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, (b) (4) 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, (b) (4) 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 [redacted] (b) (4) 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 [redacted] (b) (4)) 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

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

/s/

JULIE G BEITZ
05/01/2012