CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	761278
PDUFA Goal Date	February 17, 2023
OSE TTT #	2022-716
Reviewer Name(s)	Cristen Lambert, PharmD
Team Leader	Yasmeen Abou-Sayed, PharmD
Associate Director for REMS Design and Evaluation	Laura Zendel, PharmD
Review Completion Date	February 14, 2023
Subject	Evaluation of Need for a REMS
Established Name	velmanase alfa-tycv
Trade Name	Lamzede
Name of Applicant	Chiesi USA, Inc.
Therapeutic Class	Enzyme Replacement Therapy
Formulation(s)	Intravenous solution
Dosing Regimen	1 mg/kg IV administered once every week

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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 Lamzede (velmanase alfa) is necessary to ensure the benefits outweigh its risks. Chiesi USA, Inc. submitted a Biologic Licensing Application (BLA) 761278 for velmanase alfa with the proposed indication for the treatment of patients with confirmed diagnosis of alpha-mannosidosis (AM). The risks associated with velmanase alfa include hypersensitivity reactions, including anaphylaxis and infusion associated reactions (IARs). The applicant did not submit a proposed REMS or risk management plan with this application.

Velmanase alfa appeared efficacious in demonstrating improvement in three clinical endpoints. The Division of Rare Diseases and Medical Genetics recommends approval for velmanase alfa for the treatment of non-central nervous system manifestations of alpha-mannosidosis in adults and pediatric patients as the effect of velmanase alfa was only demonstrated on non-neurologic manifestations of AM. DRM has determined that a REMS is not needed to ensure the benefits of velmanase alfa outweigh its risks. Velmanase alfa has a risk benefit profile comparable to approved enzyme replacement therapies[a] which do not have REMS. The risks of hypersensitivity and/or anaphylaxis and infusion-associated reactions can be adequately communicated through labeling. Consistent with other approved enzyme replacement therapies, labeling will include a boxed warning for the risk of hypersensitivity reactions including anaphylaxis. Velmanase alfa is intended to be administered by healthcare providers. We expect the prescribing community and healthcare providers involved with administration of the product will be familiar with identifying and managing adverse events associated with the use of biological therapies such as velmanase alfa. Overall, in the context of AM as a very rare and serious disease with significant morbidity and mortality with an unmet therapeutic need, the review team has determined that the benefit-risk profile is favorable for the proposed IV weekly dosing regimen for the treatment of non-neurologic manifestations of AM in patients of all ages.

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) Lamzede (velmanase alfa-tycv) is necessary to ensure the benefits outweigh its risks. Chiesi USA, Inc. (Chiesi) submitted a Biologic Licensing Application (BLA) 761278 for velmanase alfa with the proposed indication for the treatment of patients with confirmed diagnosis of alpha-mannosidosis. 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.

[a] Cerezyme (imiglucerase); Elelyso (taliglucerase alfa); Mepsevii (vestronidase alfa)

2. Background

2.1. Product Information

Lamzede (velmanase alfa), a new molecular entity (NME) [b], is an enzyme replacement therapy (ERT) proposed for the treatment of patients with alpha-mannosidosis (AM). Velmanase alfa is a recombinant human alpha-mannosidase that is internalized by cells and transported to the lysosomes where it functions as an ERT for the endogenous enzyme that is deficient in AM.

Velmanase alfa is proposed to be available as a lyophilized powder for solution to be given as a 1 mg/kg intravenous infusion once every week indefinitely[c]. Velmanase alfa received orphan designation in February 2006, rare pediatric designation in December 2018, and Fast Track Designation in December 2019. As with other ERTs, velmanase alfa would likely be administered inpatient, at an infusion center, or in a home infusion setting. Velmanase alfa is approved for the treatment of non-CNS manifestations of AM in the European Union, Brazil, Saudi Arabia, and Ukraine.[1]

2.2. Regulatory History

The following is a summary of the regulatory history for BLA 761278 relevant to this review:

- 2/2/2006: Orphan drug designation granted
- 8/23/2019: IND 113186 submitted protocol for pivotal trial
- 12/11/2019: Fast track designation granted
- 6/17/2022: BLA 761278 submission for treatment of patients with confirmed alpha mannosidosis received
- 9/29/2022: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that it was conducting more detailed assessments on reported hypersensitivity adverse events and events of special interest.
- 12/15/2022: A Late cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no issues related to risk management had been identified to date.

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

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

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Alpha-mannosidosis (AM) is a very rare lysosomal storage disorder characterized by an autosomal recessive inborn error of oligosaccharide catabolism. The enzyme deficiency leads to progressive accumulation of mannose-rich N-linked oligosaccharides in various organs and tissues, including serum. AM is a serious disease that can lead to death in early childhood from recurrent bacterial infections and CNS deterioration (in the early onset severe form) and to progressive and severe motor impairment in later onset forms. [d] AM symptoms, severity, and disease progression are highly variable. The global birth prevalence of AM is 1:500,000 – 1:1,000,000 live births.[1] Of the 191 patients with an alpha-mannosidosis mutation reported in published literature, 22 are from the United States.[2] [e] AM has an impact on both patient and caregiver due to disease outcomes of progressive myopathy and ataxia, intellectual decline and decreased mobility and independence. It can take time to correctly diagnose, and caregivers experience high levels of stress and anxiety from their caregiving responsibilities.[1]

3.2. Description of Current Treatment Options

As there are no approved therapies for the treatment of AM in the US, there is an unmet need for therapeutic options. The current standard of care is addressing the medical complications of the disease.[1] The symptoms, progression, and severity of AM vary widely. Disease complications can include muscle weakness, skeletal abnormalities, hydrocephalus, speech and motor delays, intellectual disability, ataxia, hearing loss, abnormal immune system response, and psychiatric abnormalities.[3] Therapies directed at preventing and treating complications include antibiotics, hearing aids and pressure equalizing tubes for ears, physiotherapy, orthopedic interventions, insertion of a shunt to drain excess cerebrospinal fluid away from the brain, and early intervention services including special education and speech therapy. Hematopoietic stem cell transplant (HSCT) has been investigated for preservation of neurocognitive function and prevention of early death in younger AM patients; however, results are variable and HSCT is not considered a standard of care at this time.[4]

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

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

4. Benefit Assessment

The primary support for efficacy is from Trial rhLAMAN-05 (National Clinical Trial [NCT] 01681953), a phase 3, multicenter, double-blind, placebo-controlled study in 25 treatment naïve patients with AM aged 6 to 35 years. Fifteen patients (8 adult and 7 pediatric) received velmanase alfa 1 mg/kg IV and 10 patients (5 adult and 5 pediatric) received placebo once a week for 52 weeks. The study demonstrated trends of improvement favoring velmanase alfa. The primary endpoint was the 3-minute stair climb test (3MSCT) which showed +2.7 steps/min [4] treatment difference absolute change from baseline. Key secondary endpoints included the 6-minute walk test (6MWT) [4] and forced vital capacity (FVC) percent of predicted normal value (FVC%). The estimated treatment effect of velmanase alfa on the placebo-subtracted absolute change from baseline was 7.4 meters in the 6MWT[4]. Six (50%) in the velmanase group compared to 2 (22%) in the placebo group had an increased percent change from baseline in FVC of 10% or more at Week 52[4]. The study also demonstrated a statistically significant reduction (-55.6% relative change from baseline, adjusted treatment difference[4]; p<0.001) in serum oligosaccharides. Reduction in serum levels of oligosaccharides is thought to reflect a reduction in tissue levels of oligosaccharides; however, this biomarker is not a validated surrogate endpoint. The Review Team concludes that this biomarker could not provide the primary support for efficacy in this study; however, the results for the three clinical endpoints of 3MSCT, 6MWT, and FVC% (see Table 1) are thought to represent a clinically meaningful benefit[f] for AM patients.[1]

Table 1: Changes From Baseline in Primary and Key Secondary Endpoints at Week 52 (Trial rhLAMAN-05) [4]

Parameter	Velmanase (n=15)	Placebo (n=10)	Adjusted Treatment Difference (95% CI)
Serum oligosaccharides (µmol/L)	-75.8 (-84.5, -67.2)	-20.2 (-30.8, -9.7)*	-55.6 (-69.3, -41.9) p<0.001
Relative change (%) from baseline	-5.1 (-5.7, -4.6)	-1.6 (-2.3, -0.9)	-3.5 (-4.4, -2.6) p<0.001
Absolute change from baseline			
3MSCT (steps/min)	0.2 (-7.9, 8.4)	-3.2 (-13.1, 6.8)	3.4 (-9.5, 16.3) p=0.59
Relative change (%) from baseline	0.5 (-3.6, 4.5)	-2.2 (-7.1, 2.8)	2.7 (-3.8, 9.1) p=0.41
Absolute change from baseline			
FVC (% predicted)	10.5 (2.1, 18.9)	3.1 (-6.7, 12.8)	7.4 (-5.7, 20.5) p=0.25
Relative change (%) from baseline	7.9 (1.1, 14.7)	2.4 (-5.5, 10.2)	5.5 (-5.0, 16.1) p=0.28
Absolute change (% predicted) from baseline			

[f] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

6MWT (meters)			1.6 (-7.2, 10.4)
Relative change (%) from baseline	1.0 (-4.5, 6.6)	-0.6 (-7.4, 6.2)	p=0.71
Absolute change from baseline	3.7 (-20.3, 27.8)	-3.6 (-33.1, 25.9)	7.4 (-30.8, 45.5) p=0.69

Source: Adapted from Table 8. Changes From Baseline in Primary and Key Secondary Endpoints at Week 52 (Trial rhLAMAN-05) in Reference 4.

*The Applicant reports that spontaneous decreases in serum oligosaccharides in the placebo arm can be explained by natural fluctuations.

Abbreviations: 3MSCT, 3-minute stair climb test; 6MWT, 6-minute walk test CI, confidence interval; FVC, forced vital capacity

Trial rhLAMAN-08 (National Clinical Trial [NCT] 02998879) was an uncontrolled, open label study in 5 patients with AM less than 6 years of age administered velmanase alfa 1 mg/kg IV for 24 months. This study demonstrated a reduction in serum oligosaccharides from baseline that was similar in magnitude to the reduction observed in the velmanase alfa treatment group in Trial rhLAMAN-05. The absolute and percentage changes from baseline for serum oligosaccharides at 24 months were -7.7 μmol/L and -65.8% respectively.[4] The data from this study, in combination with the data from Trial rhLAMAN-05 are sufficient to establish efficacy in this age group with a pharmacodynamic (PD) extrapolation.

The Review Team concludes substantial evidence of effectiveness was established with the results of the single adequate and well-controlled clinical trial (rhLAMAN-05) taken together with confirmatory evidence. An adequate body of evidence consists of primary support derived from the additional clinical studies (rhLAMAN 03, 04, and 08), that include data on a physiologically relevant biomarker (serum oligosaccharides), and exposure-response data.[1] The effect of velmanase alfa was only demonstrated on non-neurologic manifestations of AM (b) (4) therefore, a labeled indication specifying treatment of the "non-neurologic manifestations of AM" is appropriate.

5. Risk Assessment & Safe-Use Conditions

Trial rhLAMAN-05 (n=25) provided the data for the main safety assessment. There were no deaths or permanent discontinuations. A total of 5 patients experienced serious adverse events (SAEs) in the treatment arm. Of these, 1 SAE, acute renal failure, was assessed as possibly related to velmanase alfa exposure and is described in Section 6 of labeling. No SAEs occurred in the placebo group. Trial rhLAMAN-10 consisted of an integrated analysis that pooled the cumulative database for all previous velmanase alfa trials (included 33 patients, 19 of which were pediatric patients aged 6 to 18 years, and 14 adult patients). Trial rhLAMAN-8 (which included 5 pediatric patients aged 3 to 5 years old) provided additional data to support the main safety assessment. The safety profile of velmanase alfa in these studies was generally consistent with that observed in rhLAMAN-05.[1] Additional SAEs potentially related to velmanase exposure were reported in Trial rHLAMAN-10 (seizures) and Trial rhLAMAN-08 (Henoch-Schoenlein Purpura) and are described in Section 6 of labeling. Risks in nonclinical studies include a malignant histiosarcoma of the ovary and embryofetal malformations. The clinical reviewer identified

key risks from the above studies to include hypersensitivity events (including anaphylaxis) and infusion associated reactions (IARs).

5.1. Hypersensitivity Reactions including Anaphylaxis and Infusion Associated Reactions

Based on the analysis of the integrated summary of safety (ISS) which included all patients from rhLAMAN-10 (integrated analysis) (33 patients) and rhLAMAN-08 (5 patients), 50% (19/38) of patients experienced symptoms of hypersensitivity reactions. Of these patients, 14 (74%) were pediatric patients. A total of 5 patients experienced events clinically concerning for anaphylaxis. Of these, 2 patients (1 pediatric and 1 adults) met full criteria for anaphylaxis, and an additional 3 patients (3 pediatric patients) were assessed to have severe hypersensitivity reactions.[1] All patients had at least 3 months of exposure to velmanase alfa prior to anaphylaxis. Four of the 5 patients who experienced events concerning for anaphylaxis developed anti-drug antibodies (ADAs). Excluding these 5 patients (with anaphylaxis or potential anaphylaxis), 20 patients (53%) experienced IARs varying from mild to moderate severity.

Risks of hypersensitivity, including anaphylaxis and IARs are known risks with ERTs. The clinical reviewer concluded these risks with velmanase alfa are consistent with ERTs approved for other indications and will be mitigated through labeling. The label will include a boxed warning for hypersensitivity, including anaphylaxis, and warnings for both hypersensitivity events and IARs. Labeling will also include dosage and administration modifications due to hypersensitivity reactions and/or IARs including recommendations of when to temporarily hold, slow, discontinue, or reinitiate the infusion.

5.2. Malignant histiocytoma and embryofetal malformations

In nonclinical studies, a malignant histiosarcoma of the ovary was observed in rats treated with velmanase alfa. Embryofetal malformations were observed in rats and rabbits. An increase in the incidence of skeletal and visceral embryofetal malformations that exceeded facility historical control ranges was observed in rats and rabbits. There are no available data on velmanase alfa use in pregnant females since no pregnancy or lactation was reported for subjects on velmanase alfa treatment.[5] A urine pregnancy test (if relevant) was performed at the comprehensive evaluation visit or rhLAMAN-07, rhLAMAN-08, and rhLAMAN-10, but no other risk mitigation for pregnancy took place in clinical trials.[5]

The occurrence of malignant histiocytoma seen in rats will be described in Section 13.1 of the label. The finding of embryofetal risk will be addressed with a Warnings and Precautions. Postmarketing requirements will be issued for a carcinogenicity assessment to assess the potential effects of increased alpha-mannosidase exposure on tumor formation as well as a bridging PK study in rates to support labeling for fertility and the pre- and postnatal development study.[1]

The clinical reviewer concluded the safety profile of velmanase alfa is consistent with predicted risks of ERTs in adults and pediatric patients and the overall benefit-risk profile appears acceptable.

6. Expected Postmarket Use

Velmanase alfa will likely be prescribed in an inpatient setting or outpatient setting, such as an infusion center, by a rare disease specialist working with a team of healthcare providers including cardiologists, neurologists, and nephrologists. Velmanase alfa should be administered in a clinical setting under supervision of rare disease specialists and healthcare providers who are expected to be familiar with the risks of hypersensitivity reactions, including anaphylaxis and IARs involved with ERT infusions. Velmanase alfa may potentially be administered in the home setting by an infusion nurse if a patient has previously tolerated their infusions. Healthcare providers involved in administration of ERTs are trained to monitor for and manage adverse events associated with infusions of biological therapies.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for velmanase alfa beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of velmanase alfa for the treatment of alpha mannosidosis on the basis of the efficacy and safety information currently available.

AM is a rare lysosomal storage disorder with poor outcomes and quality of life for both patient and caregivers. Currently, there is no treatment for AM. The Review Team concludes substantial evidence of effectiveness was established for velmanase alfa for alpha mannosidosis treatment with the results of the single adequate and well-controlled clinical trial (rhLAMAN-05) taken together with confirmatory evidence. DRDMG recommends approval for velmanase alfa for the treatment of non-central nervous system manifestations of alpha-mannosidosis in adults and pediatric patients based on consistent clinically meaningful improvements in all three clinical endpoints (3MSCT, 6MWT, and FVC%) and the statistically significant reduction in serum oligosaccharides. Since the effect of velmanase alfa was only demonstrated in non-neurologic manifestations of AM (b) (4) a labeled indication specifying treatment of the "non-central nervous system manifestations of AM" is warranted.

The serious risks associated with velmanase alfa are hypersensitivity events (including anaphylaxis) and infusion associated reactions (IARs) which are expected for ERT. Other approved enzyme replacement therapies, such as Cerezyme (imiglucerase[6] indicated for Gaucher disease), Elelyso (taliglucerase alfa[7] indicated for Gaucher disease), and Mepsevii (vestronidase alfa[8] indicated for mucopolysaccharidosis VII), also have a risk of hypersensitivity and/or anaphylaxis and infusion-associated reactions. None of these products are currently approved with a REMS and the risks are described and communicated through the *Warnings and Precautions* and a *Boxed Warning* in labeling.

Palynziq (pegvaliase-pqpz), an enzyme replacement therapy indicated for phenylketonuria, has a REMS with ETASU for the risk of anaphylaxis. The incidence of hypersensitivity (93%) and anaphylaxis (9%) in the clinical trials for Palynziq[9] were nearly double the rates for velmanase alfa (hypersensitivity 50%; anaphylaxis 5%)[1]. Palynziq was approved with a REMS with ETASU to help ensure prescribers are patients are educated about the risk of anaphylaxis and ensure they have auto-injectable epinephrine as a safe use condition after the review team concluded that maximizing labeling was not sufficient to mitigate the risk of anaphylaxis.[9] Notably, Palynziq is a subcutaneous injection administered one weekly with induction, titration, and maintenance dosing, and patients can self-administer this ERT. The REMS with ETASU for Palynziq was necessary to ensure the benefits outweighed the risks for this patient administered ERT and to ensure patients have a supply of auto-injectable epinephrine on hand, in contrast to the administration of velmanase alfa, which is expected to be under the supervision of a healthcare provider in a clinical setting.

Another ERT, Lumizyme (alglucosidase alfa), was approved in 2010 with a REMS with elements to assure safe use (ETASU) to ensure the benefits outweighed the risk of rapid disease progression in infantile-onset Pompe disease patients and patients with late (non-infantile) onset disease less than 8 years of age, the risks of anaphylaxis and severe allergic reactions, and potential risks of severe cutaneous and systemic immune mediated reactions. In 2014, the Lumizyme indication was expanded to include patients of all ages for the treatment of Pompe Disease therefore the elements of the REMS designed to achieve the goal of limiting treatment with Lumizyme to use in patients with non-infantile onset Pompe disease who are greater than or equal to 8 years of age were no longer necessary.[10] Also, since healthcare facilities, including home infusion agencies, have policies and procedures in place for monitoring for and managing patients with several allergic reactions, including anaphylaxis, another ETASU of the Lumizyme REMS was deemed unnecessary. The communication plan of the REMS was assessed and determined to be complete. As a result, the Lumizyme REMS was subsequently released.[10] Potential safety risks with use of Lumizyme were considered adequately communicated in labeling through the Warnings and Precautions, and a Boxed Warning.

The benefit/risk profile of velmanase alfa is comparable to the enzyme replacement therapies that do not have REMS and use labeling to mitigate the risk of hypersensitivity and/or anaphylaxis and infusion-associated reactions and support the recommendation that a REMS is not necessary.

The European Medicines Agency (EMA) approved velmanase alfa in the European Union (EU) on March 23, 2018 with important identified risks including infusion-related reactions, immunogenicity, and hypersensitivity. EMA's risk minimization measures for velmanase alfa are routine measures which consist of including statements in the summary of product characteristics (SmPC) and patient information leaflets (PIL) for these risks.[11]

DRM is not recommending a REMS for the management of the risks of velmanase alfa. The risk of hypersensitivity events, including anaphylaxis and infusion associated reactions can be adequately communicated through *Warnings and Precautions* in labeling. The nonclinical findings including risk of malignant histiocytoma and embryofetal malformations in animal models will be communicated in labeling and characterized through post-marketing requirements.

9. Conclusion & Recommendations

In the context of AM as a very rare and serious disease with significant morbidity and mortality with an unmet therapeutic need, the Review Team has determined that the benefit-risk profile is favorable for the proposed IV weekly dosing of velmanase alfa for the treatment of non-neurologic manifestations of AM in patients of all ages; therefore, a REMS is not necessary to ensure the benefits outweigh the risks of velmanase alfa. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

[1] Division of Rare Diseases and Medical Genetics. DRAFT Integrated Review for Lamzede (velmanase alfa-tycv) BLA 761278. December 27, 2022.

[2] University of Tromsø. Alpha-mannosidosis Mutation Database (Updated 2019). Available at: https://apex.jupiter.no/apex/f?p=101:7:::::: (Accessed December 28, 2022).

[3] Malm, D. Alpha-Mannosidosis- National Organization for Rare Disorders. Updated August 13, 2018. Accessed from: https://rarediseases.org/rare-diseases/alpha-mannosidosis [February 10, 2023].

[4] Division of Rare Diseases and Medical Genetics. DRAFT Integrated Review for Lamzede (velmanase alfa-tycv) BLA 761278. January 31, 2023.

[5] Chiesi USA, Inc. Summary of Clinical Safety for velmanase alfa BLA 761278. June 17, 2022.

[6] Genzyme Corporation. Cerezyme (imiglucarase) for injection USPI. Revised December 2021.

[7] Pfizer. Elelyso (taligucarase alfa) for injection USPI. Revised August 2022.

[8] Ultragenyx Pharmaceutical Inc. Mepsevii (vestronidase alfa-vjbk) injection. Revised December 2020.

[9] Zendel, L. Determination and Evaluation of the Proposed REMS for Palynziq. May 24, 2018.

[10] Griebel, D. Division of Gastroenterology and Inborn Errors Products. REMS Elimination Memo for Lumizyme (alglucosidase alfa) BLA 125291, August 1, 2014.

[11] EMA. Lamzede: EPAR- Risk Management Plan Summary. August 24, 2020.

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