Product Approval Information

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

April 24, 2003

Our STN: BL 103979/0

Genzyme Corporation
Attention: Christine Harris
Manager, Regulatory Affairs
One Kendall Square
Cambridge, MA 02139-1562

Dear Ms. Harris:

This letter hereby issues Department of Health and Human Services U.S. License No. 1596, to Genzyme Corporation, Cambridge, Massachusetts, in accordance with the provisions of Section 351(a) of the Public Health Service Act, controlling the manufacture and sale of biological products. This license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture the product Agalsidase beta. Agalsidase beta is indicated for use in patients with Fabry disease to reduce globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types.

Under this authorization, you are approved to manufacture Agalsidase beta bulk drug substance at your facility in ----------. Drug product will be formulated, filled, labeled and packaged at your ----------. In accordance with approved labeling, your product will bear the proprietary name Fabrazyme, and will be marketed in a 35 mg single-use vial.

The dating period for Agalsidase beta shall be 24 months when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the final formulated product. The dating period for bulk drug substance shall be --- months from the date of manufacture when stored at ----- °C. Results of ongoing stability studies should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots. The stability protocols in your license application are considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12.

You are not currently required to submit samples of future lots of Agalsidase beta to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release

specification.

Any changes in the manufacturing, testing, packaging or labeling of Agalsidase beta, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

As requested in your letter of June 23, 2000, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as a basis for approval of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires, among other things, that you conduct adequate and well-controlled studies to verify and describe clinical benefit attributable to this product. Verification of clinical benefit is contingent upon completion of clinical studies as outlined in your commitment letter of April 10, 2003:

1. Genzyme commits to completing the verification study AGAL-008, entitled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Recombinant Human a-Galactosidase-A (rha-Gal) on Progression of Renal Disease and Significant Clinical Events in Patients with Fabry Disease." Patient accrual was completed on March 27, 2003, the study will be completed by January 31, 2004, and a final study report will be submitted to CBER by September 30, 2004.

2. Genzyme commits to conducting the verification study AGAL-023-03, entitled "A Multicenter, Open-Label, Phase 4 Extension Study of the Safety and Efficacy of Fabrazyme in Fabry Disease." The objective of this study is to examine the effects of Fabrazyme on creatinine over time using within patient analyses. A final protocol and analytic plan for this study will be submitted to CBER by October 31, 2003. Patient accrual will be completed by January 31, 2004, the study will be completed by August 31, 2005, and a final study report will be submitted to CBER by April 30, 2006.

Design, initiation, accrual, completion, and reporting of these studies are expected to occur within the framework described in your letter of April 10, 2003. It is understood that, to fulfill the requirements of accelerated approval, these studies must be conducted with due diligence. If postmarketing studies fail to verify that clinical benefit is conferred by Agalsidase beta, or are not conducted with due diligence, the Agency may, following a hearing withdraw or modify approval.

In addition, we acknowledge the following agreed upon postmarketing commitments, as described in your letter of April 10, 2003:

3. Genzyme commits to continuing the registry of patients with Fabry disease being treated with Agalsidase beta that was established to obtain long-term clinical status information. This study will be revised so that detailed clinical status information is collected at study entry and on a 6 to12-month basis for at least 15 years. Genzyme commits to conducting a sub-study within the registry that will evaluate the effect of Agalsidase beta on pregnancy and lactation. The registry data will be analyzed at yearly intervals and the results will be submitted in your annual reports for BB-IND 7616. Information will also be collected on clinical status, adverse events, assessment of immunogenicity and potential effects of antibody formation. This study was initiated in Europe on January 30, 2001. An amended study protocol will be submitted to CBER by September 30, 2003, and this revised study will be initiated by January 31, 2004. The final study report under this registry will be submitted to CBER by September 30, 2020.

4. Genzyme commits to completing the ongoing European study AGAL-016-01, entitled "A Multicenter, Phase 1/2 Open-Label Study of Fabrazyme (Recombinant Human a-Galactosidase-A) Replacement Therapy in Pediatric Patients with Fabry Disease." This study will obtain pharmacodynamic and safety data on the use of Fabrazyme in pediatric patients. The study was initiated in Europe on March 28, 2002, and the final protocol will be submitted to CBER by September 30, 2003. Patient accrual will be completed by March 31, 2004, the study will be completed by May 31, 2005, and a final study report will be submitted to CBER by November 30, 2005.

5. Genzyme commits to introducing to the U.S. market a 5 mg vial dosage form. The supplement supporting this change will be submitted by June 30, 2003.

Protocols should be submitted to BB-IND 7616 with a cross-reference letter to the BLA.

It is required that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted in accordance with 21 CFR 600.81. Postmarketing adverse experience reports and distribution reports should be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. All adverse experience reports should be prominently identified according to 21 CFR 600.80.

You are required to submit reports of biological product deviations in accordance with 21 CFR 600.14. All manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution, should be promptly identified and investigated. 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, a report must be submitted on Form FDA-3486 to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Rockville, MD 20852-1448.

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, as specified in 21 CFR 601.45, you are required to submit any advertising and promotional labeling with FDA Form 2253 to the Advertising and Promotional Labeling Branch, HFM-602, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852-1448 at least 30 days prior to the initial publication of any advertisement or to the initial dissemination of any promotional labeling.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

--- signature ---

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

--- signature ---

Sharon T. Risso, M.A.
Acting Director
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research

Last Updated: 4/24/2003