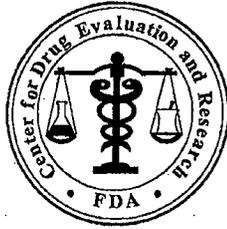


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125291**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

Date: October 21, 2009

To: Donna Griebel, M.D., Director  
Division of Gastroenterology Products (DGP)

Through: Claudia Karwoski, Pharm D., Director  
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From: OSE Lumizyme Risk Management Team  
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Subject: Review of Proposed Risk Mitigation and Evaluation Strategy (REMS)

Drug Name(s): Lumizyme (alglucosidase alfa)

Indication: Treatment of late-onset Pompe Disease patients  $\geq 8$  years of age who do not have evidence of cardiac myopathy

Application Type/Number: BLA 125291

Applicant/sponsor: Genzyme Corporation

OSE RCM #: 2008-1355

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## 1 INTRODUCTION

This review follows the request from the Division of Gastroenterology Products (DGP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Evaluation and Mitigation Strategy (REMS) for Lumizyme (alglucosidase alfa), BLA125291.

Lumizyme is a form of recombinant human acid alfa-glucosidase that degrades lysosomal glycogen to glucose. The proposed indication is for the treatment of late-onset Pompe disease patients  $\geq 8$  years of age who do not have evidence of cardiac hypertrophy. Lumizyme is not indicated for children less than 8 years of age as efficacy and safety of Lumizyme have not been established in this age group. The risks associated with the use of Lumizyme include anaphylaxis, severe allergic reactions, severe cutaneous and systemic immune complex-mediated reactions, and the potential risk of rapid disease progression in Pompe disease patients less than 8 years of age,

Because of the serious risks, the Agency notified Genzyme that a risk evaluation and mitigation strategy (REMS) will be required for Lumizyme to ensure the benefits of Lumizyme outweigh the risks. In response to this notification, the Sponsor submitted the proposed REMS for Lumizyme that includes a communication plan, elements to assure safe use, an implementation plan, and a timetable for submission of assessments.

## 2 REGULATORY HISTORY

- Alglucosidase alfa was initially approved on April 28, 2006 (BLA 125141) for the treatment of Pompe disease of all phenotypes under the TRADENAME Myozyme 160 L.
- Due to the increased demand for Myozyme, Genzyme sought approval of the scaled-up 2000 L manufacturing process for alglucosidase alfa (TRADENAME 2000 L renamed Lumizyme).
- In April of 2008, the review division determined that Lumizyme 2000 L and Myozyme 160 L were neither comparable nor interchangeable<sup>1</sup>. Therefore, the Agency required the Applicant to submit efficacy and safety data to support separate licensure of Lumizyme (BLA 125291).
- An Endocrinologic and Metabolic Drugs Advisory Committee meeting was held on October 21, 2008. The advisory committee voted in favor of approval of Lumizyme under CFR 601 Subpart E. This decision was largely based on the concerns regarding the worldwide shortage in Myozyme supplies.
- A Complete Response (CR) letter was issued to Genzyme on February 27, 2009 for deficiencies identified in facility inspections with chemistry, manufacturing, and controls, post marketing clinical study design, and the proposed REMS.

### 3 MATERIAL REVIEWED

- Proposed Lumizyme REMS dated November 7, 2008, eCTD Sequence # 0038
- Following REMS related submissions:
  - eCTD Sequence # 0063, dated February 25, 2009
  - eCTD Sequence # 0072, dated May 15, 2009
  - eCTD Sequence # 0081, dated June 30, 2009
  - eCTD Sequence # 0095, dated September 25, 2009
- FDA Comments on the proposed REMS sent December 16, 2008; March 20, 2009; May 20, 2009; and July 29, 2009
- Endocrinology and Metabolic Drugs Advisory Committee (EMDAC) Advisory Committee's Briefing Document, dated October 21, 2008
- Lumizyme Clinical Review by Lynne Yao, M.D., Medical Officer Division of Gastroenterology Products, dated February 23, 2009
- Complete Response Letter for BLA 125291/0 issued February 27, 2009

### 4 PROPOSED REMS

#### 4.1 GOALS

Initially the Sponsor had proposed the following REMS goals for Lumizyme:



The Agency recommended that the Sponsor revises these goals. The primary purpose for requiring a REMS for Lumizyme was to communicate the serious but potential risk of disease progression in patients with infantile-onset Pompe disease and severe allergic reactions with Lumizyme (communicated to the Sponsor via the CR Letter on February 27, 2009).

The Sponsor's revised goals for Lumizyme are acceptable and are as follows:

- To mitigate the potential 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 for whom safety and effectiveness of Lumizyme have not been evaluated.
- To ensure that the known risks of anaphylaxis and severe allergic reactions associated with the use of Lumizyme are communicated to patients and prescribers, and to ensure that the risks of potential severe cutaneous and systemic

immune complex-mediated reactions to Lumizyme are communicated to patients and prescribers.

## **4.2 REMS Elements**

The Lumizyme REMS elements include the following:

### **4.2.1 Communication Plan:**

Genzyme will implement a communication plan to healthcare professionals (HCPs) to support implementation of the Lumizyme ACE (Alglucosidase alfa Control and Education) Program via:

- Lumizyme Physician Introductory Letter
- Lumizyme Healthcare Professional Introductory Letter

The introductory letters will be provided to all healthcare providers at launch. These letters will outline the goals of the Lumizyme REMS, will state that Lumizyme is only available through the Lumizyme ACE Program, and will provide instructions on how to enroll in the program.

### **4.2.2 Elements to Assure Safe Use**

The elements to assure safe use for the Lumizyme REMS include:

1. Healthcare providers who prescribe Lumizyme are certified.

The certification process includes educational training that will be provided via on-line or on-site by Genzyme. Prescribers will be required to enroll on an annual basis. Prescribers who complete the educational training commit that they:

- Have completed educational training about Lumizyme and must enroll all patients being treated with Lumizyme.
- Have an understanding of the prescribing information, and risks / benefits (appropriate patient population to be treated) of Lumizyme.
- Will enroll all patients into the program and will advise them about the risks and benefits of Lumizyme
- Have access to appropriate medical support measures to treat severe allergic reactions.

The healthcare provider upon enrollment into the Lumizyme ACE Program will receive the following materials:

- Lumizyme ACE Program: Information for Healthcare Providers
- Lumizyme (alglucosidase alfa) and the Lumizyme ACE Program Training and
- Certification for Healthcare Providers

- Physician Enrollment and Attestation Form
- Patient Enrollment and Acknowledgement Form

2. Lumizyme will be dispensed and administered by healthcare facilities that are certified.

Certification of the healthcare facilities requires that the representatives of such facilities e.g., head nurse, director of infusion center, director of education, and the infusion nurse enroll in the Lumizyme ACE Program and attest to the following:

- That they have provided the Lumizyme ACE Program education materials to the facility staff that are responsible for the ordering, dispensing and administration of Lumizyme.
- That they have completed their training on procedures for ordering, dispensing, and administering Lumizyme.
- That they have procedures in place for appropriate monitoring of patients for early recognition of anaphylaxis / allergic reactions associated with Lumizyme, and to treat such reactions.
- That they have an understanding of the patient selection for Lumizyme use.
- That the Lumizyme Infusion Confirmation Form will be filled prior to each infusion.

Genzyme will ensure that the participating healthcare facilities are enrolled on an annual basis and have received the required training.

A significant modification to the Lumizyme REMS included addition of the Lumizyme Confirmation Form which is to be completed by the HCP administering the Lumizyme infusion and faxing the completed form to Genzyme/affixing the sticker section of the form to the patient's file or saving it in the patient's electronic medical record.

3. Lumizyme will be dispensed to patients with evidence of safe-use conditions.

Each patient to be treated with Lumizyme must be enrolled in the Lumizyme ACE Program and will sign a patient Enrollment and Acknowledgement Form prior to initiating each treatment. Patients will attest that they have received pertinent information regarding Lumizyme from their prescriber.

Certified healthcare facilities will be required to dispense and administer Lumizyme only after verifying the patient is enrolled in the Lumizyme ACE Program and after ensuring each patient receives his/her designated drug by completing the Lumizyme Infusion Confirmation Form.

### **4.2.3 Implementation System**

The implementation system of the Lumizyme ACE Program requires that Genzyme will maintain a database of certified healthcare providers, healthcare facilities, and enrolled patients. In addition, Genzyme will monitor the following:

- Re-enrollment of participants
- Distribution of Lumizyme to determine whether the drug is shipped to certified healthcare facilities
- Lumizyme is used in patients with late (non-infantile) onset Pompe disease, ages 8 years and older, who do not have evidence of cardiac hypertrophy and not used in infantile-onset patients of any age or late-onset disease patients less than 8 years of age
- Lumizyme is only infused in patients who are enrolled
- A Lumizyme infusion confirmation form is completed with each infusion
- Whether there is confusion between Lumizyme and Myozyme

### **4.2.4 Timetable for Submission of Assessments**

Genzyme will submit the REMS Assessment to FDA at 6 months, 1 year, and annually from the date of the approval of the REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Genzyme will submit each assessment so that it will be received by the FDA on or before the due date.

### **4.3 REMS Assessment Plan**

The information that will be needed for the REMS assessment is not a required element of the REMS Proposal. However, the Sponsor's assessment plan is outlined in the REMS Supporting Document. The REMS assessment reports will include:

- The number of certified prescribers in the Lumizyme ACE Program that have undergone training and certification during the reporting period and cumulatively
- The number of patients enrolled in the Lumizyme ACE Program during the reporting period and cumulatively
- The number of certified healthcare facilities in the Lumizyme ACE program that have undergone training and certification during the reporting period and cumulatively
- The number of healthcare facilities that have ordered/administered Lumizyme that were not enrolled in the ACE program during the reporting period and cumulatively

- The number of prescribers and healthcare facilities who were un-enrolled from the ACE Program during the reporting period and cumulatively due to noncompliance
- The number of patients with infantile-onset Pompe disease who were prescribed and administered Lumizyme during the reporting period and cumulatively
- Corrective and preventative actions taken to address noncompliance with distribution and dispensing requirements during the reporting period and cumulatively
- A narrative summary and analysis of anaphylaxis, severe allergic reactions and immune mediated reactions reported with use of Lumizyme during the reporting interval.
- Patients' and physicians' understanding of the serious risks of Lumizyme:



(b) (4)

## 5 DISCUSSION AND CONCLUSION

The proposed Lumizyme REMS has undergone a number of revisions since it was initially submitted in November 2008 in response to Agency comments. The REMS proposal dated September 25, 2009 contains the agreed REMS components including a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments. The REMS Supporting Document outlines the information that the Sponsor will use to assess the effectiveness of the REMS in meeting the goals. We believe that the REMS comprised of the elements described in this review will appropriately mitigate the risks of Lumizyme and should be approved. We note that the proposed REMS Document submitted by the Sponsor requires editing to comply with the format currently being used by the Agency. We have provided our suggested revisions to this document (see Appendix A). We understand additional formatting revisions may be necessary as this REMS goes through the final clearance process.



Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology

Date: February 25, 2009

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Zachary Oleszczuk, Safety Evaluator, Division of Medication Error  
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Nina Phuong Ton, Safety Regulatory Project Manager, OSE-IO

Subject: Review of Proposed Risk Evaluation and Mitigation Strategy (REMS),  
submitted November 7, 2008

Drug Name(s): Lumizyme (alglucosidase alfa)

Proposed Indication: Treatment of Pompe Disease

Application Type/Number: BLA 125291

Applicant/sponsor: Genzyme Corporation

OSE RCM #: 2008-1355

We acknowledge the Sponsor's November 7, 2008 submission of the proposed Risk Evaluation and Mitigation Strategy (REMS) for Lumizyme (alglucosidase alfa), BLA 125291, for the treatment of Pompe Disease. Due to the following outstanding issues, the Division of Gastroenterology Products (DGP) plans to issue a Complete Response (CR) letter for this review cycle.

- Subpart E - postapproval study to verify clinical benefit of Lumizyme. Discussions continue regarding the study design, choice of primary endpoint, sample size, effect size, and accrual feasibility.
- REMS with ETASU – Discussion continues regarding the primary goal of the REMS, the final REMS, and the documents related to the REMS (attestation forms, letters to patients and prescribers, etc).
- Facility Inspection Issues - During a recent inspection of the Allston Landing manufacturing facility for this application, and Agency field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

FDA comments regarding the proposed REMS were sent to the Sponsor on, February 18, 2008 and subsequently discussed with Genzyme in the teleconference on February 19, 2009.

The sponsor has sent FDA via email a revised REMS based on those comments and discussions and while progress is being made, there has not been an official submission and there is insufficient time left in the review cycle to come to complete agreement and resolution on the final REMS.

The Agency must reach agreement on all aspects of the REMS and other outstanding issues before Lumizyme can be approved. We will provide our final review of the Sponsor's proposed REMS for Lumizyme when the outstanding REMS issues have been addressed.