# CENTER FOR DRUG EVALUATION AND RESEARCH AND CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**125141/0**

# APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125141/0

APR 28 2006

Genzyme Corporation
Attention: Alexander Kuta, Ph.D
Vice President, Regulatory Affairs
500 Kendall Street
Cambridge, MA 02142

Dear Dr. Kuta:

We have approved your biologics license application for Alglucosidase alfa, effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Alglucosidase alfa under your existing Department of Health and Human Services U.S. License No. 1596. Alglucosidase alfa is indicated for use in patients with Pompe disease (GAA deficiency). Alglucosidase alfa has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease as compared to an untreated historical control, whereas use of Alglucosidase alfa in patients with other forms of Pompe disease has not been adequately studied to assure safety and efficacy.

Under this license, you are approved to manufacture Alglucosidase alfa drug substance at Genzyme Corporation in Framingham, Massachusetts. The final formulated product will be manufactured, filled, labeled, and packaged at Genzyme Corporation, Allston, Massachusetts. You may label your product with the proprietary name MYOZYME and will market it in 50 mg vials.

The dating period for Alglucosidase alfa shall be 24 months from the date of manufacture when stored at 2 to 8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be [redacted] when stored at 6 to 10 °C. The dating period for your formulated bulk drug product shall be [redacted] when stored at 6 to 10 °C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including results of stability studies from the first three production lots. We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

You currently are not required to submit samples of future lots of Alglucosidase alfa to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1 requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of Alglucosidase alfa, or in the manufacturing facilities.

We acknowledge your written commitments as described in your letter of April 26, 2006, as outlined below:

**Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.**

1. Genzyme commits to completing the juvenile- and adult-onset Pompe disease study AGLU02704, entitled "A randomized, double-blind, multicenter, multinational, placebo-controlled study of the safety, efficacy and pharmacokinetics of Myozyme, recombinant human acid alpha-glucosidase (rhGAA), treatment in patients with late-onset Pompe disease." Patient accrual is complete, the study is to be completed by September 30, 2007, and a final study report will be submitted to CDER by May 31, 2008.

2. Genzyme commits to conducting the extension to the juvenile- and adult-onset Pompe disease study AGLU02704 through 24 months (AGLU03206), entitled "An open-label extension study of patients with late-onset Pompe disease who were previously enrolled in protocol AGLU02704". Patient accrual is to be completed by December 31, 2007, the study is to be completed by June 30, 2008, and a final study report will be submitted to CDER by November 30, 2008.

3. Genzyme commits to completing study AGLU01702, entitled "An open-label, multicenter, multinational study of the safety, efficacy, pharmacokinetics, and pharmacodynamics of recombinant human acid alpha-glucosidase (rhGAA) treatment in patients > 6 months and ≤ 36 months old with infantile-onset Pompe disease (Glycogen Storage Disease Type II)." This study is to be completed by June 12, 2006, and a final study report will be submitted to CDER by February 28, 2007.

4. Genzyme commits to designing and implementing a registry of patients with Pompe disease being treated with alglucosidase alfa that will be established to obtain long-term clinical status information. Information will be collected on patient demographics, specifics of treatment with alglucosidase alfa, clinical status, ventilatory status, motor assessments, adverse events, assessment of immunogenicity, and potential effects of antibody formation. In patients who are less than one year of age at the start of treatment, information is to be collected on cognitive status, and auditory and visual screening assessments. This registry will be designed so that detailed clinical status information is collected at registry entry and on a 6- to 12-month basis for at least 15 years. Genzyme commits to conducting two sub-studies within the registry: one sub-study that will evaluate the effect of alglucosidase alfa on pregnancy and lactation, and one sub-study that will collect information on the clinical status of patients on ventilatory support at the time of entry into the registry. The registry data will be analyzed at yearly intervals and the results will be submitted in your annual reports for BB-IND 10780. A study protocol will be submitted to CDER by September 29, 2006, for concurrence, and the study will be initiated by March 31, 2007. The final study report under this registry will be submitted to CDER by September 30, 2022.

5. Genzyme commits to designing and implementing an infantile-onset Pompe disease study to assess growth and development with treatment with alglucosidase alfa, in patients who are less than one year of age at study entry. This study is to include blinded assessments of growth (including standardized measurements of recumbent length, height, weight, and head circumference), developmental testing (the scales used need to be prospectively agreed upon), auditory and visual screening, neuro-imaging, and antibody assessments at 6- to 12-month intervals over a 10-year period. A study protocol will be submitted to CDER by September 29, 2006, for concurrence, and the study will be initiated by January 31, 2007. The final study report for this study will be submitted to CDER by September 30, 2017.

6. Genzyme commits to designing and implementing an immune tolerance protocol in Pompe disease patients who have significant antibody titers, or the presence of neutralizing antibody, and are failing treatment. Genzyme commits to designing and implementing a preventive immune tolerance protocol in Pompe disease patients at high risk for the development of significant immune responses to the product. This would involve 1) establishing the correlation among genotype, the level of α-glucosidase protein (non-enzymatic assay), and the presence and levels of binding, IgE, and neutralizing antibodies over time, using validated assays; and 2) developing an immune tolerance regimen that would be implemented before or concomitant with onset of therapy for those at high risk. Additionally, Genzyme commits to monitoring antibody positive patients, whose immune responses are not associated with loss of efficacy or severe hypersensitivity responses, at regular intervals over an extended period of time (i.e., 18-24 months) to specifically assess if a sub-population of patients become tolerant with routine treatment. Reports from preclinical studies to assess potential tolerance regimens and a commitment for timelines for a subsequent clinical study will be submitted to CDER by December 29, 2006.

   Genzyme commits to developing a protocol that will be used to provide guidance to physicians for the use of tolerance-inducing regimens for patients who are currently failing treatment because of a robust antibody response and to submit this protocol by October 31, 2006.

7. Genzyme commits to designing and implementing a dose- and dose-interval exploration study in patients with poor responses to treatment, regardless of antibody status. This study is to include patients in the infantile-, juvenile-, and adult-onset patient populations. A study protocol will be submitted to CDER by September 29, 2006, for concurrence, and the study will be initiated by January 31, 2007. The final study report for this study will be submitted to CDER by September 30, 2009.

8. Genzyme commits to initiate a 6-month intravenous chronic toxicity study of Myozyme in neonatal/juvenile mice by September 29, 2006, and submit the full report of the study by September 30, 2007.

9. Genzyme commits to submit by June 30, 2006, the final report of (b)(4) Study 6354-163 titled "Intravenous Injection Study of Recombinant Human Acid-alfa-Glucosidase (rhGAA) on Female Fertility and Early Embryonic Development to Implantation in Mice".

10. Genzyme commits to conduct a Segment II. Teratology study of Myozyme in rabbits and submit the full report of the study by June 30, 2007. In the interest of clarity and precision for the data obtained, pretreatment of the animals with diphenhydramine should be avoided in the study.

11. Genzyme commits to conduct histopathology examination of the testes of male mice in [redacted] Study 6354-155 titled "Intravenous Injection Study of Recombinant Human Acid alfa-Glucosidase (rhGAA) on Fertility and Early Embryonic Development to Implantation in Mice" and submit the full pathology report by October 30, 2006.

12. Genzyme commits to submit the data from the third Segment I. reproductive/toxicology study in mice by December 31, 2006, for concurrence. If necessary, Genzyme commits to submit an additional protocol for the study of the effects of Myozyme on spermatocytogenesis and spermiogenesis in male rabbits. In any future protocols, animals should be treated for a minimum of 90 days.

13. Genzyme commits to conduct a Segment III. prenatal and postnatal study in rats or mice in the third quarter of 2006 and submit a full report of the study by September 30, 2007.

**Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.**

14. Regarding method validations:

    a. To complete validation of [redacted] content and quantitative [redacted]) test methods for drug substance and/or product release. Results and proposed specifications will be submitted to CDER by December 31, 2006.

    b. [redacted] substance and product release. Results and proposed specifications will be submitted by March 31, 2007.

    c. To improve the [redacted] content assay, or to develop, validate, and implement an alternative more accurate and precise assay. Results and proposed specification will be submitted by December 31, 2007.

15. To provide a revised protocol for requalification and confirmation of stability of the primary and working reference standards that incorporates the new panel of validated methods. A revised protocol will be submitted by July 31, 2006.

16. Regarding the drug substance specifications:

    a. To re-evaluate the specification for [redacted], and establish a limit for [redacted] in the specification, following assay re-validation. Results and revised specifications will be submitted by December 31, 2006.

b. To revise the specification for the (b)(4) present in the oligosaccharide mapping analysis and submit by June 30, 2006.

17. Regarding the drug product COA/specifications:

a. (b)(4) specification will be submitted by March 31, 2007.

b. To explore development of a method for an (b)(4) observed in reconstituted drug product and after dilution in saline. Results and a proposal for controlling particle content will be submitted by November 30, 2007.

18. To characterize the composition of the (b)(4) material observed after reconstitution of drug product and to investigate the nature of particle formation. Results will be submitted by November 30, 2007.

19. (b)(4) (b)(4) Validated stability indicating assays will be incorporated into the stability program (including accelerated stability on drug product, and after reconstitution and dilution). Results and revised stability protocol will be submitted by June 30, 2007.

20. To perform a study on formulated bulk drug product to confirm its hold time using the content assay and other stability-indicating assays. Results will be submitted by November 30, 2007.

21. To conduct bracketed, in use photostability studies on product diluted for infusion using current methods. Results will be submitted by December 31, 2006.

22. To provide interim summary reports regarding progress of CMC post marketing commitments every 6 months after licensure.

23. To provide information from a validated cell-based neutralizing antibody assay to evaluate the potential effect of GAA antibody on mannose-6-phosphate receptor dependent enzyme uptake using human fibroblast cells. Results will be submitted by June 30, 2006.

24. To provide results using the validated inhibition of enzyme uptake into human fibroblast assay from all patients in Studies AGLU01602 and AGLU01702, as well as all patients in clinical studies or the expanded access program for Myozyme who have become invasively ventilated since February 2, 2006. Results will be submitted by October 31, 2006.

We request that you submit clinical protocols to your IND, with a cross-reference letter to this biologics license application BLA STN BL 125141. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA STN BL 125141.

Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Protocol**
- **Postmarketing Study Final Report**
- **Postmarketing Study Correspondence**
- **Annual Report on Postmarketing Studies**

For each postmarketing study subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e., pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e., number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing studies on our Web site (http://www.fda.gov/cder/pmc/default.htm). Please refer to the April 2001 Draft Guidance for Industry: Reports on the Status of Postmarketing Studies – Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cber/gdlns/post040401.htm) for further information.

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to the Central Document Room, Center for Drug Evaluation and Research, Food and Drug Administration, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Prominently identify all adverse experience reports as described in 21 CFR 600.80.

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves

a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to the Division of Compliance Risk Management and Surveillance (HFD-330), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Biological product deviations sent by courier or overnight mail should be addressed to Food and Drug Administration, CDER, Office of Compliance, Division of Compliance Risk Management and Surveillance, HFD-330, Montrose Metro 2, 11919 Rockville Pike, Rockville, MD 20852.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels). In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Sincerely,

Julie Beitz MD 4-28-06

Julie Beitz, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research