CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125460Orig1s000

Trade Name: Vimizim

Generic Name: Elosulfase Alfa

Sponsor: BioMarin Pharmaceutical, Inc.

Approval Date: February 14, 2014

Indications: a hydrolytic lysosomal glycosaminoglycan (GAG)-specific enzyme indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome)

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125460/0

BLA APPROVAL

BioMarin Pharmaceutical Inc.
Attention: Marjorie Tano, Director, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Ms. Tano:

Please refer to your Biologics License Application (BLA) dated March 29, 2013, received March 29, 2013, submitted under section 351(a) of the Public Health Service Act for Vimizim (elosulfase alfa).

We acknowledge receipt of your amendments received March 29, 2013, April 25, 2013, April 30, 2013, May 10, 2013, June 10, 2013, June 11, 2013, June 17, 2013, June 19, 2013, July 29, 2013, August 2, 2013, August 12, 2013, August 19, 2013, August 26, 2013, September 5, 2013, September 9, 2013, September 30, 2013, October 1, 2013, October 4, 2013, October 10, 2013, October 16, 2013, October 25, 2013, November 5, 2013, November 8, 2013, November 15, 2013, November 26, 2013, November 27, 2013, December 4, 2013, December 16, 2013, December 17, 2013, December 20, 2013, December 23, 2013, January 8, 2014, January 21, 2014, and February 12, 2014.

LICENSING

We have approved your BLA for Vimizim (elosulfase alfa) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Vimizim under your existing Department of Health and Human Services U.S. License No. 1649. Vimizim is indicated for patients with Mucopolysaccharidosis type IVA (MPS IVA; Morquio A syndrome).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Vimizim (elosulfase alfa) drug substance at BioMarin Pharmaceutical Inc., 46 Galli Drive, Novato Campus, Novato CA, USA. The final formulated product will be manufactured, filled, and packaged at (b) (4) (b) (4), as the primary site and at (b) (4) as the secondary site. You may label your product with the proprietary name Vimizim and market it in vials containing 5 ml of liquid product at 1 mg/ml.

DATING PERIOD

The dating period for Vimizim (elosulfase 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 (b) (4) of the formulated drug product. The dating period for your drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4) 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. The stability protocol in your license application is considered approved for the purpose of extending the expiration dating period of your drug product as specified in 21CFR 601.12.

FDA LOT RELEASE

You currently are not required to submit samples of future lots of Vimizim (elosulfase 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.

Any changes in the manufacturing, testing, packaging, or labeling of Vimizim, 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.

APPROVAL & LABELING

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

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 [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling text for the package insert. 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.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on October 10, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the

guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125460/0**." Approval of this submission by FDA is not required before the labeling is used.

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

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher has been assigned a tracking number, P RV BLA 125460. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - the estimated demand in the U.S. for the product, and
  - the actual amount of product distributed in the U.S.
- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf1 (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) 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.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to 1) identify an unexpected serious risk of anaphylaxis and hypersensitivity reactions associated with long term exposure to Vimizim (elosulfase alfa), 2) identify an unexpected serious risk of adverse maternal, neonatal or infant outcomes associated with Vimizim (elosulfase alfa) exposure during pregnancy, and 3) identify an unexpected serious risk of immune-mediated disorders associated with the development of anti-drug antibodies, including neutralizing antibodies, associated with long term exposure to Vimizim (elosulfase alfa).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

1 Evaluate the long-term safety of Vimizim in adult and pediatric patients enrolled in the Morquio A Registry for a period of ten years, including but not limited to the occurrence of serious hypersensitivity reactions, anaphylaxis, and changes in

antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies). Pregnancy exposure data, including maternal, neonatal and infant outcomes, will also be collected and analyzed. Include incidence rate calculations as part of long-term safety evaluation assessments to monitor and characterize risk of exposure to Vimizim. In addition, assessment of clinical outcomes (e.g., anthropometric measures, progression of skeletal deformities, frequency and time to orthopedic surgeries) will be performed. All safety, immunogenicity, and clinical outcome assessments will be conducted every 6 months. Patients previously enrolled in clinical trials MOR-005 and MOR-007 may be rolled over to this study but will be monitored using the MOR-005 and MOR-007 protocols, respectively.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2014
Final Protocol Submission (Updated Final Protocol for MOR-005)	12/2014
Final Protocol Submission (Updated Final Protocol for MOR-007)	03/2015
Interim Report Submission:	09/2017
Interim Report Submission (Report for MOR-007):	03/2018
Interim Report Submission:	09/2019
Interim Report Submission (Report for MOR-005):	03/2020
Study Completion:	09/2024
Final Report Submission:	03/2025

2 Develop and validate an assay to determine the titer of anti-elosulfase alfa neutralizing antibodies that inhibits binding to the mannose-6-phosphate receptor. The final report will contain a summary of the validation exercise including supporting data, a summary of the development data showing assay suitability for parameters not assessed in the validation exercise, and the assay Standard Operating Procedure (SOP). This assay will be used to assess anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in PMRs 1, 3, and 6.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2015

3 Analyze anti-elosulfase alfa neutralizing antibody titers in patient samples obtained in the completed MOR-004 trial.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 3/2016

4 Develop and validate an IgE assay suitable for detection of anti-elosulfase IgE antibodies in the presence of high titers of IgG. This assay will be used to assess for the presence of elosulfase alfa-specific IgE antibodies in patient samples obtained in PMRs 1, 5, and 6.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 3/2015

5 Analyze elosulfase alfa-specific IgE antibody titers in patient samples obtained in the completed MOR-004 trial.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 3/2016

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected risk of serious infection in patients receiving treatment with Vimizim (elosulfase alfa) and an immune tolerance regimen.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

6 Evaluate the occurrence of serious infections associated with administration of a prophylactic immune tolerance regimen in a cohort of Morquio A syndrome patients treated with Vimizim (elosulfase alfa) who are at high risk of developing persistent neutralizing antibodies. This immune tolerance regimen will be implemented before or concomitant with the onset of Vimizim (elosulfase alfa) therapy.

The timetable you submitted on February 12, 2014, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	09/2016
Trial Completion:	03/2020
Final Report Submission:	09/2020

Submit the protocols to your IND 101234, with a cross-reference letter to this BLA. Submit all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, 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 COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

7 Develop and implement, as a release and stability test method, a potency assay that measures the K_m and k_{cat} of elosulfase alfa formulated bulk drug substance (FBDS) and drug product (DP) using a physiologically relevant substrate.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Study Completion:	06/2015
Final Report Submission:	09/2015

8 Revise the RP-HPLC test method used for elosulfase alfa FBDS and DP release and stability testing in order to improve baseline resolution between (b) (4) peak. The revised specification together with the validation report will be submitted to your BLA in accordance with 21 CFR 601.12.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Study Completion:	06/2015
Final Report Submission:	09/2015

9 Demonstrate that SEC-HPLC is able to measure the true aggregate content, using an orthogonal test method and testing in a side by side analysis samples of Vimizim that have been subjected to forced degradation conditions.

The timetable you submitted on February 12, 2014, states that you will conduct this study

according to the following schedule:

Study Completion: 09/2014
Final Report Submission: 01/2015

10 Include parallel line analysis as an additional system suitability criterion for the cellular uptake assay.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Study Completion: 06/2014
Final Report Submission: 09/2014

11 Include quantitative system suitability criteria for retention time, number of peaks and relative peak heights in the peptide map assay.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Study Completion: 06/2014
Final Report Submission: 09/2014

12 Add cellular uptake as a release assay for drug product and establish an appropriate acceptance criterion when a statistically significant number of drug product lots is tested.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/2014

13 Conduct studies to understand the mechanism of low endotoxin recovery in the formulated bulk drug substance and drug product. These studies should investigate the endotoxin degradation or association pathway and determine whether or not depyrogenation is reversible (and if so, the conditions under which depyrogenation is reversible). Based on the results of these studies, modify the endotoxin release test and/or determine the suitability of alternative endotoxin test methods.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Study Completion: 03/2015
Final Report Submission: 09/2015

14 Provide summary data and the associated reports for the endotoxin recovery studies performed under protocols QC-1209-M and QC-1224-M.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/2014

15 Conduct an additional study comparing rabbit pyrogen and LAL test results. The study should include formulated bulk drug substance spiked with 20 EU/ml and 100 EU/ml endotoxin. The time points and controls should be the same as for the previous studies.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Study Completion: 11/2014
Final Report Submission: 01/2015

16 Provide results from protocol PVP-101037 (b) (4) to be executed during the 2014 manufacturing campaign.

The timetable you submitted on February 12, 2014, states that you will conduct this study according to the following schedule:

Study Completion: 03/2015
Final Report Submission: 06/2015

Submit clinical protocols to your IND 101234 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

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 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
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, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

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:

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

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

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 http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any

identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

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

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director (acting)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
02/14/2014