DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125058/160
BL 125058/161

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

Dear Dr. Beltman:

Please refer to the supplements to your biologics license application, dated December 7, 2007, received December 10, 2007, for BL 125058/160 and dated December 10, 2007, received December 17, 2007, for BL 125058/161 submitted under section 351 of the Public Health Service Act for Aldurazyme (laronidase).

We acknowledge receipt of your amendments for BL 125058/160 dated January 31, February 8 and 13, March 21, April 25, May 7, June 10, July 11 and 15, August 15, and September 12, 2008, and February 3 and 10, April 17, and May 6, 2009. We also acknowledge receipt of your amendments for BL 125058/161 dated January 31, February 8 and 13, May 7, June 10, July 16 and 29, August 14, September 12, 2008, and February 5 and April 20, 2009.

These supplements propose to update the Adverse Reactions, Use in Specific Populations and Clinical Studies sections of the labeling with clinical data in patients less than 5 years old (STN BL 125058/160) and to update the Adverse Reactions and Clinical Studies sections of the labeling with clinical data from a 182 week, open label, uncontrolled study in 45 patients (STN BL 125058/161). Finally, these supplements update the labeling consistent with the new content and format requirements under part 201 (21 CFR 201.56(d) and 21 CFR 201.57). These supplements have been approved.

This fulfills your commitment to evaluate the treatment of patients younger than 6 years of age as stated in postmarketing study commitment (PMC) number 8 of the April 30, 2003, approval letter.

We acknowledge your written commitment to conduct the following studies and clinical trials which have been required under FDAAA and take certain other actions to which you have committed in your letter of May 6, 2009, and as outlined below.

POSTMARKETING REQUIREMENTS UNDER 505(0)

Section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Aldurazyme (laronidase) was approved on April 30, 2003, we have become aware of new cases of life-threatening anaphylaxis, including adverse event reports in pediatric patients with Mucopolysaccharidosis I (MPS I). The case reports were submitted by BioMarin. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(l) of the FDCA will not be sufficient to assess the known serious risk of allergic reactions, including anaphylaxis.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(0)(3) of the FDCA, to conduct the following studies:

1. BioMarin is required to 1) provide adequate pharmacokinetics data and 2) elucidate the correlation, if any exists, between pharmacokinetics and immunogenicity profiles, pharmacodynamic measurement (urinary glycosaminoglycans), and allergic reactions, in patients 6 years and younger.

   Final Report Submission: by September 30, 2010

2. BioMarin is required to reanalyze anti-Aldurazyme IgG levels using a validated end point titer assay and selected banked serum samples from the following: Study ALID-003-99 and the extension Study ALID-006-01, to allow integrated review of IgG levels among the different studies in the Aldurazyme clinical development program.

   Final Report Submission: by December 31, 2009

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this known serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trials:

3. BioMarin is required to conduct the following assessments using data from patients enrolled in the ongoing MPS I Registry. Immunogenicity will be studied using validated anti-

Aldurazyme IgG and IgE, and neutralizing assays. The relationship between the development of antibodies and development of spontaneous immune tolerance with changes in the following will be evaluated:

- α -L-iduronidase genotype
- endogenous α-L-iduronidase enzyme activity levels
- clinical phenotype
- allergic reactions
- functional assessments
- pharmacodynamic measurement (urinary glycosaminoglycans)

Interim analyses of the preceding assessments will be included in yearly updates submitted to IND 7,334, as part of the MPS I Registry annual report.

Protocol Submission: by December 31, 2009
Final Report Submission: by December 31, 2020

4. BioMarin is required to conduct a re-challenge trial to assess the ability to re-administer Aldurazyme to patients with suspected or confirmed Aldurazyme-related IgE mediated anaphylactic reactions. All patients will be requested to undergo skin testing and the results will be correlated with the incidence of recurrent anaphylaxis during Aldurazyme infusions. An analysis of the effectiveness of the desensitization guidelines for decreasing recurrent anaphylaxis will be performed annually for 5 years and will be submitted annually as a standalone section, clearly identifying this required trial, of your periodic safety update report submitted to your BLA, STN BL 125058.

Protocol Submission: by May 30, 2009
Final Report Submission: by June 30, 2014

5. BioMarin is required to complete the ongoing immune tolerance induction trial in treatment naïve MPS I patients under protocol ALID 02307. The trial will include assessments of pharmacodynamic response (urinary glycosaminoglycan reduction) and allergic reactions.

Final Report Submission: by May 30, 2014

6. Following completion of protocol ALID 02307, patients will be encouraged to enroll in the ongoing MPS I Registry. BioMarin is required to collect available mortality, immunogenicity, allergic reactions, and growth and development data on this subpopulation for the duration of the Registry to study the potential effects of immune tolerance induction on these outcomes. Interim reports of this trial will be submitted on a yearly basis, as part of the MPS I Registry annual report to IND 7,334.

Final Report Submission: by December 31, 2020

Submit the protocol to your IND 7,334, with a cross-reference letter to this biologics license application (BLA), STN BL 125058. Submit all final reports to your BLA, STN BL 125058.

Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing studies and clinical trials as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING STUDY COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 601.70

7. BioMarin commits to developing an assay to detect anti-Aldurazyme antibody mediated neutralization of enzyme uptake. Such an assay could be developed based on the current cell uptake assay already used for Aldurazyme lot release. BioMarin commits to developing this neutralization assay and submitting a completed validation report.

    Final Report Submission: October 30, 2009

We request that you submit clinical protocols to your IND 7,334, with a cross-reference letter to this BLA, STN BL 125058. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to your BLA, STN BL 125058. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Study Commitment Protocol**
- **Postmarketing Study Commitment - Final Study Report**
- **Postmarketing Study Correspondence**
- **Annual Status Report of Postmarketing Study Commitments**

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 February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/cder/guidance/5569fnl.htm**)** for further information.

Additionally, although your participation in FDA's Biomarker Qualification Program is not considered a postmarketing study commitment, we acknowledge your written commitment to submit urinary glycosaminoglycans data to the FDA Biomarker Qualification Review Team as described in your letter of May 6, 2009.

Within 14 days of the date of this letter, submit content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions "Product Correspondence – Final SPL for approved STN BL 125058/160 and STN BL 125058/161." In addition, within 14 days of the date of this letter, amend any pending supplement for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

Marketing the product with labeling that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this BLA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

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

This information will be included in your biologics license application file. If you have any questions, call Wes Ishihara, Regulatory Project Manager, at (301) 796-0069.

Sincerely,

Donna Griebel, M.D.
Director
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Package Insert