DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022458/S-003
NDA 022458/S-006

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT

Pfizer Inc.
Attention: Nhu Debi Tran, PharmD
Director, Worldwide Regulatory and Safety
500 Arcola Road
Collegeville, PA 19426

Dear Ms. Tran:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received October 31, 2013 and July 2, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Elelyso (taliglucerase alfa).

We acknowledge receipt of your amendments dated February 3 and 14, 2014; March 4 and 14, 2014; April 15, 2014; June 18, 2014; July 3 and 23, 2014; August 1, 5, 11(2), 13, 14(2), 18, 19(2) and 26, 2014.

Prior Approval supplemental 003 provides for the following changes: addition of efficacy, safety and pharmacokinetic data, including data on immunogenicity status, for pediatric patients treated with Elelyso (taliglucerase alfa).

Prior Approval supplemental 006 provides for the following change: update section 6.3 Postmarketing Experience to reflect the addition of text related to the occurrence of anaphylaxis-related events as a postmarketing event.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are 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 the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), 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), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(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 REQUIREMENT

1895-7 To complete the ongoing trial PB-06-005, entitled "A Multicenter, Double-blind, Randomized Safety and Efficacy Study of Two Dose Levels of Taliglucerase Alfa in Pediatric Subjects with Gaucher Disease." This trial will obtain safety and efficacy data in pediatric patients with Type 1 Gaucher disease, including data on allergic and immune-mediated reactions, and unexpected risks from antibody development. The trial was initiated in October 2010.

We have reviewed your submission and conclude that the above requirement was fulfilled.

We remind you that there are postmarketing requirements and postmarketing commitments listed in the May 1, 2012 approval letter that are still open.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 Elelyso (taliglucerase alfa) was approved on May 1, 2012, we have become aware of hypersensitivity reactions related to the development of anti-drug antibodies in pediatric patients treated with Elelyso (taliglucerase alfa) in clinical trials. However, neutralizing antibody response that interferes with cellular uptake was not assessed in clinical trials. 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 identify the unexpected serious risk of hypersensitivity reactions, including anaphylaxis, associated with the development of neutralizing antibodies.

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:

2767-1 Conduct an assessment of neutralizing anti-drug antibody (ADA) response in serum samples of pediatric patients from Study PB-06-006 using a validated assay (developed under PMR 1895-2) that is capable of sensitively detecting ADA responses that interfere with receptor-ligand binding relevant to cellular uptake. This assay will be used to analyze all archived ADA-positive samples available from pediatric patients who participated in Study PB-06-006. In addition, the impact of neutralizing ADA on safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of Elelyso (taliglucerase alfa) will be assessed.

The timetable you submitted on August 11, 2014 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2014
Study Completion:	10/2016
Final Report Submission:	03/2017

Submit the protocol to your IND 117006, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. 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 314.81(b)(2)(vii) 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 314.81(b)(2)(vii) 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 314.81(b)(2)(vii). 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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

2767-2 Evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of Elelyso (taliglucerase alfa) in at least 5 patients with body weight less than 15 kg; at least 5 patients with body weight 15-20 kg; and at least 5 patients with body weight 20-25 kg with Type 1 Gaucher disease dosed at 60 units/kg every other week. Steady state PK will be obtained in an open-label study. When applicable, PD measurements for children enrolled in the PK study may be obtained through the taliglucerase alfa registry (PMR 1895-5) and will include organ volumes (spleen and liver) as well as growth (height and weight). This trial will also collect safety data including any serious hypersensitivity reactions, such as anaphylaxis, as well as changes in antibody status (i.e., detection and titers of binding and neutralizing antibodies, and detection of IgE antibodies).

The timetable you submitted on August 14, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2015
Trial Completion:	06/2020
Final Report Submission:	12/2020

Submit clinical protocols to your IND 117006 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a

status summary of each commitment in your annual report to this NDA. 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 the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to

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

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. 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

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jessica Benjamin, Regulatory Project Manager, at (301) 796-3924.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., FAAP, CPI
Deputy Director
Division of Gastroenterology and Inborn Errors
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/

ANDREW E MULBERG
08/27/2014