DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Our STN: BLA 125117/86
BLA 125117/88
BLA 125117/90

SUPPLEMENT BLA APPROVAL
April 28, 2011

BioMarin Pharmaceutical, Inc.
Attention: Jeri Beltman, Ph.D.
Associate Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Dr. Beltman:

Please refer to your Supplemental Biologics License Applications (sBLA), dated June 25, 2010, July 16, 2010, and August 4, 2010 received June 28, 2010, July 16, 2010, and August 4, 2010, submitted under section 351 of the Public Health Service Act for Naglazyme (galsulfase).

We acknowledge receipt of your amendments dated August 27, 2010; September 16 and 17, 2010; October 4, 12 and 21, 2010; November 1, 19, and 24, 2010; December 10 and 13(2), 2010; January 25, 2011; and February 2, 2011.

These "Prior Approval" efficacy supplements to your biologics license application provide Physician Labeling Rule compliance and safety and efficacy data from clinical trials.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

FULFILLMENT OF POSTMARKETING COMMITMENTS

Your supplemental applications also addressed postmarketing commitment numbers 3, 4, 5, 6, 7, 8 and 10 identified in the May 31, 2005 approval letter for BLA 125117/0. The commitments addressed in this application are as follows:

PMC # 3	To develop and validate an improved screening assay for detecting total antibodies to galsulfase.
PMC #4	To develop and validate an improved immunogenicity assay for detecting neutralizing antibodies to galsulfase.

PMC #5 To develop and evaluate an improved immunogenicity assay for detecting IgE antibodies to galsulfase.

PMC #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.

PMC #7 To develop and validate an improved assay for detecting galsulfase in human plasma.

PMC #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.

PMC #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.

We have reviewed your submissions and conclude that postmarketing commitment numbers 3, 5, 6, and 10 are fulfilled.

We have reviewed your submissions and conclude that the terms of the commitment for postmarketing commitment number 4 and number 7 were not met.

1. PMC 4 is considered not fulfilled because a validated assay to detect neutralizing antibodies to galsulfase enzyme uptake has not been submitted for review. Additional data should be submitted for review that includes an improved immunogenicity assay for detecting neutralizing antibodies for enzyme uptake of galsulfase.

2. PMC 7 is considered not fulfilled because the galsulfase assay validation report included several deficiencies in the determination of precision, accuracy, specificity, selectivity, dilution linearity and robustness of the newly developed assay method. Additional data should be submitted for review that includes adequate validation of a new assay method with improved performance for the purpose of adequate pharmacokinetic characterization of galsulfase in patients.

Finally, we have determined that you are released from the above postmarketing commitment number 8 because the assay used to test plasma samples to evaluate galsulfase levels in human plasma was considered invalid and therefore, the data submitted to fulfill this commitment are

not reliable. A future study using the same human plasma samples could not be reasonably completed because the stability of these plasma samples is highly questionable.

In addition, we have the following comment:

> Your assay for the measurement of urinary glycosaminoglycan (uGAG) levels is considered unacceptable. This information and the major deviations in the assay validation reports were previously communicated to you in a Discipline Review Letter dated February 9, 2011. In the future, if you plan to seek additional efficacy or safety claims based on uGAG levels, the data submitted in support of such claims must be based on an appropriately validated uGAG assay.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. For administrative purposes, please designate this submission "**Product Correspondence – Final SPL for approved BLA STN 125117 86/88/90**."

Also within 14 days, amend all pending supplemental applications for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in MS Word format that includes the changes approved in this supplemental application.

The SPL will be accessible via publicly available labeling repositories.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Elizabeth Ford, Regulatory Project Manager, at (301) 796-0193.

Sincerely,

/ Andrew E. Mulberg /
Andrew E. Mulberg, M.D., FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling