

**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
Crowne Plaza Hotel, Silver Spring, Maryland
October 21, 2008
Open Session**

The Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on October 21, 2008 at the Crowne Plaza Hotel Washington DC/Silver Spring, the Kennedy Ballrooms, 8777 Georgia Avenue, Silver Spring, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Kenneth Burman, M.D. (Acting Chair); the conflict of interest statement was read into the record by Paul Tran, R.Ph. (Designated Federal Official). There were approximately 250 persons in attendance. There were 8 speakers for the Open Public Hearing sessions.

Attendance:

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):

Kenneth Burman, M.D., Katherine Flegal, Ph.D., Jessica Henderson, Ph.D., Eric Felner, M.D., Abraham Thomas, M.D., Michael Proschan, Ph.D., Clifford Rosen, M.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Non-voting):

Enrico Veltri, M.D. (Industry Representative)

Peripheral & Central Nervous System Drugs Advisory Committee Member (Voting)

Gregory Holmes, M.D., Ph.D

Pulmonary-Allergy Drugs Advisory Committee Member (Voting)

Michael Foggs, M.D.

Special Government Employee Consultants Present (Voting):

Thomas Fleming, Ph.D., Jesse Joad, M.D., John Teerlink, M.D., Tiffany House (Patient Representative), David Schade, M.D., Thomas Aoki, M.D., Roger Packer, M.D..

Regular Government Employee Consultants Present (Voting):

John Hanover, Ph.D.

FDA Participants:

Julie Beitz, M.D., Anne Pariser, M.D., Lynne Yao, M.D., Lisa Kammerman, Ph.D., Claudia Karwoski, Pharm.D.

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Open Public Hearing Speakers:

David W. Hamlin, United Pompe Foundation

Brian S. White, Patient

Diana Eggers, Patient

Jeffrey R. Harvey, Patient

Jared Salbato, Patient

Krystal Hayes, Parent of Pompe's Patient

George Fox, AMDA

Laura Case, PT, DPT, MS, PCS, Assistant Professor. Division of Physical Therapy, Duke University Medical Center

Designated Federal Official:

Paul Tran, R.Ph.

Issue:

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

The agenda was as follows:

11:40 a.m. – 11:50 a.m.	Call to Order (Open Session) Introduction of Committee	Kenneth Burman, M.D. Acting Committee Chair EMDAC
11:50 a.m. – 11:55 a.m.	Conflict of Interest Statement	Paul Tran, R.Ph. Designated Federal Official, EMDAC
11:55 a.m. – 12:00 p.m.	Open Session Introductory Remarks	Anne R. Pariser, M.D. Acting Deputy Director, Division of Gastroenterology Products, CDER, FDA
12:00 p.m. – 12:50 p.m.	SPONSOR PRESENTATION Introduction	Alexander Kuta, Ph.D Group Vice President Regulatory Affairs Genzyme Corporation

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Open Session

Overview of Pompe Disease

Priya Kishnani, M.D.
Professor and Chief,
Division of Medical Genetics
Duke University Medical Center

Clinical Experiences with 2000L
Alglucosidase alfa

Edward Kaye, M.D.
Group Vice President
Clinical Research

Discussion of Statistical Methods

P.K. Tandon, Ph.D.
Senior Vice President
BioMedical Data Sciences
& Informatics

Lee-Jen Wei, Ph.D.
Professor of Biostatistics
Department of Biostatistics
Harvard University
School of Public Health

Summary

Alexander Kuta, Ph.D.
Group Vice President
Regulatory Affairs
Genzyme Corporation

FDA PRESENTATION

12:50 p.m. – 1:40 p.m.

Alglucosidase alfa 2000 L Advisory
Committee and Statistical Review

Lynne P. Yao, M.D.
Medical Officer
Division of Gastroenterology
Products, CDER, FDA

1:05 p.m. – 1:15 p.m.

Lisa A. Kammerman, Ph.D.
Statistical Reviewer
Division of Biometrics III
CDER, FDA

1:15 p.m. – 1:35 p.m.

Lynne P. Yao, M.D.
Medical Officer
Division of Gastroenterology
Product, CDER, FDA

1:35 p.m. – 1:40 p.m.

**Claudia B. Karwoski,
Pharm.D.**
Acting Director
Division of Risk Management
CDER, FDA

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1:40 p.m. – 2:40 p.m.	Open Public Hearing (OPH) Session
2:40 p.m. – 5:00 p.m.	Discussion and Questions
5:00 p.m.	Adjourn

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= adjusting for baseline and based on re-randomization inference using ANCOVA 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? (Vote: Yes or No)

Yes: 16

No: 1

Abstain: 0

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.

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- a. If not, should an additional study be conducted to determine whether the 2000L product is effective in treating late-onset Pompe Disease? (Discuss)
- b. If additional study is recommended, should a head-to-head study vs. the 160L product be conducted, or an alternate study design? (Discuss)

The majority of the committee would like to see a head-to-head study of the 160 L vs. 2000 L product to be conducted. Many committee members felt there were insufficient data presented on a direct comparison and there were concerns regarding problems in the study design presented by the sponsor.

(Please see transcripts for detailed discussions)

2. Please consider the following decisional options for the 2000L product and state which option, based on the evidence presented, is most appropriate: (Choose a, b, or c)
 - 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. (Discuss)
 - 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. (Discuss)

The majority of the committee agreed with the Approval under Accelerated Approval (Subpart E) and as noted earlier, many members would like to see a head-to-head study of the 2000 L vs. 160 L product. Several committee members felt it was not ethical to conduct a Placebo control trial design. Fourteen members voted for Accelerated Approval and three committee members voted for Regular Approval.

(Please see transcripts for detailed discussions)

- c. Regular Approval based on the 6MWT findings in LOTS. (Discuss)

Some committee members voted for Regular Approval based on the 6MWT findings in LOTS but would like to see additional evidence. Some committee members felt that the 6MWT did not provide significant changes that had clinical significance. There was discussion of the appropriateness of the surrogate markers for this disease, but also recognition that this is a rare, but usually progressive disorder.

(Please see transcripts for detailed discussions)

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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)? (Vote: Yes or No)

Yes: 0

No: 16

Abstain: 1

There was consensus that the approval should not be restricted to patients who were diagnosed and had symptom onset over 18 years of age. The committee agreed with the proposal of limiting the approval to patients with symptom onset > 24 months of age without evidence of hypertrophic cardiomyopathy.

(Please see transcripts for detailed discussions)

- b. If you recommend approval for a restricted age group (e.g., adults only), what safeguards 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. (Discuss)

The committee agreed with the use of REMS template.

- c. Should additional studies be required as post-marketing commitments to assess efficacy? (Vote: Yes or No)

Yes: 15

No: 2

Abstain: 0

- i. If yes, please describe the design of the study(ies). (Discuss)

The majority of the committee suggested the design of the study should focus on younger patients (juvenile) as well as older adult patients. It was thought inappropriate to perform a study with a placebo control group. The committee suggested a prospective longitudinal study examining surrogate and quantitative endpoints (e.g., muscle biopsy assessing glycogen, quantitative measures of muscle strength, ventilator free survival and mortality) and the study should compare the use of 2000 L product vs. historical control.

(Please see transcripts for detailed discussions)

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- d. Should additional studies be required as post-marketing requirements to assess safety?
(Vote: Yes or No)

Yes: 17

No: 0

Abstain: 0

- i. If yes, please describe the design of the study(ies). (Discuss)

The committee suggested carefully monitoring and assessing patients for adverse events, such as anaphylactic reactions, short term infusion reactions and long term immunopathology (e.g. of skin and kidneys) The committee also suggested designing rigorous studies with specific definitions that have a high level of reliability, sensitivity and specificity to detect key events such anaphylaxis.

(Please see transcripts for detailed discussions)

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.

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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.