CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761161Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761161
PDUFA Goal Date	April 27, 2021
OSE RCM #	2020-1098
Reviewer Name(s)	Brian Caruth, Pharm.D., BCPS
Team Leader	Laura Zendel, Pharm.D., BCPS
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	April 27, 2021
Subject	Evaluation of Need for a REMS
Established Name	Pegunigalsidase alfa-iwxj
Trade Name	Elfabrio
Name of Applicant	Chiesi USA, Inc (Chiesi)
Therapeutic Class	Hydrolytic lysosomal neutral glycosphingolipid-specific enzyme
Formulation(s)	Solution for Injection
Dosing Regimen	Pegunigalsidase alfa-iwxj 1mg/kg intravenous (IV) infusion over 3 hours every 2 weeks

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Elfabrio (pegunigalsidase alfa-iwxj) is necessary to ensure the benefits outweigh its risks. Chiesi USA, Inc (Chiesi) submitted a Biologic Licensing Application (BLA) 761161 for pegunigalsidase alfa-iwxj with the proposed indication for the treatment of adults with a confirmed diagnosis of Fabry disease. Pegunigalsidase alfa-iwxj is associated with an increased risk for hypersensitivity reactions including anaphylaxis, infusion related reactions, and compromised cardiac function. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of pegunigalsidase alfa-iwxj outweigh its risks. The increased risk for hypersensitivity reactions including anaphylaxis and infusion related reactions is similar to other approved enzyme replacement therapy (ERT) for Fabry disease. Pegunigalsidase alfa-iwxj is likely to be prescribed by genetic specialists familiar with Fabry disease and administered in an outpatient infusion setting. These prescribers and outpatient infusion settings are expected to be aware of the risk and be able to treat hypersensitivity reactions including anaphylaxis and infusion related reactions associated with ERT. The safety profile of pegunigalsidase alfa-iwxj, consistent with predicted risks, can be adequately communicated in the Warnings and Precautions section in labeling.

The recommended regulatory action at this time per the interdisciplinary review team is a complete response. This recommendation is due to manufacturing deficiencies at the drug product site. Additionally, other late developing issues surrounding the accelerated approval pathway have not been resolved.

Based on the available data, the Division of Risk Management (DRM) and the Division of Rare Diseases and Medical Genetics (DRDMG) agree the there are no safety issues that require a REMS. If new safety information becomes available DRM should be consulted, to reassess the need for a REMS.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Elfabrio (pegunigalsidase alfa-iwxj) is necessary to ensure the benefits outweigh its risks. Chiesi USA, Inc (Chiesi) submitted a Biologic Licensing Application (BLA) 761161 for pegunigalsidase alfa-iwxj with the proposed indication for the treatment of adults with confirmed Fabry disease. This application is under review in the Division of Rare Diseases and Medical Genetics (DRDMG). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Pegunigalsidase alfa-iwxj, a new molecular entity[a] and hydrolytic lysosomal neutral glycosphingolipid-specific enzyme, is a PEGylated, crosslinked, chemically modified recombinant human alpha-galactosidase A enzyme proposed for the treatment of adults with confirmed Fabry disease. Pegunigalsidase alfa-iwxj provides an exogenous source of alpha-galactosidase A (α-Gal-A) that is deficient or absent in Fabry disease patients. Replacement of the α-Gal-A enzyme may reduce tissue deposition of glycosphingolipids.

Pegunigalsidase alfa-iwxj is proposed to be available as a 20 mg/10 ml (2 mg/ml) solution in a single-dose vial for intravenous infusion. The proposed dose is 1 mg/kg infused every other week as an intravenous infusion over at least 90 minutes. Duration of treatment with pegunigalsidase alfa-iwxj is expected to be long term and administered in an outpatient infusion setting.[b] Pegunigalsidase alfa-iwxj is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761161 relevant to this review:

- 12/13/2017: IND 110161 submitted with Fast Track designation request.
- 01/29/2018: FDA granted Fast Track designation for the treatment of Fabry disease.
- 05/17/2020: BLA 761161 received for pegunigalsidase alfa-iwxj under the accelerated approval pathway.
- 03/08/2021: Late-Cycle meeting held via teleconference. FDA informed the applicant that no safety issues that may require a REMS for pegunigalsidase alfa-iwxj have been identified.
- 03/15/2021: FDA informed the applicant pegunigalsidase alfa-iwxj may no longer qualify for the accelerated approval pathway citing recent full approval of a Fabry disease treatment option.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Fabry disease is a pan-ethnic, progressive, X-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal α-Gal-A activity. The enzyme deficiency results in lysosomal accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (Lyso-Gb3) in a wide variety of cells. Affected hemizygous males, with no residual α-Gal-A activity may display all the characteristic neurological (pain), cutaneous (angiokeratoma), renal (proteinuria, kidney failure), cardiovascular (cardiomyopathy, arrhythmia), cochleo-vestibular and cerebrovascular (transient ischemic attacks, strokes) signs of the disease while heterozygous females have symptoms ranging from mild to severe.[1] Irreversible renal and cardiac cell fibrosis is the predominant pathogenetic cause of premature death in

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Fabry disease.[2] End stage renal disease (ESRD) and cardiovascular complications typically develop in patients between 30 and 50 years of age.[3] The prevalence ranges from 8 to 25 cases per 1,000,000 population.[c] The life expectancy of patients with Fabry disease is 50 to 70 years of age.[4]

3.2 Description of Current Treatment Options

Replacement or restoration of enzyme activity are the primary treatment options for Fabry disease. Current FDA-approved enzyme replacement therapy (ERT) and pharmacologic chaperone therapy treatment options are listed in Table 1.

Table 1: FDA-Approved Treatment Options for Fabry Disease

Product Trade Name (Generic)	Year of Approval	Indication	Dosing/ Administration	Important Safety and Tolerability Issues
Fabrazyme (agalsidase beta IV)	2003	Treatment of patients ≥ 2 years of age with confirmed Fabry disease	1mg/kg every 2 weeks	Anaphylaxis and Hypersensitivity Reactions, Infusion Related Reactions
Galafold (migalastat)	2018	Treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene variant based on in vitro assay data	123mg every other day	Headache, Nasopharyngitis, Urinary Tract Infection, Nausea, Pyrexia

No safety issues warranting a REMS have been identified for current FDA-approved treatments for Fabry disease. ERT use varies depending on genetic factors and clinical manifestations and is limited by infusion reactions. ERT is most frequently recommended for hemizygous males regardless of clinical manifestations. ERT is also considered for female carriers and hemizygous males with atypical disease if clinical manifestations of Fabry disease are present. Only one ERT, agalsidase beta, is FDA-approved for Fabry disease at this time. The approval of agalsidase beta occurred through the accelerated approval pathway in 2003, relying on a reduction of Gb3 inclusions in renal interstitial capillary endothelial cells. Traditional approval of agalsidase beta was provided on March 11, 2021 following review and fulfillment of postmarketing requirements.

Pharmacologic chaperone therapy restores enzyme activity in patients with Fabry disease and an amenable galactosidase alpha gene (GLA) variant. Patients with a confirmed pathogenic amenable GLA variant can be considered for pharmacologic chaperone therapy rather than ERT. Use of migalastat, the only currently FDA-approved pharmacologic chaperone therapy, is limited to patients with an estimated glomerular filtration rate (eGFR) greater than 30mL/min/1.73m^2 and is only effective for a subgroup of approximately 30% of Fabry disease patients with specific amenable mutations.[5]

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Nonspecific complications of Fabry disease are treated according to guideline-based standards of care. The spectrum of disease involvement, disease progression associated with significant morbidity and mortality, and limited therapeutic options to further improve treatment of Fabry disease represent an unmet medical need.

4 Benefit Assessment

The efficacy of pegunigalsidase alfa-iwxj for the treatment of adults with confirmed Fabry disease was evaluated in one single-arm, open-label, multicenter consecutive phase 1 and phase 2 study (PB-102-F01/F02 [NCT01678898]). The study enrolled 18 patients with a definitive diagnosis of Fabry disease (11 males and 7 females), 18 to 55 years of age (median age at baseline 31 years) who were naïve to ERT or had not received ERT for at least 6 months prior to enrollment. The plasma α-Gal-A activity levels ranged between 0 and 7.8 nmol/hr/mL (median 0.4 nmol/hr/mL), and leukocyte α-Gal-A activity levels ranged between 0 and 72 nmol/hr/mg protein (median 4.5 nmol/hr/mg protein). Patients were excluded if they had a severe kidney or cardiac disease, or if angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy was initiated or dose changed in the 4 weeks prior to screening. Study PB-102-F01 evaluated a 0.2 mg, 1 mg, and 2 mg dose of pegunigalsidase alfa-iwxj administered intravenously every 2 weeks for 12 weeks. Study PB-102-F02 was a continuation of Study PB-102-F01 with a gradual switch to a 1 mg dose for all patients for a total of 52 weeks. The main evaluation of efficacy included renal accumulation of Gb3 as a surrogate endpoint and plasma Lyso-Gb3 as a supportive endpoint. The average number of Gb3 inclusions in kidney peritubular capillaries (PTC) were assessed by light microscopy using the quantitative Barisoni Lipid Inclusion Scoring System (BLISS) methodology in 14 patients. Renal accumulation of Gb3 at baseline and 6 months is summarized in Table 2 with additional endpoint data summarized in Table 3.

Table 2: Summary of Renal Accumulation of Gb3 at Baseline and 6 Months in Study PB-102-F01/F02

Efficacy Endpoint	All Patients (N = 14)	Males (N = 8)	Females (N = 6)
	Median (Range)		
Baseline	3.2 (0.4, 9)	6.8 (0.4, 9)	1.2 (0.8, 3.3)
Month 6	0.7 (0.3, 2.5)	0.7 (0.3, 2.5)	0.7 (0.3, 1.4)
Median Change from Baseline	-2.5 (-8.5, 0.5)	-5.3 (-8.5, 0.5)	-0.7 (-2.5, 0.1)
Patients with ≥ 50% Reduction	11/14 (79%)	7/8 (88%)	4/6 (67%)

Table 3: Study Summary of Surrogate and Supportive Efficacy Endpoints in Study PB-102-F01/F02

Efficacy Endpoint	Baseline	Month 6	Change from Baseline
	Mean (Standard Error)		
Plasma Lyso-Gb3 (ng/mL)	66.7 (19.5)	22.6 (5.1)	-48.9% (5.7%)
Plasma Gb3 (µg/mL)	10 (1.5)	7.1 (0.6)	-22.2% (6.1%)
eGFR (mL/min/1.73m^2) (n = 15)	111.8 (5.6)	112.1 (6)	0% (1.8%)
Mainz Severity Score Index (MSSI)	**Baseline**	**Month 12**	**Overall Mean Reduction**
Total Neurological Score	7.8 (1)	5.2 (0.7)	-2.6
Total Cardiovascular Score	3.7 (1)	2.9 (0.9)	-0.8

Source: Adapted from applicant's original submission May 27, 2020; Table 32, Appendix 2.7.3

The clinical studies submitted by the applicant were open-label with efficacy analysis considered exploratory. FDA guidance recommends surrogate endpoints that are reasonably likely to predict clinical benefit and support accelerated approval for drugs intended for the treatment of Fabry disease.[6] Specific consideration is provided by FDA for the use of histological reduction of Gb3 inclusions in PTC as a surrogate endpoint. Supportive evidence for pegunigalsidase alfa-iwxj efficacy relied on a histological reduction of Gb3 inclusions in PTC as a surrogate endpoint. Plasma Lyso-GB3 and plasma Gb3 were cited as supportive endpoints and have been used in prior approvals of treatment options for Fabry disease. The clinical reviewer relied on meaningful baseline changes of renal accumulation of Gb3 for the efficacy assessment of pegunigalsidase alfa-iwxj.[7] The review team concluded a lack of reduction in renal accumulation of Gb3 in untreated patients and reductions in plasma Lyso-Gb3 for a majority of patients supported a treatment effect of pegunigalsidase alfa-iwxj.

5 Risk Assessment & Safe-Use Conditions

The primary safety analysis of pegunigalsidase alfa-iwxj, referred to as the open-label safety analysis set (OL-SAS), relies on data from studies PB-102-F01/F02, PB-102-F03 (NCT01678898), PB-102-F30 (NCT03018730) and PB-102-F60 ([NCT0356617] an ongoing phase 3 continuation study of Study PB-102-F20 and Study PB-102-F30 for a total of 192 weeks). The OL-SAS represents 53 patients with a documented diagnosis of Fabry disease or symptomatic Fabry disease who received at least one dose of pegunigalsidase alfa-iwxj. The data pool for total exposure on pegunigalsidase alfa-iwxj represents an estimated 103 patient years.

The six most common adverse events (incidence ≥ 20%) include musculoskeletal pain, respiratory tract infection, nasopharyngitis, abdominal pain, headache, and infusion related reactions. Common and select treatment emergent adverse events (TEAE) related to the therapeutic drug class of pegunigalsidase alfa-iwxj and a Fabry disease patient cohort are summarized in Table 5.

Table 5: Summary of Adverse Events During Treatment – Open-Label Safety Analysis Set

Adverse Event (AE) Category	Pegunigalsidase alfa-iwxj (N = 53)
	n (%) patients
Any TEAE with Outcome of Death	1 (1.9)
Any TEAE	47 (88.7)
Any Serious TEAE	10 (18.9)
Related TEAE Leading to Discontinuation	3 (5.7)
Musculoskeletal Pain	14 (26.4)
Respiratory Tract Infection	13 (24.5)
Nasopharyngitis	12 (22.6)
Abdominal Pain	12 (22.6)
Headache	11 (20.8)
Infusion Related Reactions	11 (20.8)
Type I Hypersensitivity (Infusion Related Reaction)	2 (3.8)
Bronchospasm (Infusion Related Reaction)	1 (1.9)

Source: Adapted from applicant's original submission May 27, 2020; Table 10 and 13, Appendix 2.7.4

A majority of patients experienced a TEAE with pegunigalsidase alfa-iwxj therapy. One death due to pneumonia reported in the OL-SAS, and considered unrelated to pegunigalsidase alfa-iwxj, occurred in a

35 year-old male with end-stage chronic obstructive pulmonary disease (COPD) after receiving treatment with pegunigalsidase alfa-iwxj for 38 months. The clinical reviewer focused on three TEAEs hypersensitivity reactions leading to discontinuation of pegunigalsidase alfa-iwxj and infusion related reactions.

5.1 HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

Three serious hypersensitivity TEAEs leading to discontinuation of pegunigalsidase alfa-iwxj occurred in the OL-SAS (5.7% [3/53]) and were considered related to pegunigalsidase alfa-iwxj. One patient experienced severe bronchospasm 40 minutes into his first infusion of pegunigalsidase alfa-iwxj. The patient was hospitalized, recovered the next day, and discontinued pegunigalsidase alfa-iwxj therapy. Two patients experienced type I hypersensitivity reactions immediately after starting pegunigalsidase alfa-iwxj infusions. On site anaphylactic protocol therapy was administered and both patients recovered without sequelae. Hypersensitivity reactions including anaphylaxis are a predicted risk associated with ERT.[d] The applicant proposed addressing the risk of hypersensitivity reactions including anaphylaxis in the Warnings and Precaution section of the label. The clinical reviewer concluded the three serious hypersensitivity TEAEs were anaphylactic reactions and proposed detailed descriptions of the three events in the label.

5.2 INFUSION RELATED REACTIONS

Eleven infusion related reactions occurred in the OL-SAS (20.8% [11/53]) and were considered related to pegunigalsidase alfa-iwxj. Excluding the three hypersensitivity reactions, the remaining eight events, most commonly reported as pruritis, were mild or moderate in intensity and resolved under continued treatment. The applicant proposed addressing infusion related reactions in the Warnings and Precautions section of the label.

The clinical reviewer concluded the safety profile of pegunigalsidase alfa-iwxj is consistent with predicted risks of ERT and the safety profile appears acceptable.

6 Expected Postmarket Use

Pegunigalsidase alfa-iwxj is likely to be prescribed by genetic specialists familiar with Fabry disease and administered in an outpatient infusion setting. These prescribers and outpatient infusion settings are expected to be aware of the risk and be able to treat hypersensitivity reactions including anaphylaxis and infusion related reactions associated with ERT. Because of the potential for severe allergic reactions including anaphylaxis, labeling will recommend initiating appropriate emergency medical treatment and consideration for discontinuing pegunigalsidase alfa-iwxj administration should any severe hypersensitivity reaction occur.

Premedication prophylaxis with antipyretics, antihistamines, and corticosteroids are recommended to reduce infusion reactions caused by ERT therapy[1] and suggested in the label of other FDA-approved

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

ERT.[8] For patients without documented infusion related reactions, home infusion of ERT remains an option. Eligibility criteria for home infusion of ERT have been investigated including published guidelines for safe use.[9]

Standard cardiovascular care is recommended for cardiac manifestations of Fabry disease. If not already initiated, ERT is suggested when cardiac manifestations of Fabry disease are detected. Expert consensus recommends annual electrocardiogram or cardiac magnetic resonance imaging (MRI) for patients with cardiac signs of Fabry disease.[10] Cardiologists are expected to support the multidisciplinary delivery of care to patients with Fabry disease.

At the time of this review, postmarketing requirements (PMRs) are under negotiation to evaluate the long-term safety and efficacy of pegunigalsidase alfa-iwxj.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for pegunigalsidase alfa-iwxj beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

Fabry disease is a pan-ethnic, progressive, X-linked inherited disorder of glycosphingolipid metabolism due to deficient or absent lysosomal α-Gal-A activity. The enzyme deficiency results in lysosomal accumulation of Gb3 and Lyso-Gb3 in a wide variety of cells. Irreversible renal and cardiac cell fibrosis is the predominant pathogenetic cause of premature death in Fabry disease. ESRD and cardiovascular complications typically develop in patients between 30 and 50 years of age.

The serious risks associated with pegunigalsidase alfa-iwxj include hypersensitivity reactions including anaphylaxis and infusion related reactions. These risks will be found in the warnings and precautions section of the label and will recommend initiating appropriate emergency medical treatment and consideration for discontinuing pegunigalsidase alfa-iwxj administration should any severe hypersensitivity reaction occur.

Late in the review cycle, Fabrazyme received full approval for the treatment of Fabry disease, becoming available therapy. The interdisciplinary review team notes that for accelerated approval, the applicant will need to show that pegunigalsidase alfa-iwxj provides a therapeutic advantage over Fabrazyme or alternatively, the applicant could show that the reductions in Gb3 renal inclusions predict clinical benefit to support full approval. At the time of this review, these late developing issues have not been resolved. Relying on the data available and genetic specialists' likely familiarity with the risks associated with pegunigalsidase alfa-iwxj, that do not pose unique REMS considerations compared with the risks associated with other Fabry disease therapies, DRM is not recommending a REMS for the management of the risks of pegunigalsidase alfa-iwxj therapy. If new safety information becomes available, DRM can re-evaluate the need for a REMS.

9 Conclusion & Recommendations

Relying on the data available, a REMS is not necessary to ensure the benefits of pegunigalsidase alfa-iwxj outweigh the risks for hypersensitivity and infusion related reactions. The risks can be communicated in

labeling using Warnings and Precautions to include hypersensitivity reactions including anaphylaxis and infusion related reactions. The safety concerns associated with pegunigalsidase alfa-iwxj use are similar to other FDA-approved ERT for Fabry disease. In general, we expect healthcare providers who treat Fabry disease and administer ERT therapy will be familiar with treating hypersensitivity reactions including anaphylaxis and infusion related reactions associated with ERT therapy.

However, the recommended regulatory action at this time per the interdisciplinary review team is a complete response. This recommendation is due to manufacturing deficiencies at the drug product site. Additionally, other late developing issues surrounding the accelerated approval pathway have not been resolved.

Based on the available data, there were no unique safety issues that require a REMS for pegunigalsidase alfa-iwxj as compared with the risks associated with other Fabry disease therapies. If new safety information becomes available, please consult DRM and we can re-evaluate the need for a REMS.

10 Appendices

10.1 References

[1] Germain DP. Fabry disease. Orphanet J Rare Dis 2010;5:30.

[2] Eng CM, Germain DP, Banikazemi M, et al. Fabry disease: guidelines for the evaluation and management of multiorgan system involvement. Genet Med 2006;8(9):539-548.

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[6] Fabry Disease: Developing Drugs for Treatment Guidance for Industry. (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fabry-disease-developing-drugs-treatment-guidance-industry)

[7] Ongoing DRDMG Multidisciplinary Review and Evalution of pegunigalsidase alfa-iwxj, BLA 761161 accessed on April 27, 2021.

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[10] Albert H, Patricia R, Gilbert H, et al. Fabry disease in cardiology practice: Literature review and expert point of view. Archives of Cardiovascular Diseases 2019;112(4):278-287.

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