DEPARTMENT OF HEALTH AND HUMAN SERVICES
OFFICE OF DIRECTOR

ACTION REFERRAL

TO	DATE
Giese	5/25/12

DIRECTOR'S USE ONLY	ACTION REQUESTED
1. LOG NUMBER 10-446	[ ] Prepare reply for the Director's signature DATE DUE _____
2. DATE SIGNED BY DIRECTOR _____	[ ] Prepare reply for appropriate signature DATE DUE _____ [ ] FOIA DATE DUE _____ [X] Necessary Action

APPROVALS (Only when prepared for director's signature)	APPROVE	* DISAPPROVE (Note reason for disapproval and return to preparer.)	COMMENT
1.			
2.			
3.			
4.			

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022458

NDA APPROVAL

Protalix Ltd.
c/o Target Health Inc.
261 Madison Avenue, 24th Floor
New York, NY 10016

Attention: Glen D. Park, Pharm.D.
Senior Director, Clinical/Regulatory Affairs

Dear Dr. Park:

Please refer to your New Drug Application (NDA) dated April 26, 2010, received April 26, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ELELYSO (taliglucerase alfa) for injection.

We acknowledge receipt of your amendments dated April 30, 2010; May 4, 2010; June 7(2), 11, 18, and 30, 2010; July 21, 2010; August 3 and 20, 2010; September 10 and 27, 2010; October 1, 2010; November 24 and 30, 2010; December 2, 3, 10, 20, 21, 23, 27 and 28, 2010; August 1 and 8, 2011; October 5 and 7, 2011; November 1 and 15(2), 2011; December 13, 2011; January 20 and 23, 2012; February 10, 2012; March 1, 22, and 28, 2012; and April 2, 11, 18, 19, 20, 25(2), and 27, 2012.

The August 1, 2011, submission constituted a complete response to our February 24, 2011, action letter.

This new drug application provides for the use of ELELYSO (taliglucerase alfa) for injection for use as a long-term enzyme replacement therapy in patients with Type 1 Gaucher disease.

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 agreed-upon labeling text and with the minor editorial revisions listed below for the carton and container.

1. Remove the statements, "Each vial contains taliglucerase alfa 212 units* (total amount)" and "*Extractable dose of 200 units" to comply with 21 CFR 201.51 and the U.S. Pharmacopeia 10/1/10-2/1/11, USP 33/NF 28. An overfill justification is provided in section 3.2.P.2.2.

2. Please revise the statement, "Each vial contains taliglucerase alfa 212 units* (total amount)" to "Each vial contains taliglucerase alfa 200 units".

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). 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 submitted carton and immediate container labels, except with the revisions listed above, 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 "**Final Printed Carton and Container Labels for approved NDA 022458**." Approval of this submission by FDA is not required before the labeling is used.

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

ADVISORY COMMITTEE

Your application for ELELYSO (taliglucerase alfa) for injection was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug in this class.

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 assess known serious risks of allergic and immune-mediated reactions or to identify unexpected serious risks related to the development of neutralizing anti-drug antibodies or plant-specific sugar antibodies and cellular uptake inhibition in adult and pediatric patients with Type 1 Gaucher disease treated with ELELYSO (taliglucerase alfa) for injection, or to identify unexpected serious adverse effects on 1) pregnancy outcomes, 2) fetal outcomes (teratogenicity), or 3) outcomes in newborns and infants exposed to ELELYSO (taliglucerase alfa) for injection and through breast-feeding.

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:

1895-1 To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to ELELYSO (taliglucerase alfa) for injection that is expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

The timetable you agreed to on April 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	09/2012
Study Completion:	03/2013
Final Report Submission:	07/2013

1895-2 To develop a validated, sensitive, and accurate assay for the assessment of cellular uptake inhibition by cell surface mannose receptors due to the presence of neutralizing antibodies to ELELYSO (taliglucerase alfa) for injection that is expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

The timetable you agreed to on April 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2012
Study Completion:	06/2013
Final Report Submission:	10/2013

1895-3 To develop a validated, sensitive, and accurate assay for the detection of antibodies to plant-specific sugars in ELELYSO (taliglucerase alfa) for injection that is expected to be present in the serum at the time of patient sampling. A summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay SOP will be provided to FDA.

The timetable you agreed to on April 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2012
Study Completion:	06/2013
Final Report Submission:	10/2013

1895-4 To conduct an assessment of neutralizing anti-drug antibody (ADA) response and presence of antibodies against plant-specific sugars in ELELYSO (taliglucerase alfa) for injection in patient plasma samples. Validated assays (developed under 1895-1, 1895-2 and 1895-3) capable of sensitively detecting neutralizing ADA responses and antibodies to plant-specific sugars that are expected to be present at the time of patient sampling will be used. The neutralizing ADA response, cellular uptake inhibition and the presence of plant-specific sugar antibodies will be evaluated in all archived sampling time points available from all patients in Phase 3 trials (PB-06-001, PB-06-002, PB-06-003, and PB-06-005). Analysis will evaluate immunogenicity rates and individual patient titers to assess the impact of neutralizing antibody levels, cellular uptake inhibition, and plant-specific sugar antibody levels on parameters of safety as well as on the pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of ELELYSO (taliglucerase alfa) for injection where data are available.

The timetable you agreed to on April 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	12/2012
Study Completion:	11/2013
Final Report Submission:	03/2014

1895-5 To evaluate the long-term safety and efficacy of ELELYSO (taliglucerase alfa) for injection in a registry of Gaucher disease patients being treated with ELELYSO (taliglucerase alfa) for injection. Detailed clinical status information will be collected at study entry and on an annual basis for 10 years. An interim report will be submitted after completion of the first 5 years of the study.

The timetable you agreed to on April 30, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2013
Interim Report Submission:	07/2019
Study Completion:	10/2023
Final Report Submission:	07/2024

1895-6 To evaluate the effect of ELELYSO (taliglucerase alfa) for injection on pregnancy and fetal outcomes, and to collect detailed clinical status information on newborns and infants whose mothers are treated with ELELYSO (taliglucerase alfa) for injection during lactation. This study may be completed as a sub-study within the registry (1895-5). An interim report will be submitted after completion of the first 5 years of the study.

The timetable you agreed to on April 30, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2013
Interim Report Submission:	06/2019
Study Completion:	10/2023
Final Report Submission:	07/2024

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess known serious risks of allergic and immune-mediated reactions or to identify unexpected serious risks related to the development of neutralizing anti-drug antibodies or plant-specific sugar antibodies and cellular uptake inhibition in adults and pediatric patients with Type 1 Gaucher disease treated with ELELYSO (taliglucerase alfa) for injection.

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

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.

The timetable you agreed to on April 26, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion:	06/2012
Final Report Submission:	09/2012

1895-8 To complete the ongoing trial PB-06-002, entitled "A Multicenter, Open-label, Switchover Trial to Assess the Safety and Efficacy of Taliglucerase alfa in Patients with Gaucher Disease Treated with Imiglucerase (Cerezyme®) Enzyme Replacement Therapy." This trial will obtain safety and efficacy data in adult and 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 the U.S. in April 2009.

The timetable you agreed to on April 26, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion:	03/2013
Final Report Submission:	06/2013

Submit the protocol(s) to your IND 069703, 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 OF SECTION 506B

We remind you of your postmarketing commitment:

1895-9 To provide a detailed analysis of the effectiveness and safety of ELELYSO (taliglucerase alfa) for injection for 36 months obtained in the clinical development program compared with data available for the same length of treatment for other approved enzyme replacement therapies (ERT) for Gaucher disease.

The timetable you agreed to on April 26, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2013

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B

We remind you of your postmarketing commitments:

1895-10 To revise the cellular uptake potency assay release and stability acceptance criteria after 15 lots of drug product have been manufactured.

The timetable you agreed to on April 26, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2015

1895-11 To revise Experion automated electrophoresis release and stability acceptance criteria after 15 lots of drug product have been manufactured.

The timetable you agreed to on April 26, 2012, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2015

1895-12 To evaluate and revise as appropriate the minimal percentage of specific uptake of reference standard as a system suitability criterion in the cellular uptake potency assay after at least 80 independent assay runs of release and stability testing of drug substance and drug product lots have been completed.

The timetable you agreed to on April 26, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	12/2013
Final Report Submission:	03/2014

1895-13 To perform a thorough biochemical characterization of the main and acidic peaks detected in the imaging capillary electrophoresis (iCE) assay and to evaluate the impact of this heterogeneity on product quality, including any effects on potency (specific uptake, enzyme kinetics, and cellular uptake). The characterization should use additional analytical assays (e.g., peptide mapping and thiol content) to confirm the identity of the characterized peaks. Perform an assessment regarding the suitability and the implementation of the iCE method and other analytical assays as appropriate in your stability protocol. The results of these studies should guide the revision of the release and stability specifications after at least 30 lots of drug substance and at least 15 lots of drug product have been manufactured.

The timetable you agreed to on April 26, 2012, states that you will conduct this study according to the following schedule:

Study Completion:	04/2015
Final Report Submission:	07/2015

Submit clinical protocols to your IND 069703 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study 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, 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 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, 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 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).

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-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action 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.

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

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELELYSO safely and effectively. See full prescribing information for ELELYSO.

ELELYSO (taliglucerase alfa) for injection, for intravenous use
Initial US Approval: 2012

INDICATIONS AND USAGE

ELELYSO™ (taliglucerase alfa) for injection is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for adults with a confirmed diagnosis of Type 1 Gaucher disease. (1)

DOSAGE AND ADMINISTRATION

- 60 Units/kg administered every other week as a 60-120 minute intravenous infusion (2.1)
- Patients currently being treated with imiglucerase for Gaucher disease can be switched to ELELYSO. Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with ELELYSO at that same dose when they switch from imiglucerase to ELELYSO (2.1).
- Physicians can make dosage adjustments based on achievement and maintenance of each patient's therapeutic goals. Clinical trials have evaluated doses ranging from 11 Units/kg to 73 Units/kg every other week (2).

DOSAGE FORMS AND STRENGTHS

- For injection: lyophilized powder for reconstitution with diluent (3).
- Available in 200 Unit single-use vials (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Anaphylaxis: Anaphylaxis has been observed in some patients treated with ELELYSO. If anaphylaxis occurs, immediately discontinue infusion and initiate appropriate treatment (5.1).

- Allergic and Infusion Reactions: The most commonly observed symptoms of infusion reactions (including allergic reactions) were headache, chest pain or discomfort, asthenia, fatigue, urticaria, erythema, increased blood pressure, back pain, arthralgia, and flushing. If allergic or infusion reactions occur, decreasing the infusion rate, temporarily stopping the infusion, or administering antihistamines and/or antipyretics is recommended (5.2).

ADVERSE REACTIONS

The most common adverse reactions during clinical studies were infusion reactions (6.1). Other commonly observed adverse reactions in ≥10% of patients were URTI/nasopharyngitis, pharyngitis/throat infection, headache, arthralgia, influenza/flu, UTI/pyelonephritis, back pain, extremity pain(6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at (1-800-438-1985) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: May 2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ELELYSO™ (taliglucerase alfa) for injection is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for adults with a confirmed diagnosis of Type 1 Gaucher disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose is 60 Units/kg of body weight administered once every 2 weeks as a 60-120 minute intravenous infusion.

Patients currently being treated with imiglucerase for Type 1 Gaucher disease can be switched to ELELYSO. Patients previously treated on a stable dose of imiglucerase are recommended to begin treatment with ELELYSO at that same dose when they switch from imiglucerase to ELELYSO.

Dosage adjustments can be made based on achievement and maintenance of each patient's therapeutic goals. Clinical studies have evaluated dose ranges from 11 Units/kg to 73 Units/kg every other week.

ELELYSO should be reconstituted with Sterile Water for Injection and diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 100mL to 200 mL, and delivered by intravenous infusion. The initial infusion rate should be 1.3 mL/min. After patient tolerability to the infusion rate is established, the rate of infusion may be increased to 2.3 mL/min. The total volume of the infusion solution should be delivered over a period of no less than 1 hour.

Each vial of ELELYSO provides 200 Units of taliglucerase alfa and is intended for single use only. Do not use the vial more than one time. The reconstitution and dilution steps must be completed using aseptic techniques. ELELYSO should be prepared using low-protein-binding containers and administered with a low-protein-binding infusion set equipped with an in-line, low-protein-binding 0.2 micrometer filter.

2.2 Instructions for Use

ELELYSO should be reconstituted, diluted, and administered under the supervision of a healthcare professional.

Prepare and use ELELYSO according to the following steps. Use aseptic technique.

a. Determine the number of vials to be reconstituted based on the patient's weight and the recommended dose of 60 Units/kg, using the following calculations (1-3):

   (1) Total dose in Units = Patient's weight (kg) x 60 Units/kg

   (2) Total number of vials = Total dose in Units divided by 200 Units/vial

   (3) Round up to the next whole vial.

b. Remove the required number of vials from the refrigerator. Do not leave these vials at room temperature longer than 24 hours prior to reconstitution. Do not heat or microwave these vials.

c. Reconstitute each vial of ELELYSO with 5.1 mL of Sterile Water for Injection to yield a reconstituted product volume of 5.3 mL and a withdrawal volume of 5 mL. Upon reconstitution, mix vials gently. DO NOT SHAKE. Prior to further dilution, visually inspect the solution in the vials; the solution should be clear and colorless. Do not use if the solution is discolored or if foreign particulate matter is present.

d. Withdraw 5 mL of reconstituted solution from each vial and dilute with 0.9% Sodium Chloride Injection, USP, to a final volume of 100 – 200 mL. Mix gently. DO NOT SHAKE. Since this is a protein solution, slight flocculation (described as translucent fibers) occurs occasionally after dilution.

As ELELYSO contains no preservative, the product should be used immediately once reconstituted. If immediate use is not possible, the reconstituted or the diluted product may be stored for up to 24 hours at 2 to 8°C (36 to 46°F). Do not freeze. Protect from light. Discard any unused product.

3 DOSAGE FORMS AND STRENGTHS

For injection: lyophilized powder for reconstitution; 200 Units/vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis

As with any intravenous protein product, severe allergic reactions are possible. Anaphylaxis has been reported in patients treated with ELELYSO *[see Adverse Reactions (6.1)]*. If anaphylaxis occurs, ELELYSO should be immediately discontinued, and appropriate medical treatment should be initiated.

In patients who have experienced anaphylaxis during infusion with ELELYSO, caution should be exercised upon rechallenge; appropriate medical support should be readily available *[see Adverse Reactions (6)]*.

5.2 Allergic and Infusion Reactions

Infusion reactions (including allergic reactions), defined as a reaction occurring within 24 hours of the infusion, were the most commonly observed reactions in patients (44%-46%) treated with ELELYSO in clinical studies *[see Adverse Reactions (6)]*. The most commonly observed symptoms of infusion reactions were headache (16%), chest pain or discomfort (6%), asthenia (7%), fatigue (5%), urticaria (7%), erythema (5%), increased blood pressure (5%), back pain and arthralgia (7%), and flushing (6%). Other infusion or allergic reactions reactions included, angioedema, wheezing, dyspnea, coughing, cyanosis, and hypotension. Most of these reactions were mild and did not require treatment intervention.

Base the management of infusion reactions on the type and severity of the reaction, e.g., slowing the infusion rate or treatment with medications such as antihistamines and antipyretics.

Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions in those cases where symptomatic treatment was required. Patients were not routinely pre-medicated prior to infusion of ELELYSO during clinical studies.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to ELELYSO in 60 patients ages 13 to 74 years who received ELELYSO at doses ranging from 11 to 73 Units/kg every two weeks in 3 clinical studies, and included 31 males and 29 females. Thirty-two patients were naïve to ERT (Study 1) and 28 were switched from imiglucerase to ELELYSO (Study 2) *[see Clinical Studies (14)]*. Study 3 includes patients continuing treatment from Study 1 and Study 2. Twenty-four patients were treated for longer than 2 years and 4 patients were treated longer than 3 years.

Important adverse reactions including anaphylaxis, allergic reactions, and infusion reactions are described elsewhere in the label *[see Warnings and Precautions (5.1)]*. One patient experienced a Type III immune-mediated skin reaction. The most common adverse reactions requiring interventions were infusion reactions *[see Warnings and Precautions (5.2)]*.

Table 2 is a listing of adverse reactions that occurred in 10% or greater of patients.

Table 2: Adverse Reactions that Occurred in ≥10% of Patients Treated with ELELYSO

	Study 1	Study 2
Preferred Term	**N=32**	**N=28**
Infusion reaction	14 (44%)	13 (46%)
URTI/Nasopharyngitis	7 (22%)	5 (18%)
Pharyngitis/Throat infection	6 (19%)	1 (4%)
Headache	6 (19%)	3 (11%)
Arthralgia	4 (13%)	3 (11%)
Influenza/Flu	4 (13%)	1 (4%)
UTI/Pyelonephritis	3 (9%)	3 (11%)
Back pain	1 (3%)	3 (11%)
Extremity pain	0	3 (11%)

The types and incidences of adverse reactions with up to 24 months of treatment in study 3 were similar to study 1 and study 2.

In addition to those listed in Table 2, less commonly reported adverse reactions (>2%) observed in clinical trials include fatigue, pain, pharyngolaryngeal pain, pruritus, diarrhea, dizziness, nausea, bone pain, abdominal pain, erythema, flushing, edema peripheral, muscle spasms, paresthesia, dyspnea, throat irritation, asthenia, chest discomfort, infusion site pain, alanine aminotransferase increased, musculoskeletal discomfort, musculoskeletal pain, insomnia, rash, and skin irritation.

6.2 Immunogenicity

As with all therapeutic proteins, patients have developed IgG anti-drug antibodies (ADA) to ELELYSO. In study 1, seventeen of 32 treatment naïve patients (17/32, 53%) who were administered ELELYSO every two weeks developed ADA post-treatment (defined as ADA positive at one or more post-treatment time points). Two additional patients were antibody positive at baseline; one patient withdrew after developing an allergic reaction with the first dose of ELELYSO and the second patient had increasing antibody titers with continued treatment. In study 2, four of 28 patients (4/28, 14%) switched from imiglucerase treatment to ELELYSO treatment once every two weeks developed ADA after the switch. One additional patient who switched from imiglucerase in Study 2 was positive at baseline but did not develop increased ADA titers after ELELYSO treatment. The relevance of ADA to therapeutic response and adverse events is currently unclear.

Using neutralizing antibody assays of limited sensitivity, two treatment naïve patients (at 24 months of ELELYSO treatment) and one patient switched from imiglucerase (at 9 months of ELELYSO treatment) were determined to be positive for neutralizing activity in an *in vitro* enzyme inhibition assay and were negative in a cell based assay. For these patients there was no demonstrated association between positive neutralizing antibody assay results and therapeutic response. The significance of these findings is unknown at this time.

It is unknown if the presence of ADA to taliglucerase alfa is associated with a higher risk of infusion reactions. Patients who develop infusion or immune reactions with ELELYSO treatment should be monitored for ADA to ELELYSO. Additionally, patients with an immune reaction to other enzyme replacement therapies who are switching to ELELYSO should be monitored for ADA to ELELYSO.

Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to ELELYSO with the incidence of antibodies to other products may be misleading.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category B:

Reproduction studies with taliglucerase alfa have been performed in pregnant rats at intravenous doses up to 55 mg/kg/day (about 5 times the recommended human dose of 60 Units/kg based on the body surface area) and in pregnant rabbits at intravenous doses up to 27.8 mg/kg/day (about 5 times the recommended human dose of 60 Units/kg based on the body surface area). These studies did not reveal any evidence of impaired fertility or harm to the fetus due to taliglucerase alfa. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ELELYSO should be used during pregnancy only if clearly needed. .

8.3 Nursing Mothers

There are no data from studies in lactating women. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ELELYSO is administered to a nursing woman.

8.4 Pediatric Use
The safety and effectiveness of ELELYSO in pediatric patients have not been established. One 8 year-old pediatric patient experienced a serious adverse reaction (gastroenteritis).

8.5 Geriatric Use
During clinical studies 8 patients aged 65 or older were treated with ELELYSO. Clinical studies of ELELYSO did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE
There is no experience with overdosage with ELELYSO.

11 DESCRIPTION

Taliglucerase alfa, a hydrolytic lysosomal glucocerebroside-specific enzyme for intravenous infusion, is a recombinant active form of the lysosomal enzyme, β-glucocerebrosidase, which is expressed in genetically modified carrot plant root cells cultured in a disposable bioreactor system (ProCellEx®). β-Glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase, E.C. 3.2.1.45) is a lysosomal glycoprotein enzyme that catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

ELELYSO is produced by recombinant DNA technology using plant cell culture (carrot). Purified taliglucerase alfa is a monomeric glycoprotein containing 4 N-linked glycosylation sites (Mr = 60,800). Taliglucerase alfa differs from native human glucocerebrosidase by two amino acids at the N terminal and up to 7 amino acids at the C terminal. Taliglucerase alfa is a glycosylated protein with oligosaccharide chains at the glycosylation sites having terminal mannose sugars. These mannose-terminated oligosaccharide chains of taliglucerase alfa are specifically recognized by endocytic carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease.

ELELYSO is supplied as a sterile, non-pyrogenic, lyophilized product. The quantitative composition of each 200 Unit vial is D-mannitol (206.7 mg), polysorbate 80 (0.56 mg), sodium citrate (30.4 mg), and taliglucerase alfa (212 Units). Citric acid may be added to adjust the pH at the time of manufacture.

A Unit is the amount of enzyme that catalyzes the hydrolysis of 1 micromole of the synthetic substrate *para*-nitrophenyl-β-D-glucopyranoside (*p*NP-Glc) per minute at 37°C. After reconstitution with Sterile Water for Injection the taliglucerase alfa concentration is 40 Units/mL *[see Dosage and Administration (2)]*. Reconstituted solutions have a pH of approximately 6.0.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
ELELYSO catalyzes the hydrolysis of glucocerebroside to glucose and ceramide. In clinical trials, ELELYSO reduced spleen and liver size, and improved anemia and thrombocytopenia.

12.3 Pharmacokinetics
In Gaucher disease patients treated with 30 or 60 units/kg (N=29), pharmacokinetics were determined with the first dose and at 38 weeks.

The pharmacokinetics of taliglucerase alfa appeared to be nonlinear with a greater than dose-proportional increase in exposure at the doses studied. The median systemic clearance (CL) values were approximately 30 L/hr and 20 L/hr for 30 and 60 units/kg, respectively. The median volume of distribution at steady state (Vss) ranged from 7.30 to 11.7 L for both dose groups. At the end of infusion, taliglucerase alfa serum concentrations fell rapidly with a median terminal half life of 18.9 to 28.7 minutes for both dose groups.

No significant accumulation or change in taliglucerase alfa pharmacokinetics over time from Weeks 1 to 38 was observed with repeated doses of 30 or 60 units/kg.

Based on the limited data, there were no significant pharmacokinetic differences between male and female patients in this study.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with taliglucerase alfa. In a male and female fertility study in rats, taliglucerase alfa did not cause any significant adverse effect on male or female fertility parameters up to a maximum dose of 55 mg/kg/day (about 5 times the recommended human dose of 60 Units/kg based on the body surface area).

14 CLINICAL STUDIES
14.1 Study 1: Trial of ELELYSO as Initial Therapy
The safety and efficacy of ELELYSO was assessed in 31 adult patients with Type 1 Gaucher disease. The trial was a 9-month multi-center, double blind, randomized study in patients with Gaucher disease-related enlarged spleens (>8 times normal) and thrombocytopenia (<120,000 /mm3). Sixteen patients had enlarged livers and ten patients had anemia at baseline. All patients were naïve to ERT. Patients with severe neurological symptoms were excluded from the study. Patient age ranged from 19-74 years (mean age 36 years) and 48% were male. Patients were randomized to receive ELELYSO at a dose of either 30 Units/kg (n=15) or 60 Units/kg (n=16).

At baseline, mean % body weight (%BW) and multiples of normal (MN) spleen volumes were 3.1 and 3.3 (%BW) and 15.4 and 16.7 (MN) for the 30 Units/kg and 60 Units/kg dose groups, respectively. Similarly, liver volumes were 4.2 and 3.8 (%BW) and 1.7 and 1.5 (MN). Hemoglobin concentrations were 12.2 and 11.4 g/dL and platelet counts were 75,320 and 65,038/mm3, for the 30 Units/kg and 60 Units/kg dose groups, respectively. For all studies, liver and spleen volumes were measured by MRI. The changes in clinical parameters after nine months of treatment are shown in Table 3. The observed change from baseline in the primary endpoint, spleen volume, was considered to be clinically meaningful in light of the natural history of untreated Gaucher disease.

Table 3: **Mean Change from Baseline to 9 months for Clinical Parameters in Treatment-Naïve Patients with Type 1 Gaucher Disease Initiating Therapy with ELELYSO**

Clinical Parameter		30 Units/kg (N=15)	60 Units/kg (N=16)

Change in Spleen Volume	%BW Mean (SD) MN Mean (SD)	-0.9 (0.4) -4.5 (2.1)	-1.3 (1.1) -6.6 (5.4)
Change in Hemoglobin g/dL	Mean (SD)	1.6 (1.4)	2.2 (1.4)
Change in Liver Volume	%BW Mean (SD) MN Mean (SD)	-0.6 (0.5) -0.2 (0.2)	-0.6 (0.4) -0.3 (0.2)
Change in Platelet Count / mm^3	Mean (SD)	11,427 (20,214)	41,494 (47,063)

Twenty-six previously treatment naïve patients continued to be treated with ELELYSO in an extension of this study (Study 3) in a blinded manner for a total treatment duration of 24 months. For the respective 30 and 60 Units/kg groups, mean (±SD) spleen volume (%BW) decreased -1.4 (±0.6) and -2.0 (±2.0); hemoglobin increased 1.3 (±1.7) g/dL and 2.4 (±2.3) g/dL; liver volume (%BW) decreased -1.1 (±0.5) and -1.0 (±0.7); and platelet count increased 28,433 (±31,996) /mm3 and 72,029 (±68,157)/mm3.

14.2 Study 2: Trial in Patients Switching from Imiglucerase to ELELYSO

The safety and efficacy of ELELYSO was assessed in 25patients with Type 1 Gaucher disease who were switched from imiglucerase to ELELYSO. The trial was a 9-month, multi-center, open-label, single arm study in patients who had been receiving treatment with imiglucerase at doses ranging from 11 Units/kg to 60 Units/kg for a minimum of 2 years. Patients also were required to be clinically stable and to have a stable biweekly dose of imiglucerase for at least 6 months prior to enrollment. Patient age ranged from 13-66 years (mean age 45 years including pediatric) and 46% were male. Imiglucerase therapy was stopped, and treatment with ELELYSO was administered every other week at the same number of units as each patient's previous imiglucerase dose. Adjustment of dosage was allowed by study criteria if needed in order to maintain clinical parameters (i.e., hemoglobin, platelet count, spleen volume, and liver volume). One patient required a dose increase (from 9.5 Units/kg to 19 Units/kg at week 24) for a platelet count of 92,000/mm^3 at week 22, and responded with a platelet count of 170,000mm^3 at month 9.

Organ volumes and hematologic values remained stable on average through 9 months of ELELYSO treatment. At baseline, spleen volume %BW was 1.1% and MN was 5.5; liver volume %BW was 2.4% and MN was 1.0; mean hemoglobin was 13.6 (± 1.57) g/dL; and mean platelet count was 160,447 (± 79,086) /mm3. At the nine month endpoint, spleen volume %BW was 1.0% and MN was 5.1; liver volume %BW was 2.3% and MN was 0.9; mean hemoglobin was 13.4 (± 1.6) g/dL and mean platelet count was 165,654 (± 94,038) /mm3.

16 HOW SUPPLIED/STORAGE AND HANDLING

ELELYSO™ is available as a lyophilized powder, 200 Units per vial (NDC 0069 0106 01).

Store ELELYSO at 2 to 8°C (36 to 46°F). Protect vials from light.

17 PATIENT COUNSELING INFORMATION

- Inform patients that ELELYSO is administered under the supervision of a healthcare professional as an intravenous infusion every other week. The infusion typically takes 60 to 120 minutes.
- Advise patients that ELELYSO may cause severe allergic reactions or infusion reactions. Patients should be counseled that they should be carefully re-evaluated for treatment with ELELYSO if serious allergic reactions occur. Patients should also be counseled that infusion reactions can usually be managed by slowing the infusion rate, treatment with medications such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with decreased infusion rate. Patients should also be counseled that pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions *[see Warnings and Precautions (5.1, 5.2)]*.
- Advise patients to report any adverse reactions while on ELELYSO treatment.

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Additional Info:	Colors: Black, PMS 300, PMS 3275, Cool Gray 11, Dieline, No Varnish	☐ EDITOR'S COPY GS: DATE:

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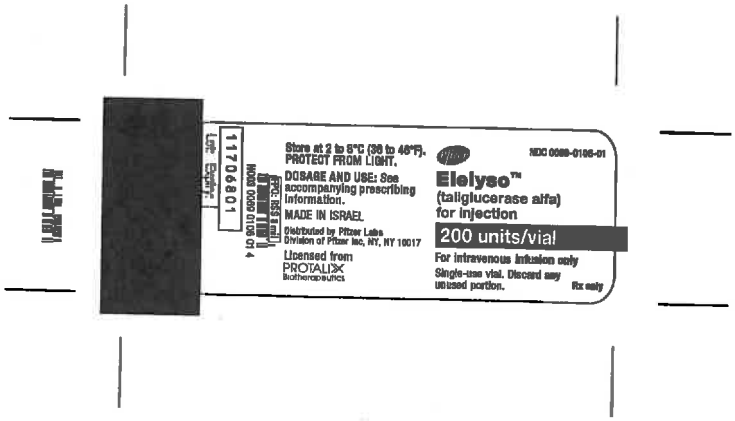
GS	B. Noel					
GA	J. Disch					



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Mgr	M. Wolpert	2		CHANGES OK	CHANGES OK	CHANGES OK
GS	B. Noel					
GA	J. Disch					

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/s/

JULIE G BEITZ
05/01/2012

Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755

88496

South Carolina
Tony Keck
Director
State of South Carolina, Department of Health & Human Services
1801 Main Street, PO Box 8206
Columbia, SC 29201-8206
Phone: (803) 898-2504
NAMD Region: III