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

Approval Package for:

APPLICATION NUMBER:

BLA 125117/0

Trade Name:	Naglazyme
Generic Name:	Galsulfase
Sponsor:	Biomarin Pharmaceutical, Incorporated
Approval Date:	May 31, 2005
Indications:	Naglazyme (galsulfase) is indicated for patients with Mucopolysaccharidosis VI (MPS VI). Galsulfase has been shown to improve walking and stair-climbing capacity.

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APPLICATION NUMBER:

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

APPLICATION NUMBER:

125117/0

APPROVAL LETTER(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125117/0

MAY 31 2005

BioMarin Pharmaceutical, Incorporated
Attention: Mary Newman, M.S.
Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Newman:

We have approved your biologics license application (BLA) for Galsulfase effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Galsulfase under your existing Department of Health and Human Services U.S. License No. 1649. Galsulfase is indicated for patients with Mucopolysaccharidosis VI (MPS VI). Galsulfase has been shown to improve walking and stair-climbing capacity.

Under this license, you are approved to manufacture Galsulfase at your facility in Novato, CA. Final formulated drug product will be filled at —. Labeling and packaging of drug product will occur at —. You may label your product with the proprietary name NAGLAZYME and will market it in 5 mL single-use vials containing 5 mg Galsulfase (expressed as protein content) per 5 mL of solution.

The dating period for Galsulfase drug product shall be 30 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 Galsulfase drug substance shall be — when stored at 2 to 8 °C. We have approved the stability protocols 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 Galsulfase 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 Galsulfase, or in the manufacturing facilities.

We acknowledge your written commitments as described in your letters of May 10, 2005 and May 26, 2005, as outlined below:

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

1. To conduct a developmental dose-range toxicity study in a non-rodent species. The study protocol will be submitted to FDA by August 1, 2005, initiated by October 1, 2005, completed by November 1, 2005, and a final study report will be submitted to FDA by April 15, 2006.

2. To conduct a definitive developmental toxicity study in a non-rodent species. The study protocol will be submitted to FDA by February 28, 2006, initiated by March 30, 2006, completed by May 4, 2006, and a final study report will be submitted to FDA by September 15, 2006.

3. To develop and validate an improved screening assay for detecting total antibodies to Galsulfase. The design and validation data for this improved antibody binding assay will be submitted to FDA by November 30, 2005.

4. To develop and validate an improved immunogenicity assay for detecting neutralizing antibodies to Galsulfase. The design and validation data for this improved neutralization assay will be submitted to FDA by November 30, 2005.

5. To develop and evaluate an improved immunogenicity assay for detecting IgE antibodies to Galsulfase. The design and validation data for this improved IgE assay will be submitted by November 30, 2005.

6. To analyze, using the improved and validated immunogenicity assays, archived serum samples from patients in the Phase 3 trials (ASB-03-05) for binding, neutralizing and IgE antibodies to Galsulfase. Analysis will evaluate immunogenicity rates and individual patient titers to assess how antibody levels increase or decrease as a function of repeated exposure to better evaluate impact of repeated dosing on potential induction of immunological tolerance. A final study report including these data will be submitted to FDA by May 31, 2006.

7. To develop and validate an improved assay for detecting Galsulfase in human plasma. The design and validation data for this improved assay will be submitted by March 31, 2006.

8. To analyze, using the improved and validated plasma level assay, archived plasma samples from the Phase 3 and remaining plasma samples from the Phase 1 and 2 trials for levels of Galsulfase. These data will be submitted to FDA by July 31, 2006.

9. To evaluate long-term safety and efficacy data in a Clinical Surveillance Program (CSP) of patients being treated with Galsulfase. Detailed clinical status information will be collected at study entry and on an annual basis for at least 15 years. Serious and severe adverse events among all patients will be collected and submitted through periodic safety update reports as specified by the regulations (21 CFR 600.80). You will

conduct a sub-study within the CSP that will evaluate the effect of Galsulfase on pregnancy and lactation. You will also conduct a second sub-study within the CSP that will include the enrollment of at least 10 children less than 5 years of age to be treated with 1 mg/kg/week of Galsulfase for at least one year and report the analysis of these data. The CSP data will be analyzed at yearly intervals and the results will be submitted in your annual reports for BB-IND 9057. Information will also be collected on clinical status, adverse events, assessment of immunogenicity, and potential effects of antibody formation. The CSP protocol will be submitted by June 30, 2005, and will be initiated by July 15, 2005. The final study report under this CSP will be submitted to FDA by December 31, 2020.

10. To conduct a study of no less than four infants with MPS VI who are less than one year of age to determine the effects of Galsulfase treatment on the development of skeletal dysplasia. Patients would be randomized in a 1:1 fashion to one of two Galsulfase dose groups, 1.0 mg/kg or 2.0 mg/kg. Randomized patients would be followed for at least one year. The protocol will be submitted to FDA by July 30, 2005. Patient accrual will be completed by September 30, 2007, and a final study report will be submitted to FDA by January 15, 2009.

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70

11. To re-evaluate — in the manufacturing of Galsulfase formulated bulk drug substance produced at commercial scale and submit a report to FDA by December 31, 2007.

12. To re-evaluate the release specifications of Galsulfase formulated bulk drug substance produced at commercial scale and submit a report to FDA by December 31, 2007.

13. To re-evaluate the release specifications of Galsulfase drug product at commercial scale and submit a report to FDA by December 31, 2007.

14. To include — as a Galsulfase formulated bulk drug substance release test starting with lot P60501. The specification will be — — The revised formulated bulk drug substance specifications will be submitted to FDA by August 31, 2005.

15. To include a limit for — in the acceptance criteria for the — — release test for Galsulfase formulated bulk drug substance starting with lot P60501. A copy of the revised Standard Operating Procedure, along with a justification for the acceptance criteria will be submitted to FDA by August 31, 2005.

16. To include an action limit for — — release test for Galsulfase formulated bulk drug substance starting with lot P60501. A copy of the revised Standard Operating Procedure, along with a justification for the acceptance criteria will be submitted to FDA by August 31, 2005.

17. To include [redacted] as a drug product release test for Galsulfase starting with lot V60502. The specification will be comparable to reference material. The revised drug product specifications will be submitted to FDA by August 31, 2005.

18. To develop and implement a release test as an alternative to the [redacted] method to quantitatively monitor [redacted] of Galsulfase formulated bulk drug substance. A supplement to the BLA including the proposed release specification and justification, the Standard Operating Procedure and a validation report of the test method will be submitted to FDA by December 31, 2006.

19. To develop and implement an [redacted] assay using a more physiologically relevant substrate. BioMarin will evaluate the feasibility of using a substrate concentration near the K_M. Activity should be reported as activity units per total protein mass. A supplement to the BLA including the proposed release specification and justification, the Standard Operating Procedure and a validation report of the test method will be submitted to FDA by December 31, 2006.

20. To evaluate enhancements to the in vitro Uptake Assay, which include determination of V_{max} values and improved quantitation of intracellular rhASB. In addition, you will evaluate potential alternate methodologies. A report of the results will be submitted to FDA by September 30, 2006.

21. To conduct integrity testing of the formulated bulk drug substance storage bags. A report of the results will be submitted to FDA by December 31, 2005.

We request that you submit clinical protocols to your IND, with a cross-reference letter to BLA STN BL 125117. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to BLA STN BL 125117. 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 Division of Drug Marketing, Advertising and

Communication (HFD-42), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane/Room 8B45, Rockville, MD 20857. 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 October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Sincerely,

Karen D. Weiss, M.D.
Director
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

CONCURRENCE PAGE

COMMUNICATION TYPE:
LETTER: Approval (AP)
REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:
- Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).
- RIS DATA CHECK:
- VERIFY SHORT SUMMARY – LTR. & SUBMISSION SCREEN SHOULD MATCH.
- CHECK LETTER FOR PMCs (IF PMCs – ADD "PMCs – APPROVED WITH" SPECIAL CHARACTERISTIC CODE.)
- Ensure entry of Major Approval code.
- Perform Review Completion Process
- Milestone: Confirm Approved Status

cc: Attached label is sent to everyone
DRMP BLA file (hard copy)
HFD-106/K. Weiss
HFD-106/G. Jones
HFD-122/A. Rosenberg
HFD-122/B. Cherney
HFD-122/G. Johnson
HFD-122/S. Beaucage
HFD-122/R. Bernstein
HFD-122/E. Guan
HFD-108/M. Walton
HFD-108/E. Unger
HFD-108/J. Hyde
HFD-108/I. Irony
HFD-108/A. Pariser
HFD-108/M. Green
HFD-108/A. Rajpal
HFD-108/W. Gao
HFD-711/B. Zhen
HFD-711/J. Derr
HFD-328/J. Li
HFD-328/C. Renshaw
HFD-328/M. Smedley
HFD-109/K. Needleman
HFD-40/Office of Medical Policy/R. Temple
HFD-123/OBP Director/S. Kozlowski

HFD-020/ Immediate Office (hard copy)
HFD-005/Mike Jones
HFM-110/RIMS R. Eastep
HFD-020/John Jenkins
HFD-400/ODS M. Dempsey
HFD-006/Exec sec P. Guinn
HFD-013/FOI H. Brubaker
HFD-240/OTCOM/B. Poole
HFI-20/Press/ L. Gelb
HFI-20/Press/ J. Brodsky
HFD-230/OTCOM/CDER WebMaster
HFD-001/ B. Duvall-Miller
HFD-42/DDMAC M. Kiester
HFD-410/ODS/DSRCS/Karen Young
HFD-950/OCTAP/T. Crescenzi
HFD-960/OCTAP/G. Carmouze
HFD-320/DMPQ/ J. Famulare
HFD-322/IPCB/ E. Rivera-Martinez
HFD-107/ C. Lee
HFD-328/TFRB Blue File/Mike Smedley
HFD-410/CDER Medwatch Safety Labeling (hard copy)
HFD-430/ODS/DDRE (hard copy)
HFD-180/J. Korvick
HFD-105/B. Harvey

History: K. Needleman: 5.23.05/5.31.05

File Name: S:\Needleman\BLA\Galsulfase\BL125117_0_ap_doc

Division	Name/Signature	Date
DKMP	K Needleman	5/31/05
DRMP	Dye	5-31-05
DTBIMP	Klara Brown	5/31/05
DTBIMP	MD for MKW	5/31/2005
DRMP	Schneider	5-31-05
DTP	B. Ades	5-31-05
ODE VC		5-31-05
DRMP	Kelly Cavanaugh	6/1/05