CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
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	761047
PDUFA Goal Date	November 16, 2017
OSE RCM #	2017-555
Reviewer Name(s)	Bob Pratt, Pharm.D.
Team Leader	Donella Fitzgerald, Pharm.D.
Deputy Division Director	Jamie Wilkins Parker, Pharm.D.
Review Completion Date	November 13, 2017
Subject	Evaluation of need for a REMS
Established Name	Vestronidase alfa-vjbk
Trade Name	Mepsevii™
Name of Applicant	Ultragenyx Pharmaceutical Inc.
Therapeutic Class	Enzyme replacement therapy
Formulation(s)	10 mg/5 mL solution
Dosing Regimen	4 mg/kg administered by intravenous infusion every 2 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Mepsevii™ (vestronidase alfa-vjbk) is necessary to ensure the benefits of the product outweigh its risks. Ultragenyx Pharmaceutical (Ultragenyx) submitted a Biologics License Application (BLA 761047) on March 16, 2017, for vestronidase alfa-vjbk with the proposed indication to treat mucopolysaccharidosis type VII (MPS VII). Administration of vestronidase alfa-vjbk is associated with the serious risk of anaphylaxis. The Applicant did not submit a REMS or risk management plan with the application.

MPS VII is a rare disease with variable phenotypes ranging from a serious, progressive, and often fatal disease of childhood, to milder forms that have a later onset and fewer clinical manifestations. There is currently no approved treatment. Vestronidase alfa-vjbk showed evidence of efficacy in the treatment of MPS VII and fulfills an unmet medical need. It is expected the drug will only be administered by prescribers with expertise in managing patients with mucopolysaccharidoses, such as medical geneticists and pediatric specialists. DRISK recommends that a REMS is not necessary to ensure the benefits of vestronidase alfa-vjbk outweigh the risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Mepsevii™ (vestronidase alfa-vjbk) is necessary to ensure the benefits of the product outweigh its risks. Ultragenyx submitted a Biologics License Application (BLA 761047) on March 16, 2017, for vestronidase alfa-vjbk with the proposed indication to treat mucopolysaccharidosis type VII (MPS VII). This application is under review in the Division of Gastroenterology and Inborn Errors Products (DGIEP). The Applicant did not submit a REMS or risk management plan with the application.

2 Background

2.1 Product Information

Mepsevii™ (vestronidase alfa-vjbk), a new molecular entity[a], is a recombinant form of human lysosomal beta-glucuronidase, an enzyme deficient in patients with MPS VII disease. Beta-glucuronidase is involved in the degradation of glycosaminoglycans (GAGs) such as chondroitin sulfate, dermatan sulfate, and heparan sulfate. In the absence of beta-glucuronidase, these GAGs accumulate in the lysosomes of many tissues leading to cellular and organ dysfunction. Vestronidase alfa-vjbk is supplied as a 10 mg/5 mL solution in single-use vials. The recommended dose is 4 mg/kg administered by intravenous infusion every two weeks as chronic therapy.[b] Beta-glucuronidase received orphan product designation on February 16, 2012. Vestronidase alfa-vjbk is not currently approved in any other jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for BLA 761047 relevant to this review:

[a] FDAAA factor (F): Whether the drug is a new molecular entity.
[b] FDAAA factor (D): The expected or actual duration of treatment with the drug.

- 2/16/2012: Orphan product designation granted for the treatment of mucopolysaccharidosis VII
- 3/16/2017: BLA 761047 submission for the treatment of mucopolysaccharidosis type VII (MPS VII, Sly syndrome)
- 6/14/2017: A post mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that the need for a REMS is still under review.
- 9/20/2017: A late-cycle meeting was held between the Agency and the Applicant. There was no discussion related to the need for a REMS.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Mucopolysaccharidosis type VII (also referred to as Sly syndrome) is a rare, heterogeneous, autosomal recessive, lysosomal storage disorder predominantly of childhood. However, the clinical presentation and disease manifestations are variable. Patients with the most severe form of MPS VII present with hydrops fetalis at birth, and many do not survive infancy. Typical clinical characteristics of the disease include moderate to severe cognitive impairment, hepatosplenomegaly, short stature, skeletal dysplasia, cardiac pathology, and respiratory symptoms related to airway obstruction and pulmonary insufficiency. The disease may also present during adolescence or later with skeletal abnormalities and other clinical manifestations.[1,c] There are currently no approved therapeutic treatments.

MPS VII is caused by various mutations in the beta-glucuronidase gene. In the absence of beta-glucuronidase, lysosomal storage materials normally metabolized by the enzyme accumulate and lead to cellular and organ dysfunction. MPS VII is an ultra-rare disease with an estimated incidence of 0.05-0.29 per 100,000 live births per year.[2] Ultragenyx estimates there are less than 100 living patients identified worldwide.[d]

3.2 Description of Current Treatment Options

There are no currently approved treatments for MPS VII. Current disease management involves supportive care and may include surgeries, antibiotics, and physical therapy. Bone marrow transplant has been attempted in a small number of patients.[1]

There are four intravenous enzyme replacement therapies currently approved for other mucopolysaccharidoses (shown below in Table 1). It is notable that each product includes boxed warnings or warnings and precautions for infusion reactions, hypersensitivity reactions, or anaphylaxis. None of these products has required a REMS to manage the risks of hypersensitivity or anaphylaxis.

[c] FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.
[d] FDAAA factor (A): The estimated size of the population likely to use the drug involved.

Table 1. Intravenous enzyme replacement therapies approved for mucopolysaccharidoses

Product Name (Trade Name) Year of Approval	Indication	Labeled Incidence	Anaphylaxis Warnings and Precautions
Laronidase (Aldurazyme) 2003	MPS I	Infusion Reactions 32% – 49%	**Boxed Warning: Life-threatening anaphylactic reactions have been observed in some patients**
Galsulfase (Naglazyme) 2005	MPS VI	Infusion Reactions 56%	W&P: Anaphylaxis and severe allergic reactions have been observed in patients
Idursulfase (Elaprase) 2006	MPS II	Hypersensitivity reactions 15% – 69%	**Boxed Warning: Life-threatening anaphylactic reactions have occurred in some patients**
Elosulfase alfa-vjbk (Vimizim) 2014	MPS IVA	Anaphylaxis 8% Hypersensitivity reactions 19%	**Boxed Warning: Life-threatening anaphylactic reactions have occurred in some patients**

4 Benefit Assessment

The clinical program included clinical study and expanded access protocols enrolling 23 patients aged 5 months to 25 years with MPS VII who received treatment with vestronidase-alfa-vjbk at doses up to 4 mg/kg once every two weeks. Of the 23 patients, 17 were evaluable for efficacy. The clinical trial (UX003-CL301) supporting the application is a single-group, Phase 3, randomized, placebo-controlled, delayed-start study in 12 patients aged 8 to 25 years. Patients were randomized to one of 4 groups, each representing a different treatment sequence, and crossed over from placebo to vestronidase alfa-vjbk at pre-defined time points (0, 8, 16, or 24 weeks) in a blinded manner. The patients and investigators did not know when the patient began and completed the treatment. All groups received a minimum of 24 weeks treatment with 4 mg/kg vestronidase alfa-vjbk every two weeks. Patients enrolled in Study 301 were eligible to enroll in a long-term, open-label extension study in which patients received treatment for up to 144 weeks.[3]

No primary efficacy endpoint was declared by the Applicant, as efficacy was based on the totality of evidence provided; the clinical review team accepted this approach. The clinical team determined that the change from baseline in 6-minute walk test (6MWT) after 24 weeks of treatment is the only secondary endpoint suitable for efficacy evaluation. Other clinical evidence of a treatment effect included improvement in pulmonary function; reduction in spleen volume; and reduction in liver volume, in certain patients.[4]

- Ten patients from Study CL301 could perform the 6MWT. After 24 weeks of treatment, the least squares mean difference between treatment with vestronidase alfa-vjbk and placebo was +18 meters (S.E. ± 33 meters). Three patients experienced an improvement of at least 60 meters during the clinical trial or long-term extension.

- In a phase 1/2 open-label dose exploration study, one patient demonstrated a 21% improvement over baseline in forced vital capacity (FVC% predicted) on pulmonary function testing in addition to a 105 meter improvement in the 6MWT after 120 weeks of vestronidase alfa-vjbk. Two other patients with baseline hepatosplenomegaly had reduction in liver volume (24% and 53%) and spleen volume (28% and 47%) after 36 weeks of treatment.
- Additionally, expanded access was provided to a pediatric patient requiring continuous ventilator support. After 160 weeks of vestronidase alfa-vjbk, the patient tolerated 8 hours daily off the ventilator.

Treatment with vestronidase alfa-vjbk also resulted in a reduction from baseline in urinary excretion of GAGs including chondroitin sulfate and dermatan sulfate in all patients evaluated, which was sustained with every other week treatment.[e]

The clinical review team concluded that evidence of efficacy has been established for the use of vestronidase alfa-vjbk in the treatment of pediatric and adult patients with MPS VII.[f]

5 Risk Assessment & Safe-Use Conditions

The safety population is comprised of 20 patients treated with vestronidase alfa-vjbk during the clinical program and expanded access who were evaluable for safety.[4]

5.1 Serious Adverse Events [g,h]

No deaths were reported in any of the clinical studies or expanded access programs. The draft clinical review concluded there were four serious adverse events (SAEs) in the clinical development program, including two cases of anaphylaxis and one potential case of anaphylaxis during infusion, and one report of head trauma that was not treatment-related.[5]

5.2 Hypersensitivity Reactions

At the request of the Agency, the Applicant performed a broad search for anaphylactic reactions using a standard MedDRA query as well as a search of the safety database for any additional investigator or healthcare professional report of anaphylaxis or anaphylactoid reaction.[6] Of the four cases identified, the

[e] The observed pharmacological activity of vestronidase alfa-vjbk is considered supportive of a pharmacodynamic effect rather than pivotal evidence of efficacy because the relationship between uGAG response and clinical outcome has not been established. In addition, the quality of the uGAG data were suboptimal due to deficiencies in the GAG assays. (Hon C. Office of Clinical Pharmacology. Clinical Pharmacology Review, BLA 761047, September 13, 2017.)

[f] FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[h] 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.

DGIEP clinical team assessed two cases as anaphylaxis and one case as potential anaphylaxis. A fifth case of hypersensitivity was reported in the 120-Day Safety Update.

- A serious and severe treatment-related anaphylactic reaction followed a bolus dose administered in error during the first hour of vestronidase alfa-vjbk infusion in an 8 year-old female on Week 22 of treatment. Symptoms included respiratory distress, decreased oxygen saturation, agitation, and diaphoresis with cyanosis. The patient was treated with epinephrine, diphenhydramine, hydrocortisone, and oxygen and recovered. The infusion was re-initiated that day and completed. The patient received subsequent infusions without a recurrence of symptoms.
- A treatment-related anaphylactic reaction occurred during the first infusion of vestronidase alfa-vjbk in a 12 year-old female. The patient's symptoms included mild temperature elevation (37.3°C), diaphoresis, and a decrease in blood pressure to 82/49. No treatment was given and the subject resumed vestronidase alfa-vjbk on the same day without further complications.
- On Week 104 of treatment, a 5-year old male experienced tachycardia 30 minutes into the vestronidase alfa-vjbk infusion with elevated blood pressure. Bronchospasm and respiratory failure occurred later during the first 24 hours post-infusion. The patient was treated with budesonide and salbutamol. Both events resolved at a later time and the patient received subsequent infusions of vestronidase alfa-vjbk with no further complications. The DGIEP clinical team considered this event as a potential case of anaphylaxis.
- Erythema with peripheral edema was experienced by the patient during the second hour of vestronidase alfa-vjbk infusion on Week 10. The infusion was interrupted, and then resumed and completed. No treatment was administered for the adverse events.
- A male patient who was enrolled in the open-label extension study experienced an episode of urticaria following administration of vestronidase alfa-vjbk. During the subsequent infusion two weeks later, he developed urticaria with cough and bronchospasm. The infusion was interrupted each time and the patient was treated with clemastine (and salbutamol for bronchospasm) with resolution. The patient continued vestronidase alfa-vjbk treatment with methylprednisolone and loratadine prophylaxis.

6 Expected Postmarket Use

Vestronidase alfa-vjbk is likely to be prescribed at specialty centers by pediatric specialists and medical geneticists, and perhaps other members of the multidisciplinary clinical teams who are involved in the care of patients with MPS, which includes treatments for the other MPS types, all of which have either boxed warnings, or warnings and precautions for anaphylaxis and/or hypersensitivity. It is expected vestronidase alfa-vjbk will be administered in the hospital outpatient setting or at infusion centers. The published literature has noted home infusion therapy may be an option for MPS patients who do not experience infusion reactions or hypersensitivity for a period of time while the treatment is administered at a healthcare setting.[7]

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a REMS or risk management plan with the application.

8 Discussion of Need for a REMS

MPS VII is a rare disease with variable phenotypes that range from that of a serious, progressive, and often fatal disease of childhood, to milder forms with a later onset and fewer clinical manifestations. There are no treatment options other than symptomatic and supportive care, though bone marrow transplant has been attempted in a small number of patients. The clinical program showed that evidence of efficacy has been established based on the 6MWT results, and that improvement in pulmonary function and reductions in spleen volume and liver volume in certain patients provided supporting information. Evidence of substrate (GAG) reduction and clinical improvement would not be anticipated in the absence of treatment.[8]

The potential serious adverse events associated with vestronidase alfa-vjbk include anaphylaxis and hypersensitivity.

The labeling for vestronidase alfa-vjbk will include a boxed warning for anaphylaxis with the recommendation that vestronidase alfa-vjbk should be administered under the supervision of a healthcare professional with the capability to manage anaphylaxis, and that patients should be observed during and for 60 minutes after administration. It is expected vestronidase alfa-vjbk will be prescribed by physicians at specialty centers with experience in treating and managing patients with MPS.

Based on the observed benefit of vestronidase alfa-vjbk, the serious and potentially life-threatening nature of the disease, the unmet medical need, and the expectation that vestronidase alfa-vjbk will only be prescribed and administered by physicians and healthcare providers with experience in enzyme replacement therapy, DRISK is not recommending a REMS for the management of the risks of vestronidase alfa-vjbk therapy.

9 Conclusion & Recommendations

Based on the available information a REMS is not necessary to ensure the benefits of vestronidase alfa-vjbk outweigh the risk of anaphylaxis, which is associated with other several enzyme replacement therapies for MPS that are approved without a REMS requirement.

Should DGIEP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References

[1] Montaño AM, et al. Clinical course of sly syndrome (mucopolysaccharidosis type VII). J Med Genet 2016; 53:403-418.
[2] Muenzer J. Overview of the mucopolysaccharidoses. Rheumatology (Oxford) 2011; 50(Suppl 5):v4-v12.
[3] Ultragenyx. Summary of Clinical Efficacy for vestronidase alfa-vjbk, BLA 761047, March 16, 2017.
[4] Ultragenyx. Draft labeling for vestronidase alfa-vjbk, BLA 761047, October 24, 2017.
[5] Zand D. Division of Gastroenterology and Inborn Errors Products. Draft Clinical Review Safety Results, BLA 761047, email communication, October 17, 2017.
[6] Ultragenyx. Response to FDA Information Request, BLA 761047 Seq. 0005, April 12, 2017.
[7] Burton BK, et al. Home infusion therapy is safe and enhances compliance in patients with mucopolysaccharidoses. Mol Genet Metab 2009; 97:234-6.
[8] Zand D. Division of Gastroenterology and Inborn Errors Products Medical Policy Council Program Review Memorandum, Vestronidase alfa-vjbk/Mepsevii, September 6, 2017.

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