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OFFICE DIRECTOR MEMO

Office Deputy Director (acting) Decisional Memo

Date	February 14, 2014
From	Amy G. Egan, MD, MPH
Subject	Office Deputy Director (acting) Decisional Memo
NDA/BLA #	BLA 125460
Applicant Name	BioMarin Pharmaceutical Inc.
Date of Submission	March 29, 2013
PDUFA Goal Date	February 28, 2014
Proprietary Name / Established (USAN) Name	Vimizim/ elosulfase alfa
Dosage Forms / Strength	Intravenous injection/5mg/5mL (1mg/mL) in single use vials
Proposed Indication(s)	1. For patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)
Action:	Approval

Summary

Mucopolysaccharidosis IV Type A (MPS IVA) or Morquio A syndrome is a rare inherited disorder resulting from deficiency or absence of the lysosomal enzyme N-acetylgalactosamine 6-sulfatase (GALNS), which degrades glycosaminoglycans (GAGs) including keratan sulfate (KS) and chondroitin-6-sulfate (C6S). The deficiency in GALNS leads to the progressive accumulation of KS and C6S in the lysosomal compartment of cells throughout the body, resulting in cellular, tissue, and organ dysfunction including progressive skeletal dysplasia, restrictive lung disease, valvular heart disease, hearing loss, cataracts, and corneal clouding. The disease is heterogeneous in presentation and progression. Unlike other mucopolysaccharidoses, MPS IVA patients have normal intelligence. The estimated incidence of MPS IVA in the United States is 1:200,000 to 1:300,000 live births, with a prevalence of approximately 520-800 cases.

There are no FDA-approved treatments for MPS IVA. Treatment is typically symptomatic and includes pain medication, antibiotics, oxygen, and surgery.

The subject of this BLA, Vimizim (elosulfase alfa), is a purified form of human GALNS produced by recombinant DNA technology in a Chinese hamster ovary cell line. It is identical to the naturally occurring human lysosomal enzyme in terms of the amino acid sequence and N-linked glycosylation sites. Vimizim is intended to provide exogenous GALNS that will be taken up into the lysosomes and increase the catabolism of KS and C6S. Elosulfase alfa uptake by cells into lysosomes is mediated by the binding of mannose-6-phosphate-terminated oligosaccharide chains of elosulfase alfa to mannose-6-phosphate (M6P) receptors.

This memo documents my concurrence with the Division of Gastroenterology and Inborn Error Products' approval recommendation for Vimizim (elosulfase alfa) for the treatment of patients with Mucopolysaccharidosis IV Type A.

Dosing

Elosulfase alfa is available as a concentrated solution (in 5 mL vials) to be diluted for infusion. The recommended dose of elosulfase alfa is 2 mg/kg administered as a 3.5-4.5 hour infusion once every week (QW). The Office of Clinical Pharmacology agrees that the proposed dosing regimen is appropriate because of greater efficacy and pharmacodynamic response of the QW dosing regimen compared to the every other week (QOW) dosing regimen and the comparable incidence rates of anaphylaxis and drug-related adverse events between the two groups. Due to the potential for anaphylaxis and hypersensitivity reactions, pre-treatment with antihistamines with or without antipyretics is recommended 30-60 minutes prior to the start of the infusion.

Regulatory History

In March 2008, FDA and BioMarin Pharmaceutical Inc. held a Type C meeting (PIND 101,234) to discuss the proposed toxicological plan in support of a Phase 1/2, first in human, multiple dose, dose escalation clinical trial of BMN 110 (elosulfase alfa) in patients diagnosed with MPS IVA.

In May 2009, Orphan Product designation was granted.

In July 2010, FDA and BioMarin held a Type B Pre-IND/End-of-Phase 2 meeting to discuss the results of the Phase 1/2 trial, the proposed Phase 3 clinical trial, and the adequacy of the CMC, nonclinical and clinical programs to support a BLA submission.

In December 2010, BioMarin submitted a Special Protocol Assessment. While agreement was reached on the use of the 6 minute walk test (6MWT) as the primary endpoint, FDA and the applicant did not agree on other key aspects of the protocol. A No Agreement letter was issued in January 2011.

In February 2012, Fast Track designation was granted.

In July 2012, FDA and BioMarin held a Type C meeting (written feedback only) to discuss clinical and statistical aspects of the clinical development plan; in November 2012, FDA and BioMarin held a Type C meeting to discuss CMC issues related to the BLA submission; in December 2012, FDA and BioMarin held a Type B pre-BLA meeting to discuss clinical and nonclinical aspects of the elosulfase alfa clinical program and to reach agreement on the content and format of the proposed BLA submission.

BLA 125460 was submitted on March 29, 2013 and granted priority review; however, a solicited major amendment submitted May 10, 2013 resulted in an extension of the user fee goal date.

Product Quality Considerations

Multiple deficiencies were noted at the time of BLA filing resulting in an information request for additional data. The submission of these data constituted a major amendment and extension of the review clock.

At this time, there are no product quality issues that preclude approval of elosulfase alfa; however, the applicant has agreed to the following post-approval commitments:

1. Develop and implement, as a release and stability test method, a potency assay that measures the K_m and k_{cat} of elosulfase alfa formulated bulk drug substance (FBDS) and drug product (DP) using a physiologically relevant substrate.

2. Revise the RP-HPLC test method used for elosulfase alfa FBDS and DP release and stability testing in order to improve baseline resolution between [redacted] (b) (4) peak. The revised specification together with the validation report will be submitted to your BLA in accordance with 21 CFR 601.12.

3. Demonstrate that SEC-HPLC is able to measure the true aggregate content, using an orthogonal test method and testing in side by side analysis samples of Vimizim that have been subjected to forced degradation conditions.

4. Include parallel line analysis as an additional system suitability criterion for the cellular uptake assay.

5. Include quantitative system suitability criteria for retention time, number of peaks and relative peak heights in the peptide map assay.

6. Add cellular uptake as a release assay for drug product and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested.

On January 26, 2014, the Division of Therapeutic Proteins recommended granting BioMarin's request for categorical exclusion from environmental assessment.

All facilities involved in the manufacturing of elosulfase alfa were evaluated by the Office of Compliance, Division of Manufacturing and Product Quality (OC-DMPQ). A final Therapeutics Biological Establishment Evaluation Request Form was issued by OC-DMPQ on February 14, 2014; no pending or ongoing compliance actions prevent approval.

Microbiology Product Quality Considerations

There are no microbiology product quality issues that preclude approval of elosulfase alfa. The applicant has agreed to the following post-approval commitments:

1. Conduct studies to understand the mechanism of low endotoxin recovery in the formulated bulk drug substance and drug product. These studies should investigate the endotoxin degradation or association pathway and determine whether or not depyrogenation is reversible (and if so, the conditions under which depyrogenation is reversible). Based on the results of these studies, modify the endotoxin release test and/or determine the suitability of alternative endotoxin test methods.

2. Provide summary data and the associated reports for the endotoxin recovery studies performed under protocols QC-1209-M and QC-1224-M.

3. Conduct an additional study comparing rabbit pyrogen and LAL test results. The study should include formulated bulk drug substance spiked with 20 EU/mL and 100 EU/mL endotoxin. The time points and controls should be the same as for the previous studies.

4. Provide results from protocol PVP-101037 (b) (4) to be executed during the 2014 manufacturing campaign.

Non-clinical Considerations

A dose-dependent increase in stillbirths was observed when elosulfase alfa was administered daily in rats during organogenesis through lactation at doses five times the clinical exposure for the weekly dose. The non-clinical reviewers and the Maternal Health Team of the Pediatric and Maternal Health Staff have recommended a pregnancy category C for this product, and labeling will reflect that this product should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Rat pup deaths occurred in the high-dose elosulfase alfa group during nursing, 1 to 4 days after birth, but because the drug is known to cross the placenta into the fetal circulation, this effect was felt to be due to a delayed reaction from *in utero* exposure, and not from exposure through milk. Nonetheless, product labeling will instruct the prescriber to exercise caution when administering elosulfase alfa to a nursing mother and to consider potential adverse effects from the drug on the breastfed child.

Clinical Pharmacology Considerations

The pharmacokinetics (PK) of elosulfase alfa were assessed in Study MOR-004 at Week 0 (after a single dose) and at Week 22 (after repeat dosing) in 24 and 23 patients with MPS IVA who received the every other week (QOW) and weekly (QW) dosing regimens, respectively. The QW dosing regimen resulted in a mean increase in AUC_{0-t} and C_{max} of 2.8- and 2.9-fold, respectively, at Week 22 compared to Week 0. Mean $t_{1/2}$ increased from 7 minutes at Week 0 to 35 minutes at Week 22 for the QW dosing regimen. These increases in elosulfase alfa exposures at Week 22 are presumed to be due to the formation of anti-elosulfase alfa antibodies, which have the ability to bind to and interfere with the cellular uptake of elosulfase alfa into target tissues.

At Weeks 0 and 22, elosulfase alfa PK were comparable between males and females. Elosulfase alfa clearance appeared to be inversely correlated with age at Week 0, i.e., decreasing clearance with increasing age (≤17 years old versus >17 years old); however, the clinical relevance of this is unclear given the small number of subjects >17 years of age. There was no correlation between body weight and elosulfase alfa clearance at Week 22. The majority of subjects studied were Asians and Whites. Mean clearance was lower in Asians than Whites at Week 0 and at Week 22 in the QW dosing group, but the clinical relevance of this finding is unclear given the small number of Asian subjects. The effect of renal impairment or hepatic impairment on the PK of elosulfase alfa has not been studied. No formal QT/QTc studies were performed for elosulfase alfa. No drug-drug interaction trials have been performed.

Efficacy

The efficacy of Vimizim (elosulfase alfa) was assessed in a 24-week, randomized, double-blind, placebo-controlled clinical trial of 176 patients with MPS IVA. Patients were randomized to Vimizim 2 mg/kg QW (n=58), Vimizim 2 mg/kg QOW (n=59), or placebo (n=59).

The age of patients ranged from 5 to 57 years, although half of the trial population was between the ages of 5 and 11 years. Forty-two percent of patients were female, and 58% were male. At baseline, all enrolled patients could walk more than 30 meters, but less than 325 meters in six minutes.

The primary endpoint was the change from baseline in the distance walked in six minutes (6MWD) at Week 24. Patients in the Vimizim 2 mg/kg QW treatment group demonstrated a

statistically significant mean change in the 6MWD of 22.5 meters (p=0.0174) relative to placebo. The mean difference between the QOW group and the placebo group was 0.5 meters and was not statistically significant (p=0.9542).

Secondary endpoints were 1) the change from baseline to Week 24 in the number of stairs climbed per minute in the 3 minute stair climb (3MSC), and 2) the change from baseline to week 24 in urine keratan sulfate (uKS) levels. Neither the Vimizim 2 mg/kg QW treatment group nor the QOW treatment group demonstrated a statistically significant change in the 3MSC. Patients in the QW treatment group demonstrated a mean change of 1.1 stairs/minute (p=0.4935) relative to placebo; patients in the QOW treatment group demonstrated a mean change of -0.5 stairs/minute (p=0.7783) relative to placebo. Both the QW and QOW treatment groups demonstrated a statistically significant reduction in uKS levels relative to placebo, 30.2% (p<0.0001) and 40.7% (p<0.0001) for the QOW and QW treatment groups, respectively. The relationship between uKS levels and other measures of clinical response has not been established.

A post-hoc responder analysis was conducted using the Delphi Panel's Responder Definitions which represented the percent change in 6MWD based on baseline 6MWD. The proportion of patients meeting the responder definition was 47% for the QW treatment group compared to 34% for the placebo group.

Exploratory analyses demonstrated a subset of 11 "high performers", defined as patients who achieved ≥100 meters change in 6MWD at Week 24 – 8 patients treated with Vimizim QW, 1 patient treated with Vimizim QOW and 2 placebo-treated patients. The 8 patients treated with Vimizim QW were all pediatric patients (mean age of 11±5 years; median age of 9 years; range of 5 to 18 years). There were otherwise no distinguishable features among this subgroup. Four of the patients were female, and four were male. Three of the patients were from the European cohort; three from North America; and two from "other". Baseline 6MWD was <200 meters in 4/8 patients, and ≥200 meters in 4/8 patients. The increase in 6MWD ranged from 101.95 meters to 228.65 meters. The two placebo-treated "high performers" were also both pediatric patients, one a 10.5 year-old white European male, the other a 9.9 year-old white North American female. Both patients had baseline 6MWD ≥200 meters. The increase in 6MWD was 220.5 meters and 114.05 meters for the 10.5 year-old and 9.9 year-old, respectively.

Exploratory subgroup analyses showed that, separately, subjects who are white, 12-18 years of age, and who are from North America appear to respond to Vimizim 2 mg/kg QW better than their respective counterparts. Additional exploratory subgroup analyses by baseline 6MWD demonstrated that patients with worse baseline 6MWD (≤200 meters) showed a greater improvement in walking ability than those who could walk more than 200 meters at baseline. Because of the exploratory nature of these analyses, they will not been included in labeling.

Patients who participated in the placebo-controlled trial were eligible to continue treatment in a 48-week open-label extension. One hundred seventy-three of 176 patients (98.3%) enrolled in the extension trial and received Vimizim 2 mg/kg QW (n=86) or Vimizim 2 mg/kg QOW

(n=87). No further increase in the 6MWD was observed at Week 72 in the QW-QW treatment group.

Safety

The safety of elosulfase alfa was assessed in 235 patients with MPS IVA who received at least 1 dose of elosulfase alfa at 0.1 mg/kg QW up to 4.0 mg/kg QW, or 2.0 mg/kg QOW for periods ranging from 1 week to 170 weeks. This included 117 patients from Trial MOR-004 (the pivotal Phase 3 clinical trial), 58 patients from Trial MOR-005 (patients treated with placebo in MOR-004, and switched to Vimizim QOW or QW in MOR-005), 20 patients from Trial MOR-002, 15 patients from Trial MOR-007 (ongoing), and 25 patients from Trial MOR-008 (ongoing). Safety information was also available for 114 patients from Trial MOR-004 who rolled over to Trial MOR-005 (patients treated with Vimizim QOW or QW in MOR-004 and continued on their respective therapies in MOR-005), and 17 patients from Trial MOR-002 who rolled over to Trial MOR-100. Of the 235 patients, 222 (94%) were exposed to the proposed marketing dose of 2 mg/kg QW, and 50 were treated for at least 52 weeks.

Ninety-six percent of patients experienced at least one adverse event, the majority of which were drug-related and included pyrexia (26%), vomiting (22%), headache (20%), nausea (18%), abdominal pain (14%), and fatigue (12%). There were no deaths in the clinical development program; 10.6% of patients experienced a drug-related serious adverse event (SAE), including events of anaphylaxis (n=13) and severe hypersensitivity (n=7); two patients discontinued due to adverse event, one with anaphylaxis and one with severe hypersensitivity reaction.

As with any intravenous protein product, severe allergic reactions are possible. Signs and symptoms consistent with anaphylaxis were reported in 18 of 235 (7.7%) patients treated with Vimizim, and 44 of 235 (18.7%) patients experienced hypersensitivity reactions, including anaphylaxis. The *Warnings & Precautions* section of product labeling will recommend that if severe hypersensitivity reactions occur, infusion of Vimizim should be immediately halted and appropriate treatment administered; practitioners should consider the risks and benefits of re-administration of Vimizim following a severe reaction. Because of the potential for hypersensitivity reactions, patients should be administered antihistamines with or without antipyretics prior to infusion. Mild hypersensitivity reactions occurring during infusion can be managed by slowing or temporarily interrupting the infusion, or administering additional antihistamines, antipyretics, and/or corticosteroids.

The risk of life-threatening complications from hypersensitivity reactions may be higher in patients with acute febrile or respiratory illness at the time of Vimizim infusion. The *Warnings & Precautions* section of product labeling will recommend that the patient's clinical status be carefully considered prior to administration of Vimizim, and consideration be given to delaying the infusion.

Since sleep apnea is common in MPS IVA patients, evaluation of airway patency should be considered prior to initiation of Vimizim treatment.

Spinal or cervical cord compression (SCC) is a known and serious complication of MPS IVA. In clinical trials, SCC was observed both in Vimizim- and placebo-treated patients. MPS IVA patients should be monitored for signs and symptoms of SCC and treated accordingly.

Immunogenicity

All patients treated with Vimizim 2 mg/kg QW in the placebo-controlled trial MOR-004 developed anti-drug antibodies (ADA) by Week 4, which were sustained or increased for the duration of Vimizim treatment. Because all patients developed ADA, their impact on the treatment effect or the occurrence of anaphylaxis or hypersensitivity reactions could not be determined. However, anti-elosulfase alfa total antibody (TAb) titers did not appear to have an impact on pharmacodynamics, efficacy, or safety. In study MOR-004, TAb titers did not correlate with the change in normalized uKS levels, 6MWT, or 3MSC at Week 24 from baseline. Furthermore, there was no association between mean TAb titer and the incidence of hypersensitivity reactions, including anaphylaxis.

All patients treated with Vimizim 2 mg/kg QW tested positive for neutralizing antibodies (NAb) capable of inhibiting the drug from binding to the M6P receptor. NAb titers were not determined in the patients, so the impact of NAb titer on the treatment effect could not be determined.

Among Vimizim-treated patients, the presence of IgE was not associated with anaphylaxis or hypersensitivity reactions. However, a RAST assay developed to detect elosulfase specific IgE was employed in the clinical trials, and RAST assay sensitivity can be severely compromised by the presence of high levels of antigen specific IgG. Results from the titering assay in the Vimizim clinical trials indicated that patients developed very high titers of IgG antibodies; this may have resulted in an under reporting of the incidence of IgE development. Therefore, the underlying mechanism of the hypersensitivity reactions may not be completely understood.

Although there are no immunogenicity deficiencies that preclude approval, two concerns will need to be addressed post-approval. First, the applicant will need to develop and validate an assay to determine the titer of anti-elosulfase alfa NAb that inhibits binding to the M6P receptor, and use that assay to analyze patient samples obtained in the completed MOR-004 trial, as well as in patients enrolled in the ongoing trials MOR-005 and MOR-007, the Morquio A registry, and in a prophylactic immune tolerance regimen trial.

Second, the applicant will need to develop and validate an IgE assay suitable for detection of anti-elosulfase IgE antibodies in the presence of high titers of IgG, and to use that assay to analyze patient samples obtained in the completed MOR-004 trial, as well as in patients enrolled in the ongoing trials MOR-005 and MOR-007, the Morquio A registry, and in a prophylactic immune tolerance regimen trial.

Pediatric Considerations

Pediatric Use. The safety and effectiveness of Vimizim have been established in pediatric patients 5 years of age and older. The median age of patients in the Phase 3 clinical trial of

Vimizim was 12 years; 53% of the trial population was aged 5 to 11 years, and 27% was aged 12 to 17 years.

An open-label trial (MOR-007) is being conducted in 15 patients less than 5 years of age (mean age 3 years; range 9 months to 4.9 years) treated with Vimizim 2 mg/kg QW. The most common adverse reactions have included vomiting (80%), pyrexia (73%), and cough (53%). Four patients have experienced at least one hypersensitivity reaction, two of whom required medical intervention.

Required Pediatric Assessments. Because elosulfase alfa for this indication has an orphan drug designation, BioMarin Pharmaceutical Inc. is exempt from conducting required pediatric studies under the Pediatric Research Equity Act (21 U.S.C. 355c). However, completion of the ongoing Phase 2 trial, MOR-007, which is assessing the safety of Vimizim in pediatric patients <5 years of age, will be required as a postmarketing requirement (PMR) under the FDA Amendments Act (FDAAA).

Pediatric Rare Disease Voucher. Section 908 of the Food and Drug Administration Safety and Innovation Act (FDASIA) modified the Rare Pediatric Disease Priority Review Voucher Incentive Program to allow the issuance of a "priority review voucher" to the sponsor of a rare pediatric disease product application. The holder of such voucher is entitled to priority review of a single human drug application submitted under section 505(b)(1) after the date of approval of the rare pediatric disease product application. Under the statute, 'rare pediatric disease' is defined as:

1. The disease primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents.
2. The disease is a rare disease or condition, within the meaning of section 526.

The term 'rare pediatric disease product application' means a human drug application that

1. is for a drug or biological product—
    a. that is for the prevention or treatment of a rare pediatric disease; and
    b. that contains no active ingredient (including any ester or salt of the active ingredient) that has been previously approved in any other application under section 505(b)(1), 505(b)(2), or 505(j) of this Act or section 351(a) or 351(k) of the Public Health Service Act;
2. is submitted under section 505(b)(1) of this Act or section 351(a) of the Public Health Service Act;
3. the Secretary deems eligible for priority review;
4. that relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population;
5. that does not seek approval for an adult indication in the original rare pediatric disease product application; and
6. is approved after the date of the enactment of the Prescription Drug User Fee Amendments of 2012.

On January 7, 2014, BioMarin Pharmaceutical Inc. submitted to FDA a Pediatric Voucher Request for Vimizim for the treatment of MPS IVA. In a memo dated January 14, 2014, the

Office of Orphan Products Development opined that MPS IVA meets the FDASIA definition of a rare pediatric disease. FDA has further determined that the Vimizim BLA submission represents a rare pediatric disease product application as defined above. While Vimizim's indication encompasses an adult population, it is understood that the indication in the adult population is merely a continuum of the pediatric indication, and does not represent a different adult indication. Therefore, a Priority Review Voucher will be granted at the time of approval.

Tradename Review

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Office of Prescription Drug Products, has concluded that the applicant's proposed tradename "Vimizim" is acceptable. In a letter dated July 25, 2013, BioMarin Pharmaceutical Inc. was notified that the proposed tradename was acceptable but that it would be re-reviewed 90 days prior to the approval of the BLA. In a memo dated January 13, 2014, DMEPA indicated that re-reviews of proposed proprietary names within 90 days of approval are no longer conducted unless there is a change in the proposed product characteristics. Since none of the proposed product characteristics were altered, DMEPA concluded that the proposed proprietary name is acceptable.

Postmarketing Requirements under 505(o)

Section 505(o)(3) of the Food, Drug and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to 1) identify an unexpected serious risk of anaphylaxis and hypersensitivity reactions associated with long term exposure to Vimizim, 2) identify an unexpected serious risk of adverse maternal, neonatal or infant outcomes associated with Vimizim exposure during pregnancy, and 3) identify an unexpected serious risk of immune-mediated disorders associated with the development of anti-drug antibodies, including neutralizing antibodies, associated with long term exposure to Vimizim.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks. Therefore, based on appropriate scientific data, the applicant will be required to:

> **PMR-1:** Evaluate the long-term safety of Vimizim in adult and pediatric patients enrolled in the Morquio A Registry for a period of ten years, including but not limited to the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. Include incidence rate calculations as part of long-term safety evaluation assessments to monitor and characterize risk of exposure to Vimizim. In addition, assessment of clinical outcomes (e.g., anthropometric measures, progression of skeletal deformities, frequency and time

to orthopedic surgeries) will be performed. All safety, immunogenicity, and clinical outcome assessments will be conducted every 6 months. Patients previously enrolled in clinical trial MOR-005 and MOR-007 may be rolled over to this study but will be monitored using the MOR-005 and MOR-007 protocols, respectively.

PMR-2: Develop and validate an assay to determine the titer of anti-elosulfase alfa neutralizing antibodies that inhibits binding to the mannose-6-phosphate receptor. The final report will contain a summary of the validation exercise including supporting data, a summary of the development data showing assay suitability for parameters not assessed in the validation exercise, and the assay Standard Operating Procedure (SOP). This assay will be used to assess anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in PMRs 1, 3, and 6.

PMR-3: Analyze anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in the completed MOR-004 trial.

PMR-4: Develop and validate an IgE assay suitable for detection of anti-elosulfase IgE antibodies in the presence of high titers of IgG. This assay will be used to assess for the presence of elosulfase alfa-specific IgE antibodies in patient samples obtained in PMRs 1, 5, and 6.

PMR-5: Analyze elosulfase alfa-specific IgE antibody titers in patient samples obtained in the completed MOR-004 trial.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected risk of serious infection in patients receiving treatment with Vimizim and an immune tolerance regimen.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

PMR-6: Evaluate the occurrence of serious infections associated with administration of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with Vimizim who are at high risk of developing persistent neutralizing antibodies. This immune tolerance regimen will be implemented before or concomitant with the onset of Vimizim therapy.

Conclusions

MPS IV A is a serious and life-threatening condition with an unmet medical need. The heterogeneity of the disease in terms of its presentation and progression makes it difficult to rely on a single endpoint that has clinical meaningfulness for all MPS IVA patients.

The 6MWT, which measures the integrated function of at least three separate organ systems that are affected by MPS IVA: the respiratory, cardiovascular, and musculoskeletal systems, was agreed to by FDA as an appropriate primary endpoint for the pivotal phase 3 trial. At the

November 19, 2013 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC), the majority of committee members agreed that the 6MWT is adequate to evaluate the treatment benefit in patients with MPS IVA, although they acknowledged that the test does not fully evaluate treatment benefit and does not include some of the important aspects of the disease manifestations, such as pain and fatigue.

The pivotal trial (MOR-004) demonstrated a statistically significant mean change in the 6MWD of 22.5 meters (p=0.0174) relative to placebo; however, the review team questioned the clinical meaningfulness of this modest treatment effect. EMDAC members opined that the totality of clinical data (including whether the magnitude of treatment difference observed in the 6MWT represented a clinically meaningful benefit) supported the effectiveness of Vimizim for treatment of MPS IVA in all (n=12) or a subgroup (n=8) of MPS IVA patients.

The treatment effect of Vimizim is further bolstered by the subset of Vimizim-treated patients who achieved an improvement in 6MWD of ≥100 meters change from baseline to Week 24. And while the extension trial data demonstrated no further improvement in the 6MWD with continued therapy to 72 weeks, it is reassuring that it did demonstrate stabilization in walking ability over time.

The safety of the product is consistent with other enzyme replacement therapies. Of concern, however, is the near universal development of sustained neutralizing antibodies in patients treated with Vimizim. The effect of these antibodies on safety and clinical outcomes will need to be carefully scrutinized in the postmarketing setting. The review team has recommended numerous postmarketing required studies and trials to address this issue. The issue of whether to require an immune tolerance trial was discussed at length by the review team. The intent of such a trial would be to determine if an immune tolerance regimen could be used to mitigate the risk of severe hypersensitivity reactions, including anaphylaxis. However, the immune tolerance regimen itself carries risks, of which serious infection is one. Therefore, in order to establish the safety of using an immune tolerance regimen in Vimizim-treated patients, the sponsor will be asked to conduct a trial to identify an unexpected risk of serious infection in patients receiving treatment with Vimizim and an immune tolerance regimen.

All review disciplines have recommended approval of BLA 125460 for Vimizim (elosulfase alfa) for the treatment of patients with MPS IVA. Eighteen EMDAC members voted for approval of Vimizim in all patients with MPS IVA; two voted for approval for a subgroup of MPS IVA patients; and one voted against approval.

I concur with the Vimizim review teams' recommendation for approval, the PMRs/PMCs detailed in this memo, and the agreed upon labeling. Vimizim will fill an unmet medical need, and ongoing and required postmarketing studies will help clarify questions of long-term efficacy and safety.

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/s/

AMY G EGAN
02/14/2014