FOOD AND DRUG ADMINISTRATION (FDA)
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
October 21, 2008

The committee will discuss the safety and efficacy of biologic license application (BLA) 125291, MYOZYME (alglucosidase alfa), Genzyme Corp., for the treatment of late onset Pompe disease.

Questions to the Committee:

The 160L product is the only commercially available alglucosidase alfa treatment in the US, and it is indicated for the treatment of all forms of Pompe disease. The 2000L product was not found to be comparable to the 160L product, and therefore, deemed to be a different drug.

Only a single study exists to support the effectiveness and safety of the 2000L product in the treatment of late-onset Pompe disease. To provide substantial evidence of effectiveness, FDA's reliance on a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect, such as mortality, and is statistically very persuasive (i.e., has a very low p-value that indicates the result is highly inconsistent with the null hypothesis of no treatment effect).[1]

FDA believes the 6MWT is the relevant parameter for deciding the efficacy of the 2000L product. The results of the analysis between 2000L product and placebo for the 6MWT at the end of the study using ANCOVA, which adjusted for baseline and re-randomization inference, gave a p-value of p=0.06. Furthermore, after an initial look at the data, the Applicant changed its statistical analysis of the 6MWT. The Applicant has proposed alternative statistical analyses that were discussed at this meeting.

Although the change from baseline in percent predicted FVC appears statistically significant, it was not the pre-specified primary endpoint. Based on the Applicant's statistical analysis plan, the formal hypothesis testing of FVC was not to be performed if the 6MWT analysis failed to reach statistical significance. Additionally, the use of FVC is not a recognized clinical benefit endpoint, nor is it a validated surrogate marker in Pompe disease.

Questions:

1. Do you believe LOTS has established the effectiveness of the 2000L product?

    a. If not, should an additional study be conducted to determine whether the 2000L product is effective in treating late-onset Pompe Disease?

[1] US Department of Health and Human Services. Guidance for Industry. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products. <http://www.fda.gov/cder/guidance/1397fnl.pdf>. May 1998.

b. If additional study is recommended, should a head-to-head study vs. the 160L product be conducted, or an alternate study design?

2. Please consider the following decisional options for the 2000L product and state which option, based on the evidence presented, is most appropriate:

   a. Not approved. If no approval is recommended, then the 2000L product can be made available to adult-onset patients under a treatment IND, whereby the Applicant may charge for product as part of the conduct of an additional study or studies. These studies would be conducted to further evaluate the 2000L product.

   b. Approval under Accelerated Approval (Subpart E), whereby the 2000L product can be approved using the FVC as a surrogate endpoint reasonably likely to predict clinical benefit, and a verification study to demonstrate clinical benefit of the 2000L product would be required of the Applicant during the post-marketing period. If you believe this is the most appropriate decision, please recommend a study design for the verification study, such as a head-to-head comparison vs. the 160L product.

   c. Regular Approval based on the 6MWT findings in LOTS.

3. If an Accelerated Approval or a regular Approval (2.b. or 2.c.) is recommended, please consider the following:

   a. The LOTS trial enrolled an inadequate number of patients with juvenile-onset Pompe disease. Only four patients were under 18 years of age at the time of enrollment in the study, one of whom was exposed to 2000L product (one patient aged 16 years). Only nine patients in LOTS developed symptoms and were diagnosed with Pompe disease under the age of 18, six of whom were exposed to 2000L product. Should the indication for the 2000L product be restricted to the adult-onset population only (i.e., patients who were diagnosed and had symptom onset over 18 years of age)?

   b. If you recommend approval for a restricted age group (e.g., adults only), what safeguards, including communication plans, should be implemented to avoid use of the 2000L product in patients less than 18 years of age, such as communication plans or restricted distribution? See attached REMS template.

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c. Should additional studies be required as post-marketing commitments to assess efficacy? If yes, please describe the design of the study(ies).

d. Should additional studies be required as post-marketing requirements to assess safety? If yes, please describe the design of the study(ies).

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REMS TEMPLATE

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name
Address
Contact Information

PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Append the printed material and web shots to the REMS Document

C. Elements To Assure Safe Use

List elements to assure safe use included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:
A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS ;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above .

E. Timetable for Submission of Assessments

Specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments at a minimum must include an assessment by 18 months, 3 years, and in the 7th year after the REMS is initially approved, with dates for additional assessments if more frequent assessments are necessary to ensure that the benefits of the drug continue to outweigh the risks.