CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategies (REMS) Memo

Date:	January 8, 2014
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Drug Name(s):	Vimizim (elosulfase alfa)
Therapeutic Class:	N-acetylgalactosamine-6-sulfatase (rhGALNS)
Indication:	Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome)
Dosage and Route:	Sterile solution for infusion
OND Review Division:	Division of Gastrointestinal and Inborn Error Products (DGIEP)
Application Type/Number:	BLA 125460
Applicant/sponsor:	Biomarin Pharmaceutical, Inc.
OSE RCM #:	2013-881

1. INTRODUCTION

This review documents the Division of Risk Management (DRISK) evaluation of the Biologic License Application (BLA) 125460 for elosulfase alfa, to assess the need for a Risk Evaluation and Mitigation Strategy (REMS). The BLA was submitted to the Division of Gastrointestinal and Inborn Error Products (DGIEP) by Biomarin Pharmaceutical on March 29, 2013. This review follows a request from DGIEP for DRISK to review and comment on the proposed "Pharmacovigilance Plan" for Vimizim (elosulfase). Although the Applicant did not propose a REMS, DRISK was consulted by DGIEP for participation in the approval process because the proposed biologic is a PDUFA V (Program) Application and to review the proposed pharmacovigilance plan.

Vimizim (elosulfase) is the only recombinant human N-acetylgalactosamine-6-sulfatase (rhGALNS) biologic currently in clinical development for the treatment of MPS IVA. The proposed indication is Mucopolysaccharidosis type IVA, a rare metabolic disorder for which there is currently no FDA approved drug or biologic. The proposed dosing is 2.0 mg/kg by intravenous infusion once a week.

1.1 MATERIALS REVIEWED

- Applicant's BLA submissions
- Midcycle Meeting Clinical Review slides
- Clinical review

1.2 OVERVIEW OF THE CLINICAL PROGRAM

A. Disease overview

Mucopolysaccharidosis type IVA (MPS IVA; Morquio A Syndrome) (orphan disease), is a rare, inherited disorder resulting from deficiency of the lysosomal enzyme N-acetylgalactosamine-6-sulfatase (GALNS). With insufficient GALNS, GAGs progressively accumulate in multiple organs and tissues, especially in bone and cornea.[1] The pervasive and progressive accumulation of GAGs leads to significant morbidities and multisystemic clinical impairments resulting in diminished functional capacity, decreased endurance, impaired quality of life, and early mortality (many patients with the severe form of the disease die before they reach 20 years old).[2] Most patients exhibit initial skeletal manifestations within the first 3 years of life.[3] The prevalence of this condition in the U.S. is estimated to be approximately 500 to 800 patients.[4]

Currently there are no approved, effective treatments for MPS IVA other than supportive care to manage pain and infections and frequent corrective surgeries with varying degrees of success.

B. Safety and Efficacy Trials

[1] Biomarin. Original Biologic License Application Submission No. 125460 for Elosulfase alfa, March 29, 2013. *See also*, Tomatsu, S, et al., MPV IV A: Clinical Review and Current Treatment: A Special Review. Current Pharmaceutical Biotechnology 2011;12:931-945.
[2] Biomarin, *supra* note 1.
[3] Tomatsu, *supra* note 1.
[4] Biomarin, *supra* note 1.

The clinical trials included 235 patients, including 174 patients exposed to elosulfase for at least 25 weeks and 86 patients exposed for at least 48 weeks. The majority of patients studied were less than 12 years old, consistent with MPV IVA disease epidemiology. The primary efficacy endpoint used by the Applicant is the 6-minute walk test (6MWT) based on a change in 6MWT in 24 weeks compared to placebo; DGIEP has questioned the appropriateness of this endpoint in the MPV IVA population and also that there is questionable confidence in the primary efficacy result. Notably, the division noted in the Midcycle meeting the need to discuss the clinical meaningfulness of the efficacy results and that that this endpoint is an indirect, versus direct, measure of cardiovascular, respiratory, and articular function.[5]

Specifically, the safety and efficacy of elosulfase was primarily assessed through data from 6 clinical studies, including 2 completed studies and 4 ongoing studies. The indication being sought in this marketing application is supported primarily by final results from the completed randomized, double-blind, placebo-controlled Phase 3 study with supporting evidence from two long term extension studies and two ongoing ancillary Phase 2 studies.

Below are summaries of the individual studies:

- MOR-004 is a completed Phase 3, randomized, double-blind, placebo-controlled, multinational study of elosulfase administered for a total of 24 weeks in 176 patients with MPS IVA. The study compared elosulfase infusions (2.0 mg/kg every other week [qow] or 2.0 mg/kg/week) with placebo in patients ranging from 5 to 57 years of age. Of note, this is the largest Phase III enzyme replacement therapy trial to date.[6]

- MOR-005 is an ongoing Phase 3 extension study designed to evaluate the long-term effects of elosulfase administered for up to 240 weeks in 173 patients with MPS IVA who completed MOR-004. In Part 1 (completed), patients who were initially randomized to elosulfase in MOR-004 remained on their assigned dose regimen of 2.0 mg/kg/week or 2.0 mg/kg/qow, and patients who were initially randomized to placebo in MOR-004 were re-randomized (1:1 ratio) to one of the two BMN 110 dose regimens (2.0 mg/kg/week or 2.0 mg/kg/qow). In Part 2 (ongoing), patients were switched to 2.0 mg/kg/week based on the analysis of the final primary efficacy and safety results in MOR-004 and Data Monitoring Committee recommendation.

- MOR-002 is a completed Phase 1/2, multicenter, open-label, dose-escalation study of BMN 110 in 20 enrolled patients with MPS IVA who were 4 to 16 years of age. Patients who completed the 36-week Dose-Escalation Period (consisting of 3 consecutive 12 week dosing periods of 0.1, 1.0, and 2.0 mg/kg/week), had the option to continue BMN 110 treatment with weekly doses of 1.0 mg/kg for an additional 36 to 48 weeks.

- MOR-100 is an ongoing Phase 1/2 extension study designed to evaluate the

[5] DGIEP, Vimzim Midcycle Meeting, Clinical Presentation, July 18, 2013.
[6] Crunkhorn S. Trial watch: enzyme replacement success in Phase III trial for rare metabolic disorder. Nat Rev Drug Discov. 2013 Jan;12(1):12. doi: 10.1038/nrd3929.

long-term safety and efficacy of BMN 110 2.0 mg/kg/week administered for up to 240 weeks in 17 patients with MPS IVA who completed MOR-002.

- MOR-007 is an ongoing Phase 2, open-label, multinational study of BMN 110 2.0 mg/kg/week for an initial treatment period of 52 consecutive weeks in 15 patients with MPS IVA who are <5 years of age at the time of first study-drug infusion. There will be an extension treatment phase of an additional 157 weeks.

- MOR-008 is an ongoing Phase 2, randomized, double-blind, multicenter study of BMN 110 2.0 mg/kg/week and 4.0 mg/kg/week administered for an initial treatment period of 27 consecutive weeks in 25 patients with MPS IVA who are ≥7 years of age and able to walk ≥200 meters in the 6-minute walk test (6MWT). There will be an extension treatment phase of an additional 130 weeks.[7]

C. Safety

Common adverse events

The most common adverse events (reported in 5% or more of patients treated with elosulfase) reported in the clinical studies were vomiting (44.8%), pyrexia (43.1%), and headache (41.4%). In general, elosulfase 2.0 mg/kg/week patients had at least 10% greater incidence of pyrexia, nausea, and abdominal pain than placebo patients.[8]

During the Midcycle meeting, DGIEP noted that the most common adverse reactions in the main trial, MOR004, included pyrexia (33%), vomiting (31%), headache (26%), and nausea (24%).[9] Although over 80% of patients in the clinical program experienced infusion adverse reactions (IARs) during one or more infusions, only 0.82% of individual infusions were interrupted or discontinued because the subject experienced an AE during infusion that also required medical intervention. In the proposed dose population, IARs were reported for 71.2% patients and the mean annualized frequency was 12.76 IARs per subject-year. In the clinical program, hypersensitivity AEs were reported for 27.2% of patients. In the proposed dose population, hypersensitivity AEs were reported for 16.2% of patients.

Serious adverse events

In the Phase 3 study MOR-004, treatment-emergent serious adverse events (SAEs) occurred in 9 (15.5%) of the patients in the elosulfase 2.0 mg/kg/week group, 4 (6.8%) of the patients in the elosulfase 2.0 mg/kg/qow group, and 2 (3.4%) of the patients in the placebo group. In the entire population of patients exposed to elosulfase, SAEs were reported in 29.4% of patients. All SAEs appeared to be associated with infusions, with procedures, or are recognized complications of MPS IVA and according to the Applicant's assessment.

[7] Biomarin, s*upra* note 1.
[8] *Id.*
[9] DGIEP, *supra* note 5.

With the exception of 1 patient in MOR-002 who experienced a grade 4 AE of Type I hypersensitivity and discontinued study participation after Week 11, all patients who experienced SAEs received and tolerated subsequent infusions. Notably, this hypersensitivity IAR occurred before mandatory premedication was required, and that after this event, mandatory antihistamine premedication was added to this and all subsequent protocols. No other subject in any study discontinued from study drug or withdrew from the study due to an AE.[10]

Anaphylaxis and hypersensitivity

7.7% (18 of 235) of patients experienced anaphylaxis and 27% (64 of 235) of patients experienced hypersensitivity reactions.[11] These events have occurred in patients as early as 30 minutes after infusion but as late as six days after infusion. Two patients discontinued treatment due to anaphylaxis.

Risk management strategy

The sponsor proposed including both hypersensitivity and (b) (4) adverse reactions in the Warning and Precautions section of the drug label. DGIEP recommended adding a boxed warning to the drug label for the risk of anaphylaxis and severe hypersensitivity reactions.[12] Section 17 of the label will also inform prescribers that they should advise patients and caregivers that infusion-related reactions, including anaphylaxis, have been associated with elosulfase infusions. This section mentions that pre-medication and reduction of the infusion rate may alleviate reactions associated with elosulfase infusions.

D. Efficacy

Patients treated with elosulfase met the primary study end point, exhibiting a mean increase of 22.5 meters in the 6-minute walk test from baseline to 24 weeks.[13] The clinical meaningfulness of this primary endpoint was one of the critical efficacy issues that DGIEP has with this application and was discussed at the Advisory Committee meeting held on November 19, 2013 (see summary below).

E. Agency and Committee Findings

Although DGIEP concluded during the Mid-cycle meeting that elosulfase was efficacious based on the primary endpoint of the six minute walk test (as stated above), DGIEP wanted to confirm with the Advisory Committee that this was a clinically meaningful measure. In terms of safety, DGIEP concluded that the primary serious risks associated with elosulfase include hypersensitivity and anaphylaxis for which a boxed warning will be required. DGIEP and DRISK support the use of labeling to manage these serious risks in light of the disease being treated, nature of the risks, and patient population.

[10] Biomarin, *supra* note 1.
[11] Dr. Tamara Johnson, Clinical Review, Elosulfase Alfa, BLA 125460, November 25, 2013.
[12] DGIEP, *supra* note 5.
[13] Crunkhorn *supra* note 6.

A meeting of the Endocrinologic and Metabolic Drugs Advisory Committee was convened on November 19, 2013 to discuss the efficacy and safety of elosulfase. The majority of the committee voted for approval for the Morquio IVA syndrome population, supported the primary endpoint employed in the clinical trials, and found that the benefits of elosulfase outweigh the risks. With respect to safety, the majority of the committee did not feel that the application raises major safety concerns in this patient population.

In the clinical review, Dr. Tamara Johnson recommended approval of elosulfase alfa with a boxed warning for anaphylaxis and postmarketing requirement (PMR) studies to further evaluate the safety and effectiveness of elosulfase in the MPS IVA population.[14]

1.3 OVERVIEW OF PHARMACOVIGILANCE PLAN

The Applicant proposed a pharmacovigilance plan for elosulfase which did not include a REMS but includes the following elements:

- Routine pharmacovigilance practices;
- Completion of ongoing clinical studies;
- The establishment of a (b) (4) disease registry to characterize and describe the MPS IVA population and to evaluate the long term effectiveness and safety of elosulfase; and
- Non-REMS risk minimization plan, which includes, in addition to labeling, the provision of educational material to guide safe and effective use of elosulfase for the treatment of MPS IVA. Specifically, the proposed education material consists of a product monograph, infusion training video, and dosing and administration guide has been prepared to educate treating physicians and healthcare practitioners in the storage, preparation, and administration of elosulfase. These materials are to be distributed, as appropriate, to healthcare providers, including infusion nurses and treating physicians.

The Applicant's proposed pharmacovigilance plan did not include a proposed REMS.

2. DISCUSSION

MPS IVA is an orphan disease which causes significant morbidity and mortality. Patients with the severe stage of this disease typically only survive until the second decade of life. Currently, there are no approved treatments for patients with this type of MPS, and those who have significantly advanced disease have severe bone dysplasia.[15]

Elosulfase showed clinical benefit in patients with MPV IVA. The adverse event profile was generally comparable to other enzyme replacement therapies (ERTs) and the clinical review team concluded that the benefits of elosulfase outweigh the risks. With respect to other enzyme replacement therapies with comparable serious risks of harm, the drug label for (b) (4) includes a contraindication for hypersensitivity, but does not have a required REMS program and (b) (4) has caused a high number of infusion reactions, including a few

[14] Johnson *supra* note 11.
[15] Tomatsu *supra* note 1.

observed cases of life-threatening anaphylactic reactions, and does not have a required REMS program in place.

In contrast, the [redacted] (b) (4) does have an ETASU REMS in place but this program is required first and foremost due to the potential risk of rapid Pompe disease progression in patients less than 8 years of age (there is not an identified comparable risk in elosulfase patients), in addition to the risk of anaphylaxis and severe allergic reactions.

In short, other comparable ERTs with comparable risks of harm do not have a REMS in place to manage these risks. Rather, the risk of anaphylaxis and hypersensitivity is managed via the drug label. Further, the PMR studies will facilitate the evaluation of the long term safety and effectiveness of elosulfase.

3. CONCLUSION

DGIEP identified no serious risks which warranted a REMS for their management in this orphan disease population and believes labeling is sufficient to manage the serious risks of anaphylaxis and hypersensitivity associated with elosulfase. DRISK believes that a REMS for elosulfase is not necessary to ensure the benefits outweigh the risks of the drug. There are currently no approved therapies for this orphan disease so this drug could offer clinical benefit to patients with MPS IVA. The risk of anaphylaxis and hypersensitivity is consistent with other enzyme replacement therapies. Prospective prescribers are likely highly specialized and familiar with the risks of enzyme replacement therapies. Finally, use of this drug is likely to be limited to the intended population. The applicant's proposal for labeling and routine pharmacovigilance is reasonable. Should DGIEP identify additional safety information that warrants risk mitigation measures, please send a consult to DRISK.

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