DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125151/152
BLA 125151/184

SUPPLEMENT APPROVAL
ACCELERATED APPROVAL
FULFILLMENT OF POSTMARKETING COMMITMENTS

Shire Human Genetic Therapies, Inc.
Attention: Janet C. Rae, RAC
Director, Regulatory Affairs
300 Shire Way
Lexington, MA 02421

Dear Ms. Rae:

Please refer to your Supplemental Biologics License Applications (sBLA), dated November 17, 2010 and September 21, 2012, received November 17, 2010 and September 24, 2012, submitted under section 351(a) of the Public Health Service Act for Elaprase (idursulfase).

We acknowledge receipt of your amendments received February 16, 2011, March 10, 2011, March 30, 2011, April 13, 2011, April 15, 2011, April 21, 2011, April 29, 2011, July 18, 2011, December 20, 2011, January 30, 2012, September 14, 2012, September 24, 2012, February 21, 2013, February 25, 2013, March 13, 2013, March 21, 2013, April 15, 2013, June 3, 2013, June 5, 2013, June 7, 2013, June 10, 2013, June 11, 2013, June 14, 2013, June 18, 2013, and June 20, 2013.

The September 24, 2012, submission to sBLA 125151/152 constituted a complete response to our September 15, 2011, action letter.

Prior Approval supplemental biologics application (sBLA) 125151/152 provides for additional safety and efficacy information to support changes to Section 2 Dosage and Administration, Section 6 Adverse Reactions (including sections 6.1 Clinical Trials Experience; 6.2 Immunogenicity; and 6.3 Postmarketing Experience), Section 12.3 Pharmacokinetics, and Section 14 Clinical Studies of the current product labeling, and to convert the product labeling to the Physician Labeling Rule (PLR) format.

Prior Approval sBLA 125151/184 provides for additional safety and efficacy information in patients 5 years of age and younger.

We have completed our review of these supplemental applications, 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 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.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes 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 these supplemental applications.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on June 14, 2013, as soon as they are available, but no more than 30 days after they are printed.

ACCELERATED APPROVAL REQUIREMENTS for sBLA 125151/184

Prior Approval sBLA 125151/184 is being approved under the accelerated approval regulations, 21 CFR 601.41. Products approved under the accelerated approval regulations require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies with due diligence. If postmarketing studies fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirements specified in your submission dated June 18, 2013. These requirements, along with required completion dates, are listed below.

These postmarketing clinical trials are subject to the reporting requirements of 21 CFR 601.70:

1. To conduct a verification trial to describe clinical benefit attributable to Elaprase (idursulfase) in a cohort of Hunter syndrome patients 5 years of age and younger.

At a minimum, this trial will assess longitudinal changes in anthropometric measures (i.e., length/height z-scores, annual growth velocity z-scores, weight z-scores) and the progression of skeletal deformities (i.e. joint stiffness, joint contractures) in children being treated with Elaprase (idursulfase). The growth parameters will be followed in these children for a minimum of 5 years from initiation of Elaprase (idursulfase) treatment or until they have reached at least 10 years of age, whichever is longer. The trials will monitor antibody response (binding, neutralizing, and IgE) at least every 6 months. Additionally, the trial will evaluate the relationship between development of immune tolerance and genetic mutations, endogenous enzyme activity level, and anthropometric measures. The trial may be conducted as a separate trial or as a sub-trial under a special protocol within the Hunter Outcome Survey.

Final Protocol Submission:	06/2014
Trial Completion:	03/2022
Final Report Submission:	09/2022

2. To evaluate a prophylactic immune tolerance regimen in a cohort of Hunter syndrome patients treated with Elaprase (idursulfase) who are at high risk of developing persistent neutralizing antibody that could result in diminished clinical benefit. This immune tolerance regimen will be implemented before or concomitant with onset of therapy. The trial will monitor antibody status (binding, neutralizing, and IgE), urinary GAG, and hypersensitivity reactions in patients at regular intervals. Additionally, the trial will evaluate the relationship between development of immune tolerance and genetic mutations, endogenous enzyme activity level, and clinical outcome. Completion of this PMR is pending the outcome of an Advisory Committee Meeting and completion of PMR 3.

Final Protocol Submission:	06/2017
Trial Completion:	03/2022
Final Report Submission:	09/2022

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing requirements must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

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.

FULFILLMENT OF POSTMARKETING COMMITMENTS

We have received your submissions dated September 27, 2007; October 1, 2008; December 31, 2008; November 17, 2010; September 24, 2012; and March 13, 2013, reporting on the following postmarketing commitments listed in the July 24, 2006 approval letter for BLA 125151/0.

125151/0-2 Shire commits to conducting a study to evaluate pharmacokinetics, pharmacodynamics, and safety in at least 18 children 5 years of age and under treated with ELAPRASE for at least 6 months. In this population, pharmacodynamics will include urinary GAG levels and changes in liver and spleen volumes. The study will assess routine developmental milestones and growth. The study will collect data on respiratory infections, surgical interventions (e.g., PE tubes and adenoidectomy), hearing loss, serious or severe infusion reactions, and other serious adverse events. The study may be conducted as a separate study or as a sub-study under a special protocol within the Hunter Outcome Survey. A study protocol will be submitted to FDA by November 30, 2006, for concurrence. The study will be initiated by March 31, 2007, enrollment will be completed by December 31, 2007, and a final study report will be submitted to FDA by June 30, 2009.

125151/0-5 Shire commits to test and provide data from study TKT024 and from the first 2 years of study TKT024EXT from patient samples that are positive in the screening assay, in the inhibition-of-entry neutralization assay. The information will be submitted to FDA by September 30, 2007.

125151/0-6 Shire commits to track binding and neutralizing antibodies using sensitive and validated assays over an extended time period to assess the loss of antibodies (immunologic tolerance) to Elaprase. Individual patient data should be provided as a function of time and a correlation of antibody status with clinical efficacy and GAG levels provided. This information will be submitted to FDA by December 31, 2008

125151/0-11 Shire commits to investigate and provide data on the nature of the genetic mutations in iduronate-2 sulfatase in a subset of patients in study TKT024,

entitled "A Phase II/III, Randomized, Double-Blind, Placebo-Controlled Clinical Study Evaluating the Safety and Efficacy of Weekly and Every Other Week Dosing Regimens of Iduronate-2-Sulfatase Enzyme Replacement Therapy in Patients with MPS II" and study TKT024EXT, entitled "An Open Label Extension study of TKT024 Evaluating Long-term Safety and Clinical Outcomes of MPS II Patients Receiving I2S Enzyme Replacement Therapy" and to correlate findings with the level of endogenous enzyme, the antibody response (binding, neutralizing and IgE), and clinical outcome. This information will be submitted to FDA by January 31, 2008.

We have reviewed your submissions and conclude that the above commitments were fulfilled.

POSTMARKETING REQUIREMENTS UNDER 505(o) for sBLA 125151/184

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.

Since Elaprase (idursulfase) was approved on July 24, 2006, we have become aware of literature reports of highly sustained antibody titers, increased hypersensitivity reactions, and poorer clinical outcomes in patients who are classified as cross-reactive immunologic material (CRIM) negative and treated with enzyme replacement therapy.[1,2,3] We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

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 assess the signal of a serious risk of hypersensitivity reactions, including anaphylaxis.

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 this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following for sBLA 125151/184:

3. To develop a validated cross-reactive immunologic material (CRIM) assay for patients with Hunter syndrome and test patient samples in a cohort of patients

[1] Wang J, et al. Neutralizing antibodies to therapeutic enzymes: considerations for testing, prevention and treatment. *Nat Biotechnol* 2008;26:901-8.

[2] Abbott M, et al. Atypical immunologic response in a patient with CRIM-negative Pompe disease. *Mol Genet Metab* 2011;104:583-86.

[3] Kishnani PR, et al. Cross-reactive immunologic material status affects treatment outcomes in Pompe disease infants. *Mol Genet Metab* 2010;99:26-33.

prior to Elaprase (idursulfase) treatment. Results will be correlated with antibody response (binding, neutralizing and IgE), genetic mutations, enzyme activity level, urinary GAG level, hypersensitivity reactions, and clinical outcome in patients who are receiving Elaprase (idursulfase) treatment. Patients with severe genetic mutations, such as complete deletions or large rearrangements, will be represented in the study. Banked patient samples from other clinical studies may be used.

The timetable you submitted on June 18, 2013 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2014
Study Completion:	06/2016
Final Report Submission:	01/2017

Submit the protocols to your IND 009579, 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.

PROMOTIONAL MATERIALS for sBLA 125151/184

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

All promotional materials for your drug product that include representations about your drug product must be promptly revised to make it consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 601.12(a)(4)]. The revisions to your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 601.12(a)(4) to the address above or by fax to 301-847-8444.

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,

{See appended electronic signature page}

Andrew E. Mulberg, M.D.
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