

Table 11.25 Proportion of patients who achieved kidney function therapeutic goals – ITT set

	PRX-102				Agalsidase beta			
	Stable N=6	Progressing N=13	Fast progressing N=33	Overall N=52	Stable N=1	Progressing N=5	Fast progressing N=19	Overall N=25
Therapeutic Goals Achieved (see Section 9.5.1.2.11 for definitions)								
n	6	13	32	51	1	5	19	25
Yes n (%)	4 (66.7%)	11 (84.6%)	26 (81.3%)	41 (80.4%)	1 (100.0%)	3 (60.0%)	16 (84.2%)	20 (80.0%)
No n (%)	2 (33.3%)	2 (15.4%)	6 (18.8%)	10 (19.6%)	0	2 (40.0%)	3 (15.8%)	5 (20.0%)
Difference in the proportions of patients who achieved therapeutic goals between treatments: PRX-102 - agalsidase beta: 0.4; 95% CI: -18.7; 19.5								

Notes:

- Kidney disease severity:
  - Stable: pre-treatment eGFR slope $\geq$ -3 mL/min/1.73 m^2/year
  - Progressing: pre-treatment eGFR slope between $\geq$ -5 and < -3 mL/min/1.73 m^2/year
  - Fast progressing: pre- treatment eGFR slope < -5 mL/min/1.73 m^2/year
- The individual annualized mean change (slope) in eGFR at baseline, estimated for each patient are used for KD classification.
- 95% confidence interval is based on Clopper Pearson
- Percentages are calculated on the number of subjects with non-missing post-treatment eGFR slope (n)

Source: Clinical Study Report for Study F20 version 1.0 (dated July 22, 2022)

Changes in concentration of Fabry Disease Biomarkers

Table 11.16 Change from baseline of plasma lyso-Gb3 concentrations at Week 104 – ITT set

	PRX-102 N=52	Agalsidase beta N=25
Plasma Lyso-Gb3 Concentration (nM)		
Baseline		
n	52	25
Mean (SE)	26.22 (3.78)	32.14 (7.08)
Change from baseline at Week 104 (nM)		
n	46	22
Mean (SE)	3.30 (1.38)	-8.74 (4.85)
Percent (%) change from baseline at Week 104		
Mean (SE)	10.34 (3.80)	-12.69 (4.60)

Source: Clinical Study Report for Study F20 version 1.0 (dated July 22, 2022)

Table 11.18 Change from baseline in urine lyso-Gb3 concentrations at Week 104 - ITT set

	PRX-102 N=52	Agalsidase beta n=25
Urine Lyso-Gb3 Concentration (pM/mM creatinine)		
Baseline		
n	48	22
Mean (SE)	48.1 (7.8)	44.5 (10.9)
Change from baseline at Week 104 (pM/mM creatinine)		
n	37	19
Mean (SE)	7.0 (7.7)	-11.2 (4.7)
PRX-102 – agalsidase beta: Difference in means (95% CI)	18.1 (0.1;36.1)	
Percent (%) change from baseline at Week 104		
Mean (SE)	33.00 (13.19)	-16.14 (9.72)
PRX-102 – agalsidase beta: Difference in means (95% CI)	49.1 (16.3;82.0)	

Note: If the confidence interval does not contain 0, that suggests a statistically significant difference between the treatment groups.

Source: Clinical Study Report for Study F20 version 1.0 (dated July 22, 2022)

Table 11.19 Change from baseline in plasma Gb3 concentrations at Week 104 – ITT set

	PRX-102 N=52	Agalsidase beta N=25
Plasma Gb3 Concentration (nM)		
Baseline		
n	52	25
Mean (SE)	5087.7 (282.9)	4695.4 (499.9)
Change from baseline at Week 104 (nM)		
n	46	22
Mean (SE)	138.0 (214.4)	-81.8 (314.7)
PRX-102 – agalsidase beta: *Difference in means (95% CI)*	219.8 (-549.3;988.9)	
Percent (%) change from baseline at Week 104		
Mean (SE)	4.59 (4.48)	2.69 (4.36)
PRX-102 – agalsidase beta: *Difference in means (95% CI)*	1.9 (-10.6;14.4)	

Note: If the confidence interval does not contain 0, that suggests a statistically significant difference between the treatment groups.

Source: Clinical Study Report for Study F20 version 1.0 (dated July 22, 2022)

Summary of the Data Used to Support the Approval of Fabrazyme

Fabrazyme is a recombinant human α-galactosidase (α-GAL) A enzyme replacement therapy that was approved on March 11, 2021, for the "treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease". To support approval, the Applicant submitted data from three clinical

studies and one matched analysis based on data from observational studies. Study 1 was a randomized, double-blind, placebo-controlled, multinational, multicenter study of 58 patients with Fabry disease (56 males and 2 females), ages 16 to 61 years, all naïve to enzyme replacement therapy. Patients were randomized 1:1 to receive either Fabrazyme 1 mg/kg every 2 weeks or placebo for 20 weeks. The primary endpoint was the proportion of patients in either group with a renal capillary GL-3 inclusion score of zero at week 20. In the Fabrazyme group, 20 of 29 (69%) patients achieved a score of zero while 0 of 29 placebo-treated patients achieved a score of zero ($p<0.001$). Similar reductions in GL-3 inclusions were observed in the capillary endothelium of the heart and skin.

Study 2 was a randomized double-blind, placebo-controlled, multinational, multicenter study of 82 patients (72 males and 10 females) with Fabry disease, ages 20 to 72 years, all naive to enzyme replacement therapy. Patients were randomized 2:1 to receive either Fabrazyme 1mg/kg every 2 weeks or placebo for up to 35months (median follow-up 18.5 months). The primary efficacy endpoint was the time to first occurrence of a clinically significant event (renal, cardiac, or cerebrovascular event, or death). In the Fabrazyme group, 14 of 51 (28%) patients experienced a clinically significant event compared to 13 of 31 (42%) patients in the placebo group (HR 0.57, 95% CI: 0.27, 1.22).

Study 3 (Pediatric Study) was an open-label, single-arm, multinational, multicenter, pediatric study of 16 patients with Fabry disease (14 males, 2 females), ages 8 to 16 years (median age 12 years). All patients received Fabrazyme 1 mg/kg every two weeks for up to 48 weeks. The median eGFR was 112.1 mL/min/1.73 m^2 at baseline and did not change during treatment.

The observational study was a long-term study that assessed the rate of decline in renal function (eGFR slope) in 122 Fabrazyme treated patients aged 16 years and older matched 1:1 to a historical cohort of untreated patients with Fabry disease with a median follow up time of 4.5 years in the Fabrazyme treated group and 3 years in the untreated group. The patients were matched based on age (at Fabrazyme initiation), sex, Fabry disease subtype (classic or non-classic), and baseline eGFR. Overall, age at Fabrazyme initiation was 35 years, 72% of patients were male, 84% of patients had the classic Fabry disease subtype, and the median baseline eGFR was 93 mL/min/1.73 m^2. The mean eGFR slope was -1.5 mL/min/1.73 m^2/year in the Fabrazyme-treated group and -3.2 mL/min/1.73 m^2/year in the untreated group for an eGFR slope difference of 1.7 mL/min/1.73 m^2/year (95% CI: 0.5, 3.0).

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/

YAA D OPPONG
04/24/2023 08:48:23 AM

REKHA KAMBHAMPATI
04/25/2023 08:26:37 AM

ALIZA M THOMPSON
04/25/2023 10:25:12 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993

MEMORANDUM TO FILE

Date of Consult Request: December 7, 2022

From: Denise N. Johnson-Lyles, Ph.D.
Senior Regulatory Project Manager
Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic, and Reproductive Medicine

Subject: Pregnancy and Lactation Labeling Rule (PLLR) consult request

BLA Number: BLA 761161
Submission Type: Class 2 Resubmission

Drug: Pegunigalsidase alfa, injection

Applicant: Chiesi USA

Indication(s): Treatment of adults with confirmed Fabry disease

The Division of Rare Diseases and Medical Genetics (DRDMG) submitted a consult request to the Division of Pediatric and Maternal Health (DPMH) – Maternal Health team on December 7, 2022, asking for assistance with the review of labeling language included in the PLLR-related subsections of the Prescribing Information (PI) for the above referenced application. The above referenced application is a Class 2 Resubmission submitted in response to a Complete Response Letter issued on April 27, 2021.

DPMH-Maternal Health was previously consulted for labeling assistance for this application (*See Maternal Health Review posted to DARRTS on October 6, 2020, by Dr. Wenjie Sun, Reviewer*). For this current review round, DPMH-Maternal Health participated in applicable team meetings and confirmed labeling recommendations from the previous review round with DRDMG for subsequent negotiation with the Applicant. There are no further comments at this time.

This memorandum will close out the consult request.

DPMH RPM- Denise Johnson-Lyles
DPMH Lead Consumer Safety Officer – George Greeley
DPMH Maternal Health Reviewer- Wenjie Sun
DPMH Maternal Health Team Leader- Miriam Dinatale
DPMH Division Director- Lynne Yao

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/

DENISE N JOHNSON-LYLES
04/14/2023 12:27:40 PM
DPMH RPM Closeout

Clinical Inspection Summary

Date	3/27/2023
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Diego Diaz, Regulatory Project Manager Mehul Desai, M.D., Medical Officer Sheila Farrell, M.D., Team Leader Division of Rare Disease and Medical Genetics Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine
NDA #/BLA #	BLA #761161; Class 2 Resubmission
Applicant	Chiesi Farmaceutici S.p.A.
Drug	Pegunigalsidase Alfa
NME	Yes
Proposed Indication	Treatment of adults with a confirmed diagnosis of Fabry disease
Consultation Request Date	1/10/2023
Summary Goal Date	3/31/2023
Action Goal Date	5/9/2023
PDUFA Date	5/9/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Bernat, Longo, and Wallace were inspected in support of this BLA and covered Protocols PB-102-F20 and PB-102-F50. The studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

The primary efficacy measure was the annualized slope of estimated glomerular filtration rate (eGFR). Serum creatinine concentrations used to calculate eGFR slope were verified for all subjects. Serum creatinine verification included both historical data used to determine subject eligibility as well as those obtained during the studies. There was no evidence of under-reporting of adverse events at these clinical sites.

II. BACKGROUND

Pegunigalsidase alfa injection for intravenous use is being developed under IND #110161 for the treatment of adults with a confirmed diagnosis of Fabry disease. Pegunigalsidase alfa is a PEGylated, recombinant human protein α-GAL-A. In 2018, Protalix Ltd. and Chiesi USA

entered into an exclusive U.S. license and supply agreement under which Protalix granted Chiesi the rights for the development and commercialization of pegunigalsidase alfa. The sponsor of IND #110161 continues to be Protalix, while Chiesi is the sponsor of BLA #761161.

BLA #761161 was originally submitted in May 2020 and received a Complete Response in April 2021. The BLA was originally submitted under the accelerated approval pathway, however, another enzyme replacement therapy was approved for Fabry disease during the review cycle such that this BLA no longer qualified for the accelerated approval pathway which relied on a surrogate efficacy endpoint.

In this BLA resubmission, the sponsor has submitted the results of two Phase 3 studies (Protocols PB-102-F20 and PB-102-F50) in which the primary efficacy endpoint is the annualized slope of estimated glomerular filtration rate (eGFR). Both protocols were ongoing at the time the BLA was originally submitted.

Protocol PB-102-F20

Title: "A randomized, double blind, active control study of the safety and efficacy of PRX-102 compared to agalsidase bets on renal function in patients with Fabry disease previously treated with agalsidase beta" *[Note: PRX-102 is pegunigalsidase alfa]*

Subjects: 77

Sites: 28 sites; United States (15), Western Europe (11), Eastern Europe (2)

Study Initiation and Completion Dates: 8/22/2016 – 10/12/2021

This was a randomized, double-blind, active control study evaluating the safety and efficacy of pegunigalsidase alfa in subjects with Fabry disease and impaired renal function. Main inclusion criteria were males or females; 18 to 60 years of age; plasma and/or leucocyte alpha galactosidase activity <30% mean normal levels (males), historic genetic test results consistent with Fabry pathogenic mutation (females); one or more characteristic features of Fabry (neuropathic pain, cornea verticillata, clustered angiokeratoma); screening estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation 40 to 120 mL/min/1.73m^2; and linear negative slope of eGFR of >2 mL/min/1. 73m^2/year based on at least 3 serum creatinine values over approximately one year (range of 9 to 18 months including the value obtained at the screening visit). Subjects had to have received a dose of 1 mg/kg agalsidase beta per infusion every 2 weeks for at least one year and, over the last 6 months, the dose had to have been stable and the subject had to have received at least 80% of the total amount (i.e., at least 10.4 of 13 infusions). Excluded were subjects with a history of renal dialysis, transplantation, or acute kidney injury in the 12 months prior to screening; and screening eGFR value of 91-120 mL/min/1.73m^2 having an historical eGFR value >120 mL/min/1.73m^2 (during 9 to 18 months before screening).

The study was comprised of a screening period and a double-blind treatment period:

Screening Period (Visit S: Day -30 ± 10 days)
The screening phase included study procedures to determine subject eligibility including, but not limited to, physical examination, ECG, chest X-ray, and labs (including plasma and leucocyte alpha-galactosidase activity and serum creatinine and cystatin C).

Double-blind Treatment Period (Visit 1 [Baseline] to Visit 53 [Week 104])
Subjects were randomized (2:1), stratified by urine protein-to-creatinine ratio, to either switch to pegunigalsidase alfa or continue treatment with agalsidase beta:

- Pegunigalsidase alfa 1 mg/kg by intravenous infusion every 2 weeks for 24 months
- Agalsidase beta 1 mg/kg by intravenous infusion every 2 weeks for 24 months

Intravenous infusions were administered over 3 hours. After 3 months of infusions, if the subject was tolerating the infusions, the infusion time could be reduced gradually to 1.5 hours based on investigator evaluation and sponsor (Protalix) approval.

Subjects previously receiving pre-medication for prevention of infusion reactions could continue after randomization for the first infusion. Pre-medication was to be tapered at the investigator's discretion during the first 3 months of the study. Subjects were to be observed clinically for a minimum of 2 hours after dosing. The study included a total of 54 visits; screening and 53 biweekly treatments (home-based or at the site) over 24 months.

The *primary efficacy endpoint* was the annualized slope of eGFR over 2 years, comparing pegunigalsidase alfa and agalsidase beta.

Protocol PB-102-F50

Title: "A Phase 3, open label, switch over study to assess the safety, efficacy and pharmacokinetics of pegunigalsidase alfa (PRX-102) 2.0 mg/kg administered by intravenous infusion every 4 weeks for 52 weeks in adult patients with Fabry disease currently treated with enzyme replacement therapy: Fabrazyme® (agalsidase beta) or Replagal® (agalsidase alfa)"

Subjects: 30

Sites: 14 sites; United States (7), Western Europe (6), Eastern Europe (1)

Study Initiation and Completion Dates: 11/13/2017 – 7/2/2020

This was an open-label, switch over study to evaluate the safety and efficacy of pegunigalsidase alfa 2 mg/kg administered every 4 weeks for 12 months in subjects with Fabry disease who were currently being treated with agalsidase alfa or agalsidase beta for at least 3 years with a stable dose for at least 6 months. Main inclusion criteria were males or females; 18 to 60 years of age; Fabry characteristics same as Protocol PB-102-F20; screening eGFR $\geq$30 mL/min/1.73m^2 per CKD-EPI equation; availability of at least 3 historical

serum creatinine evaluations since starting agalsidase alfa or beta treatment and not more than 2 years; and subjects whose clinical condition, in the opinion of the investigator, that are suitable for treatment every 4 weeks. Excluded were subjects with a history of renal dialysis, transplantation, or acute kidney injury in the 12 months prior to screening and a linear negative slope of eGFR of $\geq$2 mL/min/1.73m^2 based on at least 4 serum creatinine values over approximately 2 years (including screening value).

Following screening, subjects were enrolled and switched from their current therapy (agalsidase alfa or beta) to receive open-label intravenous infusions of pegunigalsidase alfa 2 mg/kg every 4 weeks for 52 weeks. In cases of clinical deterioration, the dose and frequency of pegunigalsidase alfa could be changed to 1 mg/kg every 2 weeks.

This study evaluated the safety and efficacy of the pegunigalsidase dosing regimen of 2 mg/kg every 4 weeks. Efficacy variables included the eGFR and eGFR slope.

Rationale for Site Selection

Sites were chosen for BIMO inspections based on risk ranking in the CDER Clinical Investigator Site Selection Tool, numbers of enrolled subjects, enrollment in both protocols, large treatment differences between study arms, data irregularities, and prior inspection history.

III. RESULTS

1. **John Bernat, M.D.**
   Site #4
   University of Iowa Hospitals and Clinics
   Division of Medical Genetics and Genomics
   200 Hawkins Drive
   Iowa City, IA 52242
   Inspection Dates: 2/21/2023 – 2/23/2023

   At this site for Protocol PB-102-F20, the double-blind efficacy study, 9 subjects were screened, 5 subjects were randomized and completed the study. For Protocol PB-102-F50, the open-label study, 8 subjects were screened and enrolled, and 7 subjects completed the study. One subject discontinued due to “withdrawal by subject”. This subject experienced the serious adverse event (SAE) of motor vehicle accident approximately one month after study enrollment. The narrative for this SAE was included in the BLA submission.

   Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data.

The primary efficacy endpoint for Protocol PB-102-F20 was the annualized slope of estimated glomerular filtration rate (eGFR) over 2 years. The eGFR and eGFR slope were also efficacy measures for Protocol PB-102-F50, the open-label, 12-month study. The focus of data verification was serum creatinine concentrations which were used to calculate eGFR using the eGFR Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD-EPI}$) equation. Serum creatinine concentrations were verified against sponsor data line listings for all enrolled subjects in both protocols; no discrepancies were identified.

One of the inclusion criteria for Protocol PB-102-F20 was that subjects have a "linear negative slope of eGFR of $\geq$2 mL/min/1.73^2/year based on at least 3 serum creatinine values over approximately one year (range of 9 to 18 months including the value obtained at the screening visit)". The historical serum creatinine concentrations were verified against sponsor data line listings; no discrepancies were identified. The review division had noted that Subject (b) (6) had serum creatinine results of 1.1 mg/dL for each of the three historical samples obtained on (b) (6), and (b) (6). The source records for these serum creatinine results were reviewed and verified.

There was no evidence of under-reporting of adverse events.

2. Nicola Longo, M.D., Ph.D.
Site #5
University of Utah
421 Wakara Way
Salt Lake City, UT 84108
Inspection Dates: 2/28/2023 – 3/10/2023

This inspection summary is based on communications with the ORA field investigator. The final Establishment Inspection Report is pending.

At this site for Protocol PB-102-F20, the double-blind efficacy study, 10 subjects were screened, 8 subjects were randomized, and 7 subjects completed the study. One subject discontinued the study due to withdrawal of consent. For Protocol PB-102-F50, the open-label study, 2 subjects were screened, enrolled, and completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data.

The focus of data verification was serum creatinine concentrations which were used to calculate eGFR using the eGFR Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD-EPI}$)

equation. Serum creatinine concentrations were verified against sponsor data line listings for all enrolled subjects in both protocols; no discrepancies were identified.

One of the inclusion criteria for Protocol PB-102-F20 was that subjects have a "linear negative slope of eGFR of ≥2 mL/min/1.73^2/year based on at least 3 serum creatinine values over approximately one year (range of 9 to 18 months including the value obtained at the screening visit)". The historical serum creatinine concentrations were verified against sponsor data line listings; no discrepancies were identified.

Protocol deviations occurring at this site had been identified by the sponsor/CRO and were included in the sponsor data line listings. Protocol deviations included administration of investigational product (IP) >24 hours after infusion preparation. After the unblinded pharmacist prepared the IP infusion, it was to be administered immediately. If immediate use was not possible, the infusion bag could be stored for up to 24 hours at 2°C to 8°C or kept at room temperature for up to 8 hours. For 3 of 8 subjects randomized in Protocol PB-102-F20, some infusions were administered >24 hours but <33 hours after IP preparation. The protocol deviation line listing included a statement referencing a Note-to-File that was issued indicating that IP was stable for 48 hours after preparation. The reason for the delay in IP infusion was noted to be due to the home health and central pharmacy schedules, no further details were provided.

There was no evidence of under-reporting of adverse events.

Reviewer comments: Reviewers in the Office of Pharmaceutical Quality stated that the sponsor had submitted data supporting the stability of IP for up to (b) (4) *hours and microbial data supporting the in-use storage at 2°C to 8°C for up to* (b) (4) *hours. The protocol deviations relating to delayed administration of IP after preparation are within these parameters supporting IP administration.*

3. Eric Wallace, M.D
Site #2
University of Alabama at Birmingham
Nephrology Clinic at The Kirklin Clinic
2000 6th Ave S
Birmingham, AL 35233
Inspection Dates: 2/21/2023 – 2/24/2023

At this site for Protocol PB-102-F20, the double-blind efficacy study, 9 subjects were screened, 7 subjects were randomized, and 6 subjects completed the study. Subject # (b) (6) randomized to pegunigalsidase alfa, withdrew consent approximately 3 weeks after randomization. For Protocol PB-102-F50, the open-label study, 3 subjects were screened, 1 subject was enrolled and completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all

subjects who were screened. An audit of the study records for 3 of 7 (42.8%) subjects randomized in Protocol PB-102-F20 and the one subject enrolled in Protocol PB-102-F50 was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data.

The focus of data verification was serum creatinine concentrations which were used to calculate eGFR using the eGFR Chronic Kidney Disease Epidemiology Collaboration ($eGFR_{CKD\text{-}EPI}$) equation. Serum creatinine concentrations were verified against sponsor data line listings for all enrolled subjects in both protocols; no discrepancies were identified.

One of the inclusion criteria for Protocol PB-102-F20 was that subjects have a "linear negative slope of eGFR of $\geq$2 mL/min/1.73^2/year based on at least 3 serum creatinine values over approximately one year (range of 9 to 18 months including the value obtained at the screening visit)". The historical serum creatinine concentrations were verified against sponsor data line listings; no discrepancies were identified.

There was no evidence of under-reporting of adverse events.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/BLA #761161
DRDMG/Division Director/Kathleen Donohue
DRDMG/Deputy Division Director/Patroula Smpokou
DRDMG/Medical Team Leader/Sheila Farrell
DRDMG/Medical Officer/Mehul Desai
DRDMG/Project Manager/Diego Diaz
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Jenn Sellers
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Clinical Analyst/Cara Alfaro
OSI/DCCE/GCPAB Program Analyst/Yolanda Patague
OSI/DCCE/GCPAB Program Analyst/Loreto-Corazon Lim

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/

CARA L ALFARO
03/27/2023 02:07:01 PM

PHILLIP D KRONSTEIN
03/27/2023 02:13:47 PM

JENN W SELLERS
03/27/2023 03:12:41 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 17, 2023
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761161
Product Name, Dosage Form, and Strength:	Elfabrio (pegunigalsidase alfa-iwxj) injection, 20 mg/10 mL (2 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Chiesi Farmaceutici S.p.A.
FDA Received Date:	November 9, 2022
TTT ID #:	2022-2771
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

As part of the approval process for Elfabrio (pegunigalsidase alfa-iwxj)[a] injection, the Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the proposed Elfabrio prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

On November 9, 2022 Chiesi resubmitted BLA 761161 for Elfabrio after the application had received a Complete Response[b] on April 27, 2021 citing facility issues and availability of other therapies preventing accelerated approval.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed prescribing information (PI), container labels, and carton labeling for Elfabrio to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We identified some areas of concern for the proposed PI and the proposed container label. The carton labeling was acceptable. We provide our recommendations below in section 4.1 and 4.2.

---

[a] Harris, D. Nonproprietary Name Suffix Advice for pegunigalsidase alfa-iwxj. Silver Spring (MD): FDA, CDER, OSE (US); 2021 APR 27. BLA 761161

[b] Joffe, H. Complete Response for Elfabrio. Silver Spring (MD): FDA, CDER, DRDMG (US); 2021 APR 27. BLA 761161

4 CONCLUSION & RECOMMENDATIONS

The prescribing information and container label can be improved for safety. The carton labeling is acceptable from a medication error perspective.

4.1 RECOMMENDATIONS FOR DIVISION OF RARE DISEASES AND MEDICAL GENETICS (DRDMG)

A. Prescribing Information

1. Dosage and Administration (Section 2), Full PI
   a. We recommend the addition of further instructions on how to titrate the administration rate in the case of hypersensitivity reactions or at the start of treatment to inform healthcare professional's judgement.
   b. We recommend presenting the total volumes based on weight in a separate table as follows within the preparation section-

Patient's Actual Weight (kg)	Total volume (mL)
up to 70	150
70 -100	250
> 100	500

   c. (b) (4) We recommend deleting the (b) (4) for clarity.
   d. (b) (4) We recommend separating initial and maintenance infusion rates into 2 tables to facilitate presentation of information.
   e. The abbreviation "µm" is error-prone and therefore we recommend using "micron" when referring to the 0.2 micron filter required for administration.
2. Dosage Forms and Strengths (Section 3) and How Supplied/Storage and Handling (Section 16)
   a. Delete the following statement (b) (4) " to reduce redundancy.

4.2 RECOMMENDATIONS FOR CHIESI FARMACEUTICI S.P.A.

We recommend the following be implemented prior to approval of this BLA:

A. Container Labels

1. Add "Discard unused portion." to the principal display panel or side panel where space permits for clarity.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Elfabrio received on November 9, 2022 from Chiesi Farmaceutici S.p.A. .

Table 2. Relevant Product Information for Elfabrio	
Initial Approval Date	NA
Nonproprietary Name	pegunigalsidase alfa-iwxj
Indication	Indicated for the treatment of adults with confirmed Fabry disease.
Route of Administration	Intravenous
Dosage Form	injection
Strength	20 mg/10 mL (2 mg/mL)
Dose and Frequency	1 mg/kg administered every 2 weeks or (b) (4)
How Supplied	Sterile, preservative-free, clear and colorless 20 mg/10 mL (2 mg/mL) solution supplied in a single-dose glass vials as follows: • NDC 10122-160-02: carton containing one vial • NDC 10122-160-05: carton containing five vials • NDC 10122-160-10: carton containing ten vials
Storage	Store refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze or shake.
Container Closure	(b) (4) rubber stoppers closed with aluminum seal

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 29, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, pegunigalisidase. Our search identified 4 previous reviews[c,d,e,f], and we considered our previous recommendations to see if they are applicable for this current review.

[c] Abraham, S. Label and Labeling Review for (b) (4) (BLA 761161). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 23. OSE RCM No.: 2020-1097.

[d] Abraham, S. Label and Labeling Review for (b) (4) (BLA 761161). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 23. OSE RCM No.: 2020-1097-1.

[e] Abraham, S. Label and Labeling Review for Elfabrio (BLA 761161). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 26. OSE RCM No.: 2020-1097-2.

[f] Abraham, S. Label and Labeling Review for Elfabrio (BLA 761161). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 APR 01. OSE RCM No.: 2020-1097-3.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Elfabrio labels and labeling submitted by Chiesi Farmaceutici S.p.A.

- Container label received on November 9, 2022
- Carton labeling received on November 9, 2022
- Prescribing Information (Image not shown) received on November 9, 2022, available from \\CDSESUB1\EVSPROD\bla761161\0058\m1\us\1-14-1-3-draft-label-09nov2022-redline.docx

G.2 Label and Labeling Images

Container Label

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

---

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/

SALI MAHMOUD
03/17/2023 02:09:23 PM

ASHLEIGH V LOWERY
03/17/2023 03:51:05 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

TO: Michael G. White, PhD, Chief, Project Management Staff (CPMS)
Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Rare Diseases & Medical Genetics (DRDMG)

FROM: Tinya Sensie, MHA, Senior Regulatory Project Manager
Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Pediatric and Maternal Health (DPMH)

SUBJECT: New BLA 761161 Requesting PREA/PeRC Assistance

BLA: 761161

DRUG: pegunigalsidase (PRX-102)

On November 18, 2020, DPMH received a consult from DRDMG for new BLA 761161 requesting PREA/PeRC assistance. There was no pediatric data in the labeling for this submission. (b) (4)

The sponsor submitted a major amendment on November 4, 2020, which changed the PDUFA goal date to April 27, 2021. DPMH attended labeling meetings on December 8, 2020 and January 5, 2021, and an internal late cycle on February 22, 2021. We also attended a pre-industry late-cycle and sponsor late-cycle on March 8, 2021. DPMH helped DRDMG prepare for PeRC and review possible PREA PMRS ahead of PeRC on March 9, 2021.

A Complete Response was issued on April 27, 2021 for various deficiencies.

This memorandum will close out the consult request.

DPMH RPM- Tinya Sensie
DPMH RPM Team Leader- George Greeley
DPMH Pediatric Reviewer- Ethan Hausman
DPMH Pediatric Team Leader- Tamara Johnson
DPMH Deputy Division Director- John J. Alexander

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/

TINYA J SENSIE
05/06/2021 02:38:42 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 5, 2021

To: Michael White, PhD, Chief, Project Management Staff
Division of Rare Diseases and Medical Genetics (DRDMG)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for PRX-102 (pegunigalsidase alfa)

BLA: 761161

This memo is in response to Division of Rare Diseases and Medical Genetics (DRDMG) labeling consult request dated June 30, 2020. Reference is made to a Complete Response letter that was issued on April 27, 2021. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DRDMG submit a new consult request during the subsequent review cycle. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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/

ADEWALE A ADELEYE
05/05/2021 01:55:32 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	April 1, 2021
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761161
Product Name and Strength:	Elfabrio (pegunigalsidase alfa) injection, 20 mg/10 mL (2 mg/mL)
Applicant/Sponsor Name:	Chiesi USA, Inc.
OSE RCM #:	2020-1097-3
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 31, 2021 for Elfabrio. Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container labels and carton labeling for Elfabrio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

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

[a]Abraham, S. Label and Labeling Review for Elfabrio (BLA 761161). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 26. RCM No.: 2020-1097-2.

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/

SHERLY ABRAHAM
04/01/2021 03:17:41 PM

IDALIA E RYCHLIK
04/01/2021 03:21:39 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 26, 2021
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761161
Product Name and Strength:	Elfabrio (pegunigalsidase alfa) injection, 20 mg/10 mL (2 mg/mL)
Applicant/Sponsor Name:	Chiesi USA, Inc.
OSE RCM #:	2020-1097-2
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on March 17, 2021 for Elfabrio. Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container labels and carton labeling for Elfabrio (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. Please find below the recommendation for Chiesi USA, Inc.

[a]Abraham, S. Label and Labeling Review for Elfabrio (BLA 761161). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 23. RCM No.: 2020-1097-1.

3 RECOMMENDATIONS FOR CHIESI USA, INC.

A. Carton labeling and Container Labels Comments

1. Consider increasing the prominence of the strength statement to avoid overlooking this important information.

B. Container Labels

1. Consider decreasing the prominence of the Rx only statement and NDC number. The increased prominence of the "Rx only statement" and NDC number takes the reader's attention away from other important information on the PDP such as established name, dosage form, and strength.
2. Consider bolding the storage statement to increase the prominence of this important information and minimize the risk of the storage information being overlooked.

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

---

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/

SHERLY ABRAHAM
03/26/2021 09:11:52 AM

IDALIA E RYCHLIK
03/26/2021 10:37:57 AM

Clinical Inspection Summary

Date	3/2/2021
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Michael White, Regulatory Project Manager Anita Zaidi, M.D., Medical Officer Division of Rare Disease and Medical Genetics Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine
BLA #	761161
Applicant	Chiesi USA
Drug	Pegunigalsidase Alfa
NME	Yes
Proposed Indication	Treatment of adults with a confirmed diagnosis of Fabry disease
Consultation Request Date	7/21/2020
Summary Goal Date	10/27/2020, extended to 3/5/2021
Priority/Standard Review	Priority
Action Goal Date	3/27/2021
PDUFA Date	1/27/2021, extended to 3/27/2021 due to major amendment

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigators (CIs) Drs. Goker-Alpan, Holida, and Schiffmann were inspected in support of this BLA, covering Protocols PB-102-F01 and PB-102-F02. An inspection of the sponsor was not conducted because, at the current time, the COVID-19 global pandemic has significantly limited our ability to conduct on-site GCP inspections. In addition, the sponsor was able to provide requested certified copies of source documents to the three CI sites that were needed to verify the primary endpoint data.

During the CI inspections, discrepancies in the Barisoni Lipid Inclusion Scoring System (BLISS) scores were identified (see below). In addition, a review of BLISS scores identified some significant variability between reader scores for 2 of 16 enrolled subjects (see below). Nevertheless, based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

During the clinical investigator (CI) inspections, primary efficacy endpoint data including BLISS scores and plasma globotriaosylsphingosine (Lyso-Gb3) concentrations were reviewed.

Sponsor data line listings for BLISS scores and Lyso-Gb3 concentrations were verified against certified source documents that the sponsor had obtained from the vendor ((b) (4) and sent to the CI sites. Discrepancies were noted in BLISS scores for subjects enrolled at all three sites. Based on these discrepancies, the Office of Scientific Investigations (OSI) recommended that the sponsor verify all BLISS scores for all subjects at all sites and to submit revised datasets to the BLA. OSI also recommended that these datasets include BLISS scores for all three readers in cases where capillaries were adjudicated since the original BLA datasets only included two of the three closest scores for such cases.

In their 11/4/2020 response, the sponsor provided an updated line listing of all BLISS scores (juxtaposed with the original line listings) and a revised dataset. This updated line listing, the BLISS Score Verification/Reconciliation document, highlighted discrepancies between certified source documents and the original line listings. Previously, this reviewer had verified BLISS scores from the original line listings against the certified source for the nine subjects enrolled at the three inspected sites. This reviewer was able to verify that the sponsor had identified all discrepancies noted by this reviewer for those nine subjects, which comprised 56% (9/16) of the enrolled population, in the BLISS Score Verification/Reconciliation document. The sponsor also highlighted additional discrepancies that were not identified by this reviewer. The sponsor indicated that the root cause of some of the discrepancies was identified as the introduction of a manual step in the BLISS score process. Specifically, after final scoring data was received from (b) (4) a manual transcription of data occurred during final reconciliation of the adjudicated scoring process which resulted in some errors.

During verification of source data for BLISS scores, wide variability between reader scores was noted for some capillaries (see Table 3 of CIS). A review of the BLISS score datasets identified approximately 3% of capillary scores with a $\geq$20 unit difference in BLISS score between readers. This $\geq$20 unit variability ranged from 0% of capillaries scored in three subjects up to 28% of capillaries scored in one subject. The sponsor did not provide a reason for this variability. We recommend that the review division examine the overall variability in BLISS scores when determining data quality and reliability.

The sponsor had excluded Subject (b) (6) from the efficacy analysis for BLISS scores due to a "mix-up" of biopsy samples by the pathology laboratory. Upon request, the sponsor provided more information regarding this error, including correspondence between the sponsor and pathology laboratory. The pathology laboratory confirmed that two slides had been mislabeled, but all other slides for this subject were reportedly labeled correctly. The sponsor had requested that the pathology laboratory prepare new slides from the original block for this subject, which were subsequently sent to (b) (4) and scored. If it can be determined which data in the dataset correspond to the new and/or correctly labeled slides, the review division might consider using the data for this subject in their efficacy analyses, especially given the small number of enrolled subjects in this rare disease.

II. BACKGROUND

Pegunigalsidase alfa injection for intravenous use is being developed under BLA 761161 (IND 110161) for the treatment of adults with a confirmed diagnosis of Fabry disease. In 2018, Protalix Ltd. and Chiesi USA entered into an exclusive U.S. license and supply agreement under which Protalix granted Chiesi the rights for the development and commercialization of pegunigalsidase alfa. The sponsor of IND 110161 continues to be Protalix, while Chiesi is the sponsor of the BLA.

Pegunigalsidase alfa is a PEGylated, recombinant human protein α-GAL-A. The sponsor has submitted the results of a Phase 1/2 study, Protocol PB-102-F01/F02, to support the safety and efficacy of pegunigalsidase alfa for the treatment of Fabry disease. A confirmatory study is currently ongoing.

Protocol PB-102-F01

Title: "A phase 1/2, open label, dose ranging study to evaluate the safety, tolerability, pharmacokinetics and exploratory efficacy parameters of PRX-102 [pegunigalsidase alfa] administered by intravenous infusion every 2 weeks for 12 weeks to adult Fabry patients"

Subjects: 19 enrolled

Sites: 13; United States (9), Western Europe (2), Australia (1), and Latin America (1)

Study Initiation and Completion Dates: 11/5/2012 – ~5/2015

This was an open-label, dose ranging study to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and exploratory efficacy parameters of pegunigalsidase alfa in adults with Fabry disease.

Included were male or female subjects with symptomatic Fabry disease; ≥18 years of age; globotriaosylceramide (Gb3) concentration in urine >1.5 times upper limit of normal; eGFR ≥60 mL/min/1.73m^2; never received enzyme replacement therapy (ERT) in the past or have not received ERT in the past 6 months and have a negative anti-pegunigalsidase alfa antibody test.

Subjects were enrolled in one of three pegunigalsidase alfa intravenous infusion treatment groups (up to 6-8 subjects per group with a minimum of 4 males and 2 females per group):

- Group 1: Pegunigalsidase alfa 0.2 mg/kg every two weeks for 12 weeks
- Group II: Pegunigalsidase alfa 1 mg/kg every two weeks for 12 weeks
- Group III: Pegunigalsidase alfa 2 mg/kg every two weeks for 12 weeks

Subjects received infusions sequentially and stepwise in order to evaluate tolerability. The first subject in Group I was given the lowest dose (0.2 mg/kg) for at least 4 infusions and, if tolerated, the second subject in Group I was to be given at least 4 infusions. The last 4 subjects of Group I were to receive infusions only if the entire series of 7 infusions was well-tolerated in the first subject and 4 infusions were well-tolerated in the second subject. After all 6 subjects of Group I tolerated all 7 infusions, the 6 subjects in Group II were given the 1 mg/kg dose following the same stepwise progression.

The first four infusions in each subject were to be administered over 4 hours. Tolerability of the infusion was determined by signs and symptoms during the infusion and observation post-dosing during hospitalization. If the rate was well tolerated during all four infusions, the rate of infusion could be increased and administered over 2 hours for all subsequent infusions. All infusions were to be administered during hospitalization, and subjects were to remain in the hospital for at least 24 hours after completion of the infusion. If the first 4 infusions were well-tolerated in Groups II and III, and hospitalization was a significant burden for the subject, an outpatient setup at a selected medical center with adequate emergency treatment facilities could be considered based on approval of the Protalix Medical Director.

The protocol included stopping criteria for the 2 mg/kg dose. At the time of enrollment of the fourth subject into the 2 mg/kg group (Group III), the sponsor opted to stop enrollment in Group III and made the decision to use the 1 mg/kg dose for the pivotal studies.

Protocol PB-102-F02

Title: "An extension of phase 1/2, open label, dose ranging study to evaluate the safety, tolerability, pharmacokinetics and exploratory efficacy parameters of PRX-102 administered by intravenous infusion every 2 weeks for 38 weeks (9 months) to adult Fabry patients"

Subjects: 16 enrolled

Sites: 10; United States (7), Western Europe (2), and Latin America (1)

Study Initiation and Completion Dates: ~5/2015 – 3/6/2016

Subjects who completed Protocol PB-102-F01 could enroll in this extension study. Subjects continued to receive the same dose of pegunigalsidase alfa as an intravenous infusion every 2 weeks for 38 weeks (9 months).

Kidney biopsies were taken at baseline in Protocol PB-102-F01 and Month 3 (corresponding to 6 months of treatment) in Protocol PB-102-F02. Gb3

concentrations in the kidney were assessed histologically in the kidney biopsy samples and scored using the Barisoni Lipid Inclusion Scoring System (BLISS).

Protocol PB-102-F01 included a number of exploratory efficacy parameters and surrogate endpoints. The ***primary efficacy surrogate endpoints*** were changes from baseline in Protocol PB-102-F01 to a timepoint, 6 month or 12 months, occurring in Protocol PB-102-F02. The two main surrogate endpoints included:

- Change from Baseline to Month 6 in average BLISS score
- Change from Baseline to Month 12 in plasma Lyso-Gb3.

Rationale for Site Selection

The clinical sites for the purpose of surveillance inspection were chosen primarily based on the number of enrolled subjects. The studies covered for these inspections enrolled subjects with a rare disorder and most sites enrolled one or two subjects. Therefore, sites with ≥3 subjects were chosen for inspection.

Verification of BLISS Scores and Plasma Lyso GB3 Data

As part of the clinical investigator inspections, the review division requested that source data for two surrogate endpoints, BLISS scores and plasma Lyso-Gb3 data, be verified against the sponsor data line listings provided in the BLA submission. The process to evaluate Gb3 in kidney biopsies utilized analysis of digital images in which nephropathologists assigned capillaries a BLISS score. The source digital imaging and scoring sheets per slide resided at the vendor, (b) (4). Plasma Lyso-GB3 were analyzed at the Enzyme Laboratory of the (b) (4) Since these data were centrally read, they would not be available at the clinical investigator sites.

An information request was sent to the sponsor on 8/6/2020 to ascertain whether certified copies of BLISS scores could be provided from the vendor to the clinical sites. In an 8/11/2020 response, the sponsor indicated that (b) (4) would not have the ability to provide certified copies of the BLISS scoring sheets. Following this response, OSI and the sponsor held a teleconference on 8/13/2020 to discuss the scope of the request (certified copies of data limited to subjects at the sites to be inspected) as well as explaining what could be acceptable as a certification process. The sponsor agreed to pursue certified copies of BLISS scores as well as plasma Lyso-GB3 data from the vendors to send to the clinical investigator sites and noted that these data would not be available to send to the clinical sites until mid-September 2020. The sponsor also submitted these data to the BLA on 10/21/2020.

III. RESULTS

1. Raphael Schiffmann, M.D.
Site # 09/51 (the reason for two site numbers is unclear)
Baylor Scott & White Research Institute
3600 Gaston Avenue
Suite 1202
Dallas, TX 75246-1827

Inspection Dates: 9/21/2020 – 9/24/2020

At this site for Protocol PB-102-F01, 2 subjects were screened, all of whom were enrolled and completed the study. At this site for Protocol PB-102-F02, the 2 subjects who completed PB-102-F01 were enrolled. Another subject, (b) (6), moved and was transferred to this site from Site #06 at Visit 8 (Week 16). All 3 subjects completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (BLISS scores and plasma Lyso-GB3).

BLISS scores and plasma Lyso-GB3 are centrally read and the data are not present at the clinical investigator sites. By request, the sponsor provided certified copies of BLISS scores obtained from (b) (4) and certified copies of plasma Lyso-GB3 concentrations from (b) (4) to the clinical sites for verification purposes. The FDA field investigator verified these data against the sponsor data line listings provided in the BLA submission. Several BLISS score discrepancies were identified (Table 1); no discrepancies were identified for the plasma Lyso-GB3 data.

Table 1. BLISS Score Discrepancies – Site 09/51

Subject	Visit	Capillary and Block Number	BLISS Score Certified Source			BLISS Score Sponsor Line Listing	
			Reader 1	Reader 2	Adjudicator	Reader 1	Reader 2
(b) (6)	Baseline	34; A1*	3	8	13	8	8
		64; A1	10	4	1	1	1
		74; A1	15	23	none	3	3
		77; A1	8	4	none	4	4
		80; A1	11	5	2	2	2
		88; A1	5	2	none	5	4
	Week 26	45; A2	0	10	16	0	3
		69; A2	0	6	2	0	0

*This was later acknowledged not to be a discrepancy based on prespecified adjudication rules (median value for equal differences among three scores), refer to Adjudication Criteria and Process section of CIS

There was no evidence of underreporting of adverse events.

Reviewer comments: BLISS score discrepancies between certified source and sponsor data listings were identified for one of three subjects at this site. The clinical investigator is not involved in generating these data. Data integrity issues described in Table 1 were the responsibility of the sponsor and not the clinical investigator. Please see further discussion regarding the BLISS score discrepancies below.

2. Myrl Holida, PA-C

Site #15
200 Hawkins Dr.
Iowa City, IA 52242
Inspection Dates: 10/5/2020 – 10/8/2020

The sponsor had named John Bernat as the clinical investigator (CI) in the BLA submission. Therefore, when this site was selected for inspection, the review division listed Dr. Bernat in their consult to OSI. The sponsor later provided updated lists of clinical investigators in which Myrl Holida was identified as the clinical investigator at this site for Protocols PB-102F01 and PB-102-F02.

At this site for Protocol PB-102-F01, 5 subjects were screened, 4 were enrolled, and 3 subjects completed the study. One subject was discontinued due to withdrawal of consent. At this site for Protocol PB-102-F02, the 3 subjects who completed PB-102-F01 were enrolled and completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all enrolled subjects was

conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (BLISS scores and plasma Lyso-GB3).

BLISS scores and plasma Lyso-GB3 are centrally read and the data are not present at the clinical investigator sites. By request, the sponsor provided certified copies of BLISS scores obtained from (b) (4) and certified copies of plasma Lyso-GB3 concentrations from (b) (4) to the clinical sites for verification purposes. In addition, the sponsor provided a "BLISS Data Verification Addendum" for this site (on the second day of the inspection) that identified the BLISS score discrepancies between the certified source and the BLA data line listings.

The FDA field investigator verified the source data against the sponsor line listings for approximately 30% of the BLISS scores and plasma Lyso-GB3 data. No discrepancies were noted for the 30% of data that was reviewed.

This reviewer compared all BLISS scores in the certified source against the sponsor data line listings and noted several discrepancies (Table 2). The sponsor had identified these discrepancies in the "BLISS Data Verification Addendum".

Table 2. BLISS Score Discrepancies – Site #15

Subject	Visit	Capillary and Block Number	BLISS Score Certified Source			BLISS Score Sponsor Line Listing	
			Reader 1	Reader 2	Adjudicator	Reader 1	Reader 2
(b) (6)	Week 26	8; B	5	n/a	42	Capillary not in listing	
	Baseline	5; C*	2	8	14	8	8
		46; C	7	11	none	7	3
		83; C	0	4	4	4	5
		84; C	1	2	none	1	4
		91; C	2	7	none	2	3
	Week 26	54; C	0	3	none	0	2
	Week 26	27; C	0	1	none	1	1

*This was later acknowledged not to be a discrepancy based on prespecified adjudication rules (median value for equal differences among three scores), refer to Adjudication Criteria and Process section of CIS

During review of the BLISS scores for Subject (b) (6) this reviewer found wide variability in some scores between Reader 1, Reader 2, and the Adjudicator for the baseline and Week 26 visits. Table 3 includes some of the BLISS scores with wide variability; this is not a complete list of all capillary scores with wide variability for this subject.

Table 3. Marked BLISS Score Differences Among Reader 1, Reader 2, and Adjudicator

Subject	Visit	Capillary and Block Number	BLISS Score Certified Source		
			Reader 1	Reader 2	Adjudicator
(b) (6)	Baseline	2; D	7	36	0
		3; A	6	24	0
		4; B	10	38	1
		6; B	3	23	0
		7; B	9	32	1
		14; A	6	21	0
		16; A	6	30	2
		26; C	7	29	0
		100; A	13	41	3
	Week 26	13; A	5	0	32
		14; C	10	4	28
		17; A	11	0	42
		22; B	12	5	41
		31; B	7	0	17
		39; C	9	0	29
		42; B	20	1	31
		43; B	16	0	28

There was no evidence of underreporting of adverse events.

Reviewer comments: *BLISS score discrepancies between certified source and sponsor data listings were identified for all three subjects at this site. The clinical investigator is not involved in generating these data. Data integrity issues described in Table 2 were the responsibility of the sponsor and not the clinical investigator.*

It is unknown why large variability between BLISS scores occurred among the readers for Subject (b) (6)*. However, per adjudication rules (see discussion below), the two closest BLISS scores of the three readers was used to score each capillary. Therefore, the exclusion of the outlier values for Subject* (b) (6) *occurred for baseline scores as well as Week 26 scores such that there did not appear to be a bias (e.g. exclusion of the high outlier scores at baseline would not favor the study drug).*

This reviewer reviewed BLISS scores for all readers (including adjudicator) for all subjects submitted by the sponsor in a 11/4/2020 response. Subject (b) (6) *appears to be an outlier with regard to the percentage of capillary scores with wide variability among readers. Please see further discussion regarding the BLISS score variability and discrepancies below.*

3. Ozlem Goker-Alpan, M.D

Site #12
Lysosomal and Rare Disorders Research and Treatment Center
3702 Pender Drive
Suite 170
Fairfax, VA 22030-6066
Inspection Dates: 10/13/2020 – 10/16/2020

At this site for Protocol PB-102-F01, 4 subjects were screened and 3 subjects were enrolled, all of whom completed the study. At this site for Protocol PB-102-F02, the 3 subjects who completed PB-102-F01 were enrolled in and completed the study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and primary efficacy endpoint data (BLISS scores, plasma Lyso-GB3).

BLISS scores and plasma Lyso-GB3 are centrally read and the data are not present at the clinical investigator sites. By request, the sponsor provided certified copies of BLISS scores obtained from (b) (4) and certified copies of plasma Lyso-GB3 concentrations from (b) (4) to the clinical sites for verification purposes. In addition, the sponsor provided a "BLISS Data Verification Addendum" for this site that identified the BLISS score discrepancies between the certified source and the BLA data line listings.

The FDA field investigator verified the plasma Lyso-GB3 data in the certified source against the line listings provided in the BLA submission; no discrepancies were noted. Verification of a random sample of the BLISS scores in the certified source for the three enrolled subjects did not reveal any discrepancies.

This reviewer compared BLISS scores in certified source against the sponsor data line listings and noted several discrepancies (Table 4). The sponsor had identified these discrepancies in the "BLISS Data Verification Addendum".

Table 4. BLISS Score Discrepancies – Site #12

Subject	Visit	Capillary and Block Number	BLISS Score Certified Source			BLISS Score Sponsor Line Listing	
			Reader 1	Reader 2	Adjudicator	Reader 1	Reader 2
(b) (6)	Baseline	81; A*	2	7	12	7	7
	Baseline	89; B	12	6	9	9	9
		1-120; D	Scores not available	Scores available[1]	Scores available[1]	n/a[2]	Scores available[1]

*This was later acknowledged not to be a discrepancy based on prespecified adjudication rules (median value for equal differences among three scores), refer to Adjudication Criteria and Process section of CIS

[1]Scores for capillaries 1 through 120 were available but are not listed in the table

[2]Sponsor line listing "n/a" for missing value, see text for explanation

For Subject (b) (6) (capillaries 1-120, block D), the sponsor data line listings specified "n/a" for Reader 1. However, there were scores in the certified source available for two readers (Reader 2 and Adjudicator). In the "BLISS Data Verification Addendum" provided to the site, the sponsor stated that Reader 1 decided not to score an entire block considering that enough capillaries were available based on previous blocks assessed. Of note, there were no pre-defined rules in the protocol to manage such a case, and the two original scores (Reader 1 and Reader 2) were kept as the scores, including the n/a "score" for Reader 1. Scores were, however, available from the Adjudicator but were not included in the BLA listing.

There was no evidence of underreporting of adverse events.

Reviewer comment: *BLISS score discrepancies between certified source and sponsor data listings were identified for all three subjects at this site. The clinical investigator is not involved in generating these data. Data integrity issues described in Table 4 were the responsibility of the sponsor and not the clinical investigator.*

In resubmitted datasets per request of the review division (see below), the sponsor replaced the Reader 1 missing values (n/a per data line listing) with the Adjudicator values. The Reader 1 missing values were not reported as a protocol deviation. Please see further discussion regarding the BLISS score discrepancies below.

Information Requests and Sponsor Responses

BLISS Score Discrepancies

Due to the BLISS score discrepancies identified for subjects enrolled at all three inspected clinical investigator sites, an information request (IR) was sent to the sponsor on 10/27/2020 asking that they themselves verify the BLISS scores in the BLA data line listings against the certified copies obtained from (b) (4) for all subjects and to explain any discrepancies. This IR also requested information about the adjudication process used for the BLISS scores.

In their 11/4/2020 response, the sponsor identified several types of BLISS discrepancies (See Table 5), specifically:

1. Capillaries/rows with a missing adjudicator score when adjudication criteria were met. The sponsor identified 44 discrepancies in this category, 40 of which occurred at Site #17.
2. Capillaries/rows in which there were differences in BLISS scores between certified source and data line listings. The sponsor identified 69 discrepancies in this category.
3. Capillaries/rows in which BLISS scores were present in certified copies but not found in data line listings. The sponsor identified 762 discrepancies in this category.

Table 5. BLISS Score Discrepancies Noted by Sponsor

	Adjudicator Score Missing *(see #1 above)*	**BLISS Score Discrepancies Between Line Listing and Source** *(see #2 above)*	**BLISS Scores Not in Line Listing but with Source** *(see #3 above)*	**Number of Capillaries Read**	**% Discrepancies (discrepancies / number of capillaries)**
Site 01	0	0	0	635	0
Site 03	1	1	0	649	0.31
Site 04	0	12	0	632	1.90
Site 07	0	1	0	643	0.16
Site 09/51	0	17	0	1912	0.89
Site 12	1	3	122	1713	0.74
Site 15	2	14	4	1876	0.96
Site 17	40	21	636	1296	50.7
Site 26	0	0	0	616	0
Total	**44**	**69**	**762**	**9972**	**8.35**

Reviewer comments: The sponsor reviewed BLISS scores for all subjects at all clinical sites and submitted a BLISS Score Verification/Reconciliation document listing all BLISS score discrepancies (similar to the BLISS Data Verification Addendum provided to the inspected sites). Among the three categories of discrepancies listed above, the sponsor identified 833 discrepancies for 9972 capillaries, an overall discrepancy rate of 8.35%.

The most significant discrepancies were BLISS scores that were not included in the data line listings but were available in the certified source, specifically 636 BLISS scores for Subject (b) (6) *and 122 BLISS scores for Subject* (b) (6) *(see Table 4) that were not in the line listings. The sponsor stated that the biopsies for Subject* (b) (6) *were "by accident mixed up by the laboratory" such that attribution of Visit 1 (baseline) versus Visit 7 (Week 26) could not be determined. Therefore, these data were not included in the efficacy analysis. The sponsor had reported the exclusion of data for Subject* (b) (6) *in the Clinical Study Report; however, this was not reported as a protocol deviation.*

In their 11/4/2020 response, the sponsor provided an updated line listing of all BLISS scores (juxtaposed with the original line listings) and a revised dataset. This updated line listing, the BLISS Score Verification/Reconciliation document, highlighted discrepancies between certified source documents and the original line listings. Previously, this reviewer had verified BLISS scores from the original line listings against the certified source for the nine subjects enrolled at the three inspected sites. This reviewer was able to verify that the sponsor had identified all discrepancies noted by this reviewer for those nine subjects, which comprised 56% (9/16) of the enrolled population, in the BLISS Score Verification/Reconciliation document. The sponsor also highlighted additional discrepancies that were not identified by this reviewer. The sponsor indicated that the root cause of some of the discrepancies was identified as the introduction of a manual step in the BLISS score process. Specifically, after final scoring data was received from (b) (4) *a manual transcription of data occurred during final reconciliation of the adjudicated scoring process which resulted in some errors.*

<u>Adjudication Criteria and Process</u>

According to the Clinical Study Report, approximately 12% of capillaries met criteria for adjudication. The sponsor stated that the criteria for adjudication were discussed and agreed to on 11/13/2014 during a meeting between the three renal pathologists, (b) (4) (vendor, data management), and Protalix (original sponsor). The sponsor provided a (b) (4) Memorandum-to-File (MTF) dated 12/5/2014 that outlined these criteria in preparation for a planned interim analysis that was to be conducted with a data cutoff of 11/30/2014. The MTF, however, did not document the date on which the adjudication criteria were discussed and agreed upon. The sponsor stated that the first biopsy data transfer to (b) (4) occurred on 11/20/2014 (no documentation was provided).

An information request was sent to the sponsor on 11/12/2020 requesting the submission of materials available that could document the 11/13/2014 meeting in which the adjudication process and criteria were determined. On 11/18/2020, the sponsor submitted meeting

minutes for the 11/13/2014 meeting described above.

BLISS score adjudication was required if:

- Both scores were ≤10 and there was a ≥5 unit difference between the two scores
- At least one of the scores was >10 and the lower score was ≤50% of the upper score

(b) (4) transferred the scores determined by Reader 1 and Reader 2 pathologists to (b) (4) which reviewed the scores to determine if adjudication was required. For capillaries requiring adjudication, Reader 3 (original annotator/adjudicator) scored the selected capillaries. This adjudicator was blinded to Reader 1 and Reader 2 BLISS scores. (b) (4) selected the two out of the three scores that were closest in value (or median, when equal differences among the three occurred) and used these for the final analysis.

Reviewer comments: The sponsor submitted information documenting that the adjudication process and rules were determined on 11/14/2014 prior to the first stated biopsy data transfer to (b) (4) on 11/20/2014.

Variability in BLISS Scores

In response to our questions about variability in BLISS scores and interrater reliability, the sponsor stated that the renal pathologists involved in this study were the developers of the BLISS protocol and had previously tested and validated the methodology in a different clinical trial in Fabry disease. The sponsor did not comment on the marked differences noted in some capillary BLISS scores among the three readers for some capillaries (Table 3).

Reviewer comments: When the BLA was submitted, the sponsor had included only the closest two out of three BLISS scores for adjudicated capillaries. In an effort to examine the extent of BLISS score variability among readers (including adjudicator, where applicable), this reviewer reviewed all scores in the datasets submitted in the sponsor's 11/4/2020 response, focusing on BLISS scores with a ≥20 unit difference between readers' scores. This ≥20 unit difference was arbitrarily chosen.

For baseline and Week 26 capillaries, the overall rate of wide variability in scores (defined as ≥20 unit difference) was 3.5% and 2.5%, respectively. However, this differed significantly between subjects, ranging from a 0% to 28.3% (Subject (b) (6)) of capillaries scored with wide variability. The numbers of capillaries scored per subject ranged from 300 – 330 for both baseline and Week 26 for most subjects.

Table 6. BLISS Score Variability (>20 units) Between Readers

Subject	BLISS Score Capillaries with Variability Between Readers (%)	
	Baseline	Week 26
(b) (6)	0.6%	0
	0	0
	2.9%	0.3%
	4.3%	0
	0.3%	1.0%
	0.9%	0
	1.3%	0
	0.3%	0.3%
	n/a*	0.3%
	28.3%	9.5%
	0.3%	0
	0.3%	0.3%
	7.1%	14.8%
	0	0
	3%	0.3%
	0	0
Total	3.5%	2.5%

*Per CSR "biopsy sample did not include cortex kidney tissue making sample unreadable"
**Subject (b) (6) was excluded from the efficacy analysis. Due to laboratory error, attribution of baseline and Week 26 could not be determined.

Reviewer comment: The sponsor did not provide a rationale for the variability in some BLISS scores among Reader 1, Reader 2, and/or the Adjudicator. We recommend that the review division examine the overall variability in BLISS scores when determining data quality and reliability.

Exclusion of Subject (b) (6) in Efficacy Analysis

As noted above under BLISS Score Discrepancies, the biopsy data from Subject (b) (6) was excluded from the efficacy analysis since the biopsies were "by accident mixed up by the laboratory". The sponsor was asked to provide more detailed information regarding this error, including how the error occurred (root cause), the date the error was discovered, documentation/correspondence from the laboratory regarding the error, and any corrective actions taken to prevent recurrence.

The sponsor was able to provide email correspondences between Protalix and the (b) (4) pathology laboratory regarding this issue. For unspecified reasons, on December 12, 2014, the Medical Director of Protalix requested the (b) (4) pathology laboratory to confirm that the last slides, pertaining to Subjects (b) (6) and (b) (6), sent to (b) (4) were

given the right numbers that matched the correct patients and visits. On December 28, 2014, Protalix requested that the (b) (4) laboratory prepare new slides from the original blocks for Subject (b) (6) since the results for this subject were very different from the other subjects and did not correlate with other disease parameters for this subject. On December 31, 2014, the (b) (4) laboratory confirmed that 2 slides for Subject (b) (6) had been mislabeled. However, (b) (4) stated that the remainder of the original slides had been labeled correctly. Although the (b) (4) laboratory confirmed that the mislabeling error was limited to two slides, the new slides requested by Protalix were prepared, sent to (b) (4) and scored by the readers on 1/20/2015. The sponsor was unable to provide a root cause for this error and no corrective actions were subsequently taken.

Reviewer comments: The sponsor provided additional information confirming that some slides for Subject (b) (4), (b) (6) had been mislabeled. If it can be determined which data in the dataset correspond to the new and/or correctly labeled slides, the review division might consider using the data for this subject in their efficacy analyses, especially given the small number of enrolled subjects in this rare disease.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Document Room/BLA #761161
DRDMG/Medical Team Leader/Jane Filie
DRDMG/Medical Officer/Anita Zaidi
DRDMG/Project Manager/Michael White
CDER/OTS/OB/DBIV/Statistician/Yared Gurmu
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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/

CARA L ALFARO
03/02/2021 02:58:57 PM

PHILLIP D KRONSTEIN
03/02/2021 03:17:39 PM

KASSA AYALEW
03/02/2021 03:40:49 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 23, 2020
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761161
Product Name and Strength:	(b) (4) (pegunigalsidase alfa) injection, 20 mg/10 mL (2 mg/mL)
Applicant/Sponsor Name:	Chiesi USA, Inc.
OSE RCM #:	2020-1097-1
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on November 3, 2020 for (b) (4) Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container labels and carton labeling for (b) (4) (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. Please find below the recommendation for Chiesi USA, Inc.

[a]Abraham, S. Label and Labeling Review for (b) (4) (BLA 761161). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 23. RCM No.: 2020-1097.

3 RECOMMENDATIONS FOR CHIESI USA, INC.

A. Carton labeling and Container Labels Comments

1. As currently displayed, the dosage form, "injection" is bolded and takes the prominence away from other more important information such as the established name and strength. Unbold the dosage form statement.
2. The letter, 'I' in the established name is bolded. Ensure that all letters have the same prominence throughout the established name.

B. Container Labels

1. Relocate the net quantity statement away from the product strength statement to avoid numerical confusion between the strength and net quantity.

2. The CTPA code is located directly below the NDC number, consider relocating the CTPA xxx-xxxx-xx to the side panel. The NDC number may be utilized by pharmacist as a secondary check in product verification during dispensing. The close proximity of the CTPA code to the NDC number may cause numerical confusion.

3. The primary display panel for the container label should be reserved for only the most important product information, such as drug name, strength, route of administration, etc. Relocating the usual dose statement, "Recommended Dosage: See Prescribing Information" to the side panel.

C. Carton Labeling

1. Revise the net quantity statement to read, "1x 10 mL single-dose vial, 5x 10 mL single-dose vials, and 10 x 10 mL singe-dose vials to prevent confusion with the net quantity statement on the container label.

2. It is unclear where the machine-readable product identifier is located on the label. The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance also recommends that the human-readable portion be located near the 2D data matrix barcode.

   NDC: [insert NDC]
   SERIAL: [insert serial number]
   LOT: [insert lot number]
   EXP: [insert expiration date]

We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 3, 2020

Prescribing Information received on November 3, 2020

\\CDSESUB1\evsprod\nda213969\0026\m1\us\114-label\1141-draft-label\proposed-patient-info.docx

Instructions for Use (IFU) received on November 3, 2020

\\CDSESUB1\evsprod\nda213969\0026\m1\us\114-label\1141-draft-label\ifu.docx

Container labels

Carton labeling

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

---

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/

SHERLY ABRAHAM
11/23/2020 02:28:28 PM

IDALIA E RYCHLIK
11/23/2020 04:23:47 PM

LABEL AND REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 23, 2020
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	BLA 761161
Product Name, Dosage Form, and Strength:	(b) (4) (pegunigalsidase alfa) injection, 20 mg/10 mL (2 mg/mL)
Total Product Strength:	20 mg/10 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Chiesi USA, Inc.
FDA Received Date:	May 27, 2020 and June 5, 2020
OSE RCM #:	2020-1097
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for [redacted] pegunigalsidase alfa) injection, the Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the proposed [redacted] prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E-NA
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

We performed a risk assessment of the proposed prescribing information (PI), container labels, and carton labeling for [redacted] to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We identified some areas of concern for the proposed PI and the proposed carton and container labels. We provide our recommendations below in Table 2 for the Division and Section 3.1 for Chiesi USA, Inc.

Table 1. Identified Issues and Recommendations for Division of Rare Diseases and Medical Genetics (DRDMG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Use of confusing symbols or abbreviation(e.g.,	The usage of symbols and abbreviations can cause misinterpretation and confusion.	Replace the symbols and abbreviations with their intended meaning.

Table 1. Identified Issues and Recommendations for Division of Rare Diseases and Medical Genetics (DRDMG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	">", "<", "IV", "-", "hrs" etc.)		
2.	The package type terms, "single-use" and "single-dose" are both noted throughout the PI.	The correct package type term is important for the medication to be safely handled and used.	We defer to Office of Pharmaceutical Quality (OPQ) for the correct package terminology, please ensure consistent use throughout the PI.
3.	As currently presented, in the highlights and Section 3, the concentration statement (2 mg/mL) is not immediately after the product strength statement of 20 mg/10 mL.	Ensuring the product strength is expressed as total quantity per total volume followed by the concentration per milliliter (mL) mitigates the potential for medication dosing errors.	Revise the strength presentation to express total quantity per total volume followed by the concentration statement. For example, 20 mg/10 mL (2 mg/mL)
4.	Appropriate description of product characteristics important to facilitate identification of the product dosage form are missing from Section 3 Dosage forms and Strengths and Section 16 How Supplied/Storage and Handling.	Per CFR 201.57(c)(4)(ii), this information is necessary to facilitate identification of the dosage form.	For parental dosage forms (e.g., injection) include information about color (e.g., clear solution) and other identifying characteristics to help facilitate product identifications and mitigate the potential use of adulterated product.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The title of Table 1 is missing.	Titling the table appropriately is important to avoid errors	Add a title for Table 1.

Table 1. Identified Issues and Recommendations for Division of Rare Diseases and Medical Genetics (DRDMG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		involving preparation of the product.	
2.	As currently presented, important information in sections 2.2 and 2.3 are burdensome to read and difficult for the reader to decipher.	Presenting important information to the reader in a text heavy format may decrease readability and lead to misinterpretation of medication preparation instructions and administration errors.	Consider utilizing bullets to enhance the visibility of important information For example, (b) (4)

Table 1. Identified Issues and Recommendations for Division of Rare Diseases and Medical Genetics (DRDMG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(b) (4) [redacted]
3.	The storage information of the supplied drug before dilution is included in Section 2.	Drug storage information before dilution is reserved for Section 16 How Supplied/Storage and Handling.	Relocate the storage information of the supplied drug to Section 16.
4.	The first temperature numerical is missing the degree symbol.	Lack of clarity.	Revise the sentence to read (b) (4) [redacted]
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The National Drug Code (NDC) number of the container label is missing.	Per 21 CFR 207.33 and 21 CFR 201.2, drug products subject to listing with the FDA is requested to have a unique NDC number to identify its labeler, product, and package size and type.	Add the NDC number of the container label in section 16.

3.1 CARTON LABELING AND CONTAINER LABELS RECOMMENDATIONS FOR CHIESI USA, INC.

A. General Comments

1. Confirm there is no text on the ferrule and cap overseal of the vials.
2. 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.
3. As currently displayed, "Elfabrio" is used instead of the conditionally approved name, "(b) (4) Proposed proprietary name, (b) (4) found conditionally acceptable by DMEPA on July 16, 2020 under BLA 761161. Replace the "Elfabrio" with conditionally approved name, "(b) (4) on all container labels and carton labeling.
4. The strength statement lacks prominence. Prominence and readability of the strength presentation is required per 21 CFR 201.15(a)(6). Increase the prominence of the strength presentation on all label and labeling.
5. Bolded font is noted throughout the entirety of the text located on the label and labeling. Overuse of bold font may diminish its effect on prominence for important product information. Reserve the use of bolded font only for the most important product information on the label and labeling; unbold font on all other text.
6. The format for expiration date is undefined. The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors. Submit expiration date in the format that is stated below. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Container Label

1. If space permits, consider adding the dosage form, "injection", underneath the proper name and consider adding parenthesis around the proper name.
2. The strength statement is on the side panel. Consider relocating the strength statement to appear underneath the dosage form, "injection" on the principal display panel, and in the same vertical visual field of the Proprietary and proper names to increase prominence of this important information per 21 CFR 201.15.
3. The route of administration (ROA) is missing from the Principal Display Panel (PDP). Consider relocating the ROA to appear underneath the strength statement in the

customary position for FDA labels on the principal display panel. Revise the ROA statement to read "For intravenous infusion after dilution" and delete the separate "(b) (4)" statement from the label.

4. The net quantity statement is missing from the PDP. Per 21 CFR 201.51, add a net quantity, "(b) (4)", statement to the PDP.
5. Revise to the appropriate package-type term for this product, which is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose.
6. Consider revising the statement of dosage from "(b) (4)." to read "Recommended Dosage: See Prescribing Information" on the side panel.
7. Consider relocating the storage information to the side panel and revise to read as "Refrigerate at 2 °C to 8 °C (36 °F to 46 °F). Do not freeze. Do not shake."
8. The manufacturer's name and address are identified on the PDP. PDP is reserved for the most important information. Other less important statements should be on the side panel. Relocate the manufacturer's name and address to the side panel.
9. The linear barcode is presented in a horizontal position on the container label. If the linear barcode is presented in a horizontal position, then the barcode may wrap around the curvature of a vial and will not be scannable. Reorient the linear barcode to a vertical position to improve the scannability of the barcode on container label. Ensure the barcode is scannable.

C. Carton Labeling

1. Consider adding the dosage form, "injection", underneath the proper name and consider adding parenthesis around the proper name.

2. Per 21 CFR 610.61, The following items shall appear on the label affixed to each package containing a product: (e) The preservative used and its concentration, or if no preservative is used and the absence of a preservative is a safety factor, the words "No Preservative"

3. The storage statement lacks prominence. We recommend this to increase the prominence of this important information and minimize the risk of the storage

information being overlooked. Revise and bold the statement "Must be refrigerated, store at 2°to 8°C (36° to 46°F).".

4. If space permits, consider adding the post-dilution storage information to the side panel after the supplied product's storage information as "Used immediately once diluted. If immediate use is not possible, store up to 24 hours at 2 °C to 8 °C (36 °F to 46 °F) or at room temperature [20 °C to 25 °C (68 °F to 77 °F)] for up to 8 hours."

5. Revise the ingredient information from "20 mg pegunigalsidase alfa (2 mg/mL), 0.7% Sodium chloride…." to read "(b) (4)
(b) (4)

6. Consider deleting "(b) (4)t" from the principal display panel to reduce clutter.

7. Revise to the appropriate package-type term for this product, which is "single-dose". Add the statement "Discard unused portion." to appear after the package type term "single-dose vial".

8. Consider revising from "(b) (4)" to read "Recommended Dosage: See Prescribing Information".

9. As currently displayed, the manufacturer name("Chiesi") is more prominent in size than the most important information (i.e., established name and strength). The primary display panel (PDP) should be reserved for important product information. Duplicative manufacturer information located on the PDP takes readers' attention away from more important information such as established name, and strength. Consider removing the manufacturer name ("Chiesi") for increased readability of more important information.

10. The "Rx only statement" is overly prominent. The increased prominence of the "Rx only statement" takes the reader's attention away from other important information on the PDP such as established name, dosage form, and strength. Decrease the prominence of the "Rx only statement" by decreasing the font size and relocate it to a corner of the PDP. The human readable product identifier required under the Drug Supply Chain Security Act (DSCSA) is incomplete, the serial number is omitted. Additionally, it is unclear where the machine-readable product identifier is located on the label. The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier. The DSCSA guidance on product identifiers recommends the format below for the human-readable portion of the product identifier. The guidance

also recommends that the human-readable portion be located near the 2D data matrix barcode.

NDC: [insert NDC]
SERIAL: [insert serial number]
LOT: [insert lot number]
EXP: [insert expiration date]
We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.

4 CONCLUSION

Our evaluation of the proposed (b) (4) prescribing information (PI), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 1 for the Division and Error! Reference source not found. labeling and container labels. We ask that the Division convey our carton labeling and container labels recommendation to Chiesi USA, Inc. so that recommendations are implemented prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for (b) (4) received on June 5, 2020 from Chiesi.

Table 3. Relevant Product Information for (b) (4)	
Initial Approval Date	N/A
Nonproprietary Name	pegunigalsidase alfa
Indication	Treatment of adults with a confirmed diagnosis of Fabry disease
Route of Administration	intravenous infusion
Dosage Form	injection
Strength	20 mg/10 mL (2 mg/mL)
Dose and Frequency	1 mg/kg every other week
How Supplied	1, 5, and 10 single use vials 20 mg (10 mL) vials
Storage	Store vials at 2˚C to 8˚C (36˚F to 46˚F). Do not freeze or shake. The product contains no preservative. Diluted solutions should be used immediately. If immediate use is not possible, the diluted solution may be stored for up to 24 hours at 2˚C to 8˚C (36˚F to 46˚F) or 8 hours at room temperature.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by Chiesi USA, Inc..

- Container label received on May 27, 2020
- Carton labeling received on May 27, 2020
- Prescribing Information (Image not shown) received on June 5, 2020, available from \\CDSESUB1\evprod\bla761161\0002\m1\us\1-14-1-3-draft-labeling-text.docx

F.2 Label and Labeling Images

(b) (4)

[redacted]

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

---

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/

SHERLY ABRAHAM
10/26/2020 12:55:29 PM

IDALIA E RYCHLIK
10/26/2020 01:03:15 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 10/6/2020 **Date consulted:** 06/29/2020

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Carrie Ceresa, Pharm D., MPH, Acting Team Leader, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health (DPMH)

To: Division of Rare Diseases and Medical Genetics (DRDMG)

Drug: (b) (4) (pegunigalsidase alfa) injection, for intravenous use

BLA: 761161

Applicant: Chiesi USA, Inc.

Subject: new BLA

Proposed Indication: for the treatment of adults with a confirmed diagnosis of Fabry disease.

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 761161
- DAAP consult form for DPMH, DARRTS Reference ID 4633151
- DPMH labeling review of Fabrazyme, BLA 103979 on October 31, 2018, DARRTS Reference ID: 4349127[1]

[1] The labeling review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

- DPMH labeling review of Galafold, NDA 208623 on June 8, 2018, DARRTS Reference ID: 4278478[2]

Consult Question:

- DAAP is seeking assistance from DPMH in developing Sections 8.1, 8.2 and 8.3 of the product's labeling.

INTRODUCTION AND BACKGROUND

On May 27, 2020, the applicant (Chiesi USA, Inc.) submitted a new original BLA 761161 for pegunigalsidase alfa injection for approval. The Division of Rare Diseases and Medical Genetics (DRDMG) consulted the Division of Pediatric and Maternal Health (DPMH) on June 29, 2020, to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- On May 27, 2020, the applicant submitted a BLA for pegunigalsidase alfa injection with the proposed indication for the treatment of adults with a confirmed diagnosis of Fabry disease under the accelerated approval provision of FDASIA in section 506(c) of the FD&C Act. However, this is not been approved yet. Pegunigalsidase alfa carries a Fast Track designation.
- (b) (4)
- Pegunigalsidase alfa has not been approved previously for use in the U.S. or any other country.

Drug Characteristics Based (b) (4)

Drug Class	enzyme replacement drug (PEGylated recombinant human alpha-galactosidase A (prh alpha-GAL-A) enzyme
Proposed Mechanism of action	Pegunigalsidase alfa is intended to provide an exogenous source of alpha-GAL-A which enters the cells of patients with Fabry disease where it localizes in the lysosome and reduces accumulated Gb3.
Proposed Dose and Administration	1 mg/kg body weight administered every other week as an intravenous infusion.
Metabolism	Cell uptake is considered to be combination of endocytosis and mannose mediated receptor uptake.
Molecular weight	116 kDa (112000-121000 Da)
Half life	80 hours
Protein Binding	NA
Bioavailability	100%
Serious Adverse Reactions	Life-threatening and severe allergic reactions. Infusion related reactions may occur.

[2] The labeling review was part of the materials reviewed but was not a source relied upon for the labeling recommendations in this consult review.

REVIEW
PREGNANCY
Fabry Disease[3]
Fabry disease (FD) is a progressive lysosomal storage disease caused by X-linked deficiency of the enzyme alpha galactosidase-A (α-GAL-A). The enzymatic deficiency leads to the progressive accumulation of glycosphingolipids, most notably Gb-3, in lysosomes of a variety of cell types and tissues.

- FD is regarded as a rare disease, FD is present in approximately 1:22,000 to 1:40,000 males, and mutations associated with atypical, so called "later-onset", presentations are present in approximately 1:1000 to 1:3000 males and 1:6000 to 1:40,000 females.[4] The estimated prevalence in the general population is 1 in 117,000.[5]
- The αGAL gene mutation is carried by the X chromosome, thus males typically have the classical, severe form of the disease, while females have a more variable phenotype, ranging from asymptomatic to severe. The current hypothesis for the occurrence of disease manifestations in female patients is skewed X inactivation, although other authors were unable to support such a hypothesis.[6]
- The clinical features of FD include acroparesthesias and pain crises, angiokeratomas, gastrointestinal symptoms (neuropathic abdominal pain, nausea, vomiting, and diarrhea), renal impairment, cardiac disease, and cerebrovascular disease.
- Current treatments for FD include enzyme replacement (agalsidase alfa and agalsidase beta) and enzyme stabilizer (migalastat). Agalsidase alfa is not currently approved in US.

The incidence of FD in pregnancy is very rare. Published literature on the natural history of FD in pregnancy is sparse.

- A retrospective study conducted in 2014 surveyed 100 women with Fabry disease about their pregnancy outcomes; 41 women completed the survey and provided a medical record release.[7] This study found severe Fabry disease symptoms may worsen during pregnancy. This study also found an elevated risk of preeclampsia, proteinuria, gestational diabetes, hypertension, and preterm delivery in women with Fabry when compared to the general population in women with Fabry disease. This was consistent with prior studies by Bouwanman et al.[8] and Wang et al.[9] In this study, only 4 out of 41 women continued enzyme replacement therapy (ERT) throughout pregnancy.

[3] DPMH labeling review of Fabrazyme, BLA 103979 on October 31, 2018, DARRTS Reference ID: 4349127
[4] Mauer M, et al. Fabry disease: Clinical features and diagnosis. UptoDate, https://www.uptodate.com/contents/fabry-disease-clinical-features-and-diagnosis?search=fabry%20disease%20and%20pregnancy&source=search_result&selectedTitle=4~67&usage_type=default&display_rank=4 Accessed 7/6/2020.
[5] Meikle PJ, Hopwood JJ, Clague AE, Carey WF (1999). Prevalence of lysosomal storage disorders. JAMA Jan 20; 281(3):249-54.
[6] Maier EM et al. Disease manifestations and X inactivation in heterozygous females with Fabry disease. Acta Paediatr. Suppl 2006; 95: 30–38.
[7] Holms A, et al. A retrospective survey studying the impact of Fabry disease on pregnancy. JIMD Reports JIMD Rep. 2015; 21:57-63. doi: 10.1007/8904_2014_384. Epub 2015 Feb 22.
[8] Bouwman MG, et al. Prevalence of symptoms in female Fabry disease patients: a case-control survey. J Inherit Metab Dis 2012;35(5):891-898
[9] Wang RY, et al. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med 2007;9(1):34-45

Limitations of this study include small sample size and retrospective nature of the study which might have led to recall bias.

Nonclinical Experience

Applicant's Proposed Labeling states:

(b) (4)

The reader is referred to the Nonclinical comments within the unireview.

Review of Clinical Trials

One female patient within the clinical trials became pregnant despite the use of birth control while receiving pegunigalsidase alfa injections (Study PB-102-F03). The patient had normal ultrasound findings at week 13 of gestation but decided to terminate the pregnancy at week 14 for personal reasons.

Review of Literature

DPMH's Review of Literature

DPMH conducted a literature review in Embase, Pubmed, Micromedex,[10] and ReproTox.[11]

Embase and Pubmed were searched for "pegunigalsidase alfa" and "pregnancy," "pegunigalsidase alfa" and "fetal malformations/congenital malformations/birth defects/stillbirth/spontaneous abortion/miscarriage."

- There is no published literature on the use of pegunigalsidase alfa in pregnancy.

There are case reports describing pregnancy outcomes on the use of other α-GAL-A ERT in the literature. See APPENDIX A for a table of case reports and case series of pregnancy outcomes treated with agalsidase alfa, agalsidase beta, or migalastat.

- Past experience with 13 published case reports with other ERT use in pregnancy has not shown any results of malformation.

Micromedex[8] and ReproTox[9] contain no information on pegunigalsidase alfa.

Reviewer comment:

There are no data on the use of pegunigalsidase alfa in pregnancy. As an enzyme replacement, pegunigalsidase alfa replaces α-GAL-A and prevents accumulation of glycosphingolipids in lysosomes in various tissues and FB progression. Therefore, the use of pegunigalsidase alfa is

[10] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/7/2020

[11] Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 7/7/2020.

not expected to cause major birth defects, miscarriage, and adverse maternal and fetal outcomes. ERT in FB is necessary to maintain maternal health.

Overall, the applicant provided an adequate review of their clinical trial database regarding pegunigalsidase alfa and use in pregnant women. The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission and recommendations.

LACTATION

Nonclinical Experience

There are no data on the presence of pegunigalsidase alfa in animal milk.

Review of Clinical Trials

There were no lactating women participating in any of the clinical trials, and lactation studies have not been conducted.

Review of Literature

DPMH's Review of Literature

A search was performed using the sources noted below, and the following findings were retrieved:

A search in PubMed and Embase was performed using the search terms "pegunigalsidase alfa" AND "lactation" and "pegunigalsidase alfa" AND "breastfeeding."

- No articles were found on the use of pegunigalsidase alfa during lactation.

There are case reports of the use of other α-GAL-A ERT in lactation.

- A case series consisting of 6 women with FB received agalsidase alfa through pregnancy reported that 3 out 6 women exclusively breastfed for 6 months and continued breastfeeding for the first year. The other 3 breastfed their infants nonexclusively to 5-12 months of age.[12] The authors did not report any adverse effects.

LactMed,[13] Briggs,[14] and Hale[15] contain no information on pegunigalsidase alfa.

Reviewer comment:
There are no human or animal data on the presence of pegunigalsidase alfa in breastmilk. Based on its size, 116 kDa (112000-121000 Da), it is unlikely to be present in milk.

[12] Fernandez P, et al Enzyme replacement therapy in pregnant women with Fabry disease: a case series. JIMD Reports DOI 10.1007/8904_2018_141

[13] http;//toxnet nlm nih.gov/newtoxnet/lactmed htm. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Accessed 7/6/2020.

[14] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 7/6/20

[15] Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY. Accessed 7/6/20

Additionally, biologic products with large molecular weights are likely denatured and digested by passage through the infant's gastrointestinal tract and therefore unlikely to attain significant levels in breastfed infants.[16] This reviewer concludes the use of pegunigalsidase alfa during lactation is not expected to cause adverse effect to the breastfed infant.

The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data submission and recommendations.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Applicant's Proposed Labeling states:

(b) (4)

The reader is referred to the Nonclinical comments within the unireview.

Review of Clinical Trials

There were reported cases of accidental pregnancy in both male and female subjects of the study, and there were no cases of infertility/sterility reported in any of the clinical trials.

Review of Literature

DPMH's Review of Literature

DPMH conducted a published literature review by using the sources noted below, and the following findings were retrieved:

DPMH conducted a published literature review on PubMed and Embase using term "pegunigalsidase alfa" and "fertility," "pegunigalsidase alfa" AND "reproduction," "pegunigalsidase alfa" AND "contraception." No relevant articles were retrieved.

ReproTox[17] contains contain no information on pegunigalsidase alfa.

Reviewer comment:

The reader is referred to the Discussion and Conclusion section at the end of this review for DPMH's opinion of the data, submission and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

As an enzyme replacement for alpha galactosidase-A, pegunigalsidase alfa prevents progressive accumulation of glycosphingolipids in lysosomes of a variety of cell types and tissues. Therefore, pegunigalsidase alfa is not expected to cause major birth defects, miscarriage, and adverse maternal and fetal outcomes. There are no data on the use of pegunigalsidase alfa in pregnancy. Case reports of other ERT use in pregnancy have not identified a drug-associated

[16] Soh MC, et al. The use of biologics for autoimmune rheumatic diseases in fertility and pregnancy. Obstetric Medicine 2020; 13(1): 5–13

[17] ReproTox. Accessed 7/7/2020.

risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies indicate no effects on embryofetal development in rats at 3.6x the MRHD and ≥3.2x the MRHD in rabbits.

FB is a rare disease present in approximately 1:22,000 to 1:40,000 males, and mutations associated with atypical, so called "later-onset", presentations are present in approximately 1:1000 to 1:3000 males and 1:6000 to 1:40,000 females. There are no data on the use of pegunigalsidase alfa in pregnancy. Therefore, DPMH recommends a postmarketing pregnancy safety study, which can be accomplished as a sub-study to the post-marketing requirement (PMR) for the long-term safety study that DRDMG is requiring.

Lactation

Based on the physical characteristic of pegunigalsidase alfa, namely its size of 120kDa, it is unlikely to be present in milk or reach the infant in a significant quantity after an oral ingestion. There are no data on the presence of pegunigalsidase alfa in either human or animal milk, the effects of the drug on the breastfed infant, or on milk production. As an enzyme replacement, the use of pegunigalsidase alfa during lactation is not expected to cause adverse effect to the breastfed infant. DPMH recommends using the standard risk/benefit language in subsection 8.2.

Although pegunigalsidase alfa is expected to be used in females of reproductive potential, Fabry disease is very rare; a lactation study would not be feasible. In addition, based on the drug's physical characteristics, it is unlikely to be present in milk. Biological products with high MW are expected to be denatured through digestion, therefore, systemic exposure in the breastfed infant is not expected. DPMH does not recommends a post-marketing lactation study.

Females and Males of Reproductive Potential

As an enzyme replacement and based on the findings from the animal reproduction study, the use of pegunigalsidase alfa is not expected to adversely affect fertility. There are no data to suggest pegunigalsidase alfa interacts with systemic hormonal contraceptive. DPMH recommends omitting subsection 8.3.

LABELING RECOMMENDATIONS

DPMH proposes subsections 8.1, and 8.2 of labeling for the new BLA and in compliance with the PLLR (see below). DPMH refers to the final BLA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)

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

APPENDIX A Pregnancy outcomes of treated Fabry disease (FD): case reports and case series

Publication; author/date/Country	Type of Study	Drug	N	Exposure time	Case	Outcome
Fernandez P, et al.[18] (2018) Argentina	Case series	Agalsidase alfa	6	All (3 of them only exposed in 2nd and 3rd trimester)	A case series with pregnancy outcomes of 6 Fabry cases in pregnancy.	All normal deliveries at team except one delivered at 36 weeks due to eclampsia. All children were followed at least 1 year (up to 5 years). One child was diagnosed with FD.
Haninger-Vacariu N, et al.[19] (2019) Austria	Case report	Migalastat	1	1st and 2nd trimester (up to 18 weeks)	37-year-old woman G3P2 with one 18-week loss and diagnosis of Fabry disease after her second pregnancy with preeclampsia, placed on agalsidase alfa postpartum after renal biopsy. She was switched to migalastat and became pregnancy unknowingly despite hormonal contraceptive. Pregnancy was diagnosed at 18 weeks. Migalastat was stopped at this time. she smokes 20 cigarettes per day Fetal MRI normal at 29 weeks.	Delivery at 37 weeks of a healthy girl with low birth weight (2.29kg).
Iwafuchi Y, et al.[20] (2017) Japan	Case report	Agalsidase beta	1	8 weeks to end of pregnancy	22-year-old with Fabry disease with renal symptoms was pregnancy and initiated ERT at 8 weeks.	Delivered at 40 weeks healthy girl weight 2734g, Apgar 8 and 9. Baby girl with FD.
Maden CV, et al.[21] (2019) Denmark	Case report	Agalsidase beta	1	All	38-year-old G1 with Fabry disease and history of ischemic stroke at age of 23, HTN, albuminuria and moderately reduced renal function. ERT initiated at 23-year-old. This was continued	Preeclampsia (third trimester) Delivery at 38+6 weeks of a healthy boy by C-section.

[18] Fernandez P, et al Enzyme replacement therapy in pregnant women with Fabry disease: a case series. JIMD Reports DOI 10.1007/8904_2018_141

[19] Haninger-Vacariu N, et al. Pregnancy outcome after exposure to migalastat for Fabry disease: a clinical report. Case Rep Obstet Gynecol . 2019 Dec 21; 2019:1030259.

[20] Iwafuchi Y, et al. Enzyme replacement therapy in a patient of heterozygous Fabry disease: clinical and pathological evaluations by repeat kidney biopsy and a successful pregnancy. CED Case Rep 2017;6: 210-214.

[21] Maden CV, et al. Enzyme replacement therapy during pregnancy in Fabry patients. JIMD Reports 2019; 44:93-101. doi: 10.1007/8904_2018_129. Epub 2018 Aug 17.

					throughout pregnancy. She switched from enalapril to labetalol 100mg tid acetylic acid 75mg/d she has dev preeclampsia, placed on methyldopa.	
Tasci ES, et al.[22] (2015) Turkey	Case series	Agalsidase beta	2	8 weeks on Entire pregnancy	26-year-old woman with FD during family screening. She was 8 weeks pregnant and agree to initiate agalsidase beta treatment 29-year-old with Fabry during family screening. she was started on agalsidase beta and became pregnant 2 month later and continued treatment,	Delivery at 40 weeks of a health girl weight 3100g. Delivery of a healthy girl weight 3400g at 40 weeks
Thurberg BL, et al.[23] (2012) USA Politei JM, et al.[24] (2010) Argentina	Case report	Agalsidase beta	1	Entire pregnancy	37-year-old woman d became pregnant 2 years after ERT	Delivery at 38 weeks of a healthy boy weight 3300g. Baby boy with FD.
Germain DP, et al.[25] (2010) France	Case report	Agalsidase beta	1	Entire pregnancy	A woman with FD while on ERT and this was continued through pregnancy.	Delivery at 38 weeks of a healthy boy weight 3120 kg.

[22] Tasci ES, et al. Safe and Successful Treatment with Agalsidase Beta During Pregnancy in Fabry Disease. IJKD 2015; 9:406-8

[23] Thurberg BL, et al. Histologic abnormalities of placental tissues in Fabry disease: a case report and review of the literature. Human Pathology 2012; 43: 610–614

[24] Politei JM. Treatment with agalsidase beta during pregnancy in Fabry disease. J Obstet Gynaecol Res. 2010 Apr;36(2):428-9

[25] Germain DP, Bruneval P, Tran TC, Balouet P, Richalet B, Benistan K. Uneventful pregnancy outcome after enzyme replacement therapy with agalsidase beta in a heterozygous female with Fabry disease: A case report. Eur J Med Genet. 2010 Mar-Apr;53(2):111-2. Epub 2010 Jan 1

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/

WENJIE SUN
10/05/2020 03:45:26 PM

CARRIE M CERESA
10/05/2020 04:28:34 PM

LYNNE P YAO
10/06/2020 05:47:21 AM