CENTER FOR DRUG EVALUATION AND RESEARCH

022458Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 022458

COMPLETE RESPONSE

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; and December 2, 3, 10, 20, 23 and 27, 2010.

We also acknowledge receipt of your amendments dated December 21 and 28, 2010, which were not reviewed for this action. You may incorporate applicable sections of these amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. The immunogenic potential of taliglucerase alfa and its impact on efficacy and safety cannot be adequately evaluated.

    a. Propose an acceptable cut-point for your confirmatory anti-product IgG antibody assay and submit a re-analysis of the impact of anti-product antibody development on the efficacy and safety of taliglucerase alfa.
    b. Develop an acceptable neutralizing antibody assay and submit a re-analysis of the impact of neutralizing antibody development on the efficacy and safety of taliglucerase alfa.

2. There are insufficient data provided to assess the efficacy and safety of taliglucerase alfa in patients switched from other enzyme replacement therapies. Submit the final study

report from PB-06-002, and a minimum of 12 months of efficacy and safety data from PB-06-003 for patients switched from other enzyme replacement therapies to taliglucerase alfa.

3. Longer-term safety data were insufficient to evaluate the chronic immune-mediated adverse events that are typically associated with enzyme replacement therapies, and Gaucher disease-specific bone events. Provide additional long-term safety data from PB-06-003.

CLINICAL PHARMACOLOGY

4. The immunogenic potential of taliglucerase alfa and its impact on pharmacokinetic and pharmacodynamic (PK and PD) parameters cannot be adequately evaluated.

    a. Propose an acceptable cut-point for your confirmatory anti-product IgG antibody assay and submit a re-analysis of the impact of anti-product antibody development on PK and PD parameters in patients treated with taliglucerase alfa.
    b. Develop an acceptable neutralizing antibody assay and submit a re-analysis of the impact of neutralizing antibody development on PK and PD parameters in patients treated with taliglucerase alfa.

PRODUCT QUALITY

Specifications and Assay Validation

5. Results of USP <788> particulate testing and appearance testing on reconstituted drug product have not been submitted to the NDA. Both tests provide a useful measure of product quality that is not monitored by other tests you have proposed. Add these tests to the release and stability specifications and provide available results for release and stability testing of the three conformance lots and any additional results you may have.

6. A potency assay that quantitatively measures specific receptor binding and/or high affinity internalization into cells is required since internalization is a critical component of taliglucerase alfa's mechanism of action and it is not fully assessed in your current potency assay. The assay should use multiple taliglucerase alfa concentrations to generate a complete dose-response curve in order to calculate the half-maximal effective concentration (EC_{50app}). Develop and implement this assay for use in release and stability testing.

7. Some SE-HPLC chromatographs (b) (4). Because this shoulder may reflect variability in a product-related variant, it should be identified and, if necessary, controlled. Characterize the protein (b) (4) and determine whether a control strategy that better monitors this product attribute(s) should be implemented. Provide the results of your analyses and any proposed changes to your specifications.

8. RP-HPLC chromatograms suggest that taliglucerase alfa variants are [(b) (4)] The risk to product quality is expected to vary depending on the nature of the variant. Thus, in order to establish an appropriate control strategy, you should identify and control for the quantity of these variants, if present. It may be useful to alter assay conditions or gradients to [(b) (4)]. Provide information on the presence of unresolved variants and, if present, provide a revised specification that more accurately quantitates and controls these variants together with supporting data.

9. Enzyme kinetic parameters and specific activity are measured using synthetic p-nitrophenyl-glucopyranoside (pNP-Glc) substrate. pNP-Glc [(b) (4)] Provide enzyme kinetic data to determine the enzyme kinetic parameters, Km and kcat, [(b) (4)] Include a detailed description of the assay, supporting assay qualification data, as well as a justification for why this test should not be added to the release and stability specifications.

10. Stability testing of diluted drug product in infusion bags did not include USP <788> particulate testing or information on the impact of dilution on subvisible particulates that are between [(b) (4)]. USP <788> testing results are critical to mitigate the risk associated with occlusion of small blood vessels and small subvisible particles may pose an immunogenicity risk. Provide USP <788> particulate testing data for in-use stability studies and an analysis of particulates between [(b) (4)].

11. The mannose content specification is based on a MALDI-TOF analysis of taliglucerase alfa. However, the property that is being measured in the MALDI-TOF analysis is mass to charge ratio, not mannose content. Thus, the acceptance criterion should be set around the mass to charge ratio and the mannose content acceptance criterion should be removed from the MALDI-TOF specification. Provide the new specification together with supporting data.

12. The acceptance criterion for moisture content in drug product is [(b) (4)] for both release and stability testing. Release and stability testing results consistently show moisture content to be below [(b) (4)] and no data were submitted indicating that a [(b) (4)] moisture content would not have an adverse impact on product stability throughout the product's dating period. Amend the moisture content acceptance criterion to reflect your manufacturing capability and consideration of any additional knowledge you may have concerning the impact of moisture on product stability and provide the new specification, if appropriate, together with supporting data.

13. Monosaccharide content and glycan structure analysis submitted in the characterization section of the NDA contained inconsistent results. Monosaccharide content analysis on two batches indicated that the [(b) (4)] whereas the glycan analysis data determined that [(b) (4)] of the glycan structures have a [(b) (4)] [(b) (4)]. Provide an explanation for these results or

submit data that identify the more accurate analysis using batches made [redacted]

14. The acceptance criteria for the enzyme kinetic parameters K_m and V_{max} are [redacted] respectively. An analysis of 40 drug substance batches resulted in mean and standard deviations for K_m and V_{max} equal to [redacted] µM/min, respectively. Consequently, the acceptance criteria appear too wide and should be amended to reflect process capability and clinical experience. Provide the revised specification for enzyme kinetic parameters or your justification as to why your proposal ensures reproducible product potency.

15. In a [redacted] vial drug product fill, the sampling plan calls for [redacted] to be collected for moisture content testing. [redacted] are tested and the mean value is reported on the certificate of analysis. Because the moisture content in an individual vial will vary within any given lot, the proposed sampling plan should provide a reasonable assessment of the variability of the results within a lot. While data from a robust validation study will provide a basis for establishing the sampling plan for the moisture specification, your current sample size and the mean value set as the reportable result are insufficient to assess the moisture content of the final drug product. Submit the revised specification for moisture content with these considerations in mind and provide a justification for your proposal.

16. Chromatograms for drug substance and drug product RP-HPLC analyses contain data from [redacted]. Perform the RP-HPLC analysis such that data from 0-10 and from [redacted] is included so that all potential impurities and contaminants can be detected and controlled if necessary. Provide chromatograms where all data are shown (0-80 minutes) on lots evaluated in the [redacted] comparability studies.

17. The isoelectric focusing (IEF) assay has acceptance criteria of [redacted] in a pI range of [redacted] reportedly because of assay variation. This level of assay variability is not consistent with the expected validation characteristics for this type of assay. Develop, implement and provide data on a validated IEF method in which the reference standard always produces the same number of bands in a consistent pI range. In addition, each gel should have a quantity of reference standard loaded near the limits of detection to verify the sensitivity of the analysis.

18. The [redacted] assay results are rounded off to the nearest integer which can mask significant differences in [redacted] between lots. Report all [redacted] assay results to two significant digits without rounding off to the nearest integer, revise the acceptance criterion accordingly and submit the revised specification.

19. [redacted]

(b) (4)

20. The peptide map specification calls for (b) (4) peptide peaks where a countable peak is defined as (b) (4). Justify the use of this acceptance criterion in light of the potential amounts of impurities and contaminants that would be acceptable, or revise the criteria for countable peaks. Also, include a revision of the acceptance criteria such that relative peak areas on several selected peptides are specified. Provide the new specification together with supporting data.

21. A host cell protein standard curve is used to determine the levels of host cell proteins in the drug substance. The data from the standard curve is fit to a four parameter logistic regression model even though the data do not reach a plateau and the fitted curve is not fully determined. However, there is a simple linear relationship between host cell protein and assay response. Provide a justification for the use of a four parameter logistic regression model or use a linear regression model to generate a host cell protein standard curve. Submit the revised specification along with the supporting analytical method validation data.

Comparability

22. The relative amounts of the individual glycans in the glycan profile shifted upon the (b) (4). Since the glycan structures are critical to taliglucerase alfa's mechanism of action, a change in the concentration of the glycan structures has the potential to adversely impact clinical performance. Using a potency assay that quantitatively measures specific receptor binding and/or high affinity internalization into cells (see previous comment), perform a head-to-head comparison of three drug substance lots of taliglucerase alfa manufactured (b) (4)

23. Results for SE-HPLC data provided in the NDA are reported as (b) (4) As (b) (4) may represent a different risk to product quality, they should be independently monitored and controlled. To support your revised acceptance criteria, provide all SE-HPLC data available to date in the application with (b) (4) reported separately. For comparison purposes, provide tabulated drug product stability SE-HPLC data separating drug product lots that were manufactured with drug substance made exclusively (b) (4)

24. Your SE-HPLC test method employed a UV detector. However, use of a light scattering detector may (b) (4) following SE-HPLC. This provides a much more sensitive qualitative method for monitoring this product attribute. Perform a head-to-head comparison of three drug

product lots manufactured exclusively from drug substance made [redacted] using light scatter detection and provide the results in your resubmission.

Process Validation

25. The time limits for individual manufacturing steps and for the complete manufacturing process are not clearly defined in the NDA. For example, strict limits for [redacted] Provide this information and relate it to the processes used to manufacture clinical study lot PB-06-001, commercial validation lots, and the genomic stability sequencing study.

26. Process validation reports indicate that vials containing drug product were put on only [redacted] lyophilizer shelves. Validation of the lyophilization process should include assessment of vials [redacted] to confirm consistency of the lyophilization process. Provide a revised validation protocol and report including the results for moisture content testing.

27. [redacted]

Control of Impurities

28. The testing to demonstrate that the master cell bank was free of plant specific viruses tabulated the results without providing data on the suitability of the PCR methods to detect viruses. In order to interpret the results you provided, the suitability of methods for their intended purpose needs to be assessed. Provide the assay qualification data and a description of the system suitability controls for each PCR method used to detect plant specific viruses.

29. The compound [redacted] is a component [redacted] and levels in drug substance or drug product were not determined. [redacted] may exhibit toxicity to humans [redacted] and is

therefore viewed as a [redacted] impurity that should be well controlled. Provide a control strategy to either include a limit on [redacted] to a level that will not impact product quality as it may relate to safety or efficacy, or validate that the [redacted] to an appropriate level.

30. [redacted] The label should accurately describe the final concentration of all excipients which should be confirmed at release. Provide the results on the [redacted] concentration for three drug product lots and provide your justification for not implementing the determination of [redacted] as a drug product release test.

IMMUNOGENICITY

31. The concentration of rabbit anti-taliglucerase alfa IgG antibodies [redacted] that you used for the positive control-1 (PC-1) for the anti-product IgG assay quality assessment (binding assay) was high. The agency recognizes that the limit of detection may be different due to affinity differences of the antibodies in the assay. However, in order to ensure reliable performance of the assay, a lower concentration for the positive control that will produce a signal close to the established cut-point of the assay should also be used. Confirm that your assay contains a low concentration positive control that can reproducibly produce a response closer to the established cut-point of your assay.

32. You set the cut-point at [redacted] for the immunodepletion assay to confirm the antibody status of patients. The agency recommends that the confirmatory cut-point be set based on assay precision. Re-establish the immunodepletion assay cut-point based on assay precision using serum from healthy human subjects and from treatment-naïve patients, if available.

33. In your drug tolerance study, you used control antibodies at a concentration of [redacted] to assess drug tolerance. Your assay is insufficient to address drug tolerance at low concentrations of anti-product antibodies. Repeat your drug tolerance study in the presence of low concentrations of control antibodies.

34. Develop appropriate quality controls in the neutralizing antibody assay and establish acceptance criteria based on these controls.

35. The specificity assessment should be designed to show that the drug product specifically binds to the antibodies induced by the product in human serum in the presence of exogenously added interfering molecules of similar size and charge (e.g., inclusion of IgG in IgE assay development).

36. We recognize that an alternative control for the anti-product IgE antibody assay may be required if a human positive control is not available, and that the detection limit may vary depending on antibody affinity. However, an estimation of assay sensitivity expressed in mass units is necessary to ensure assay suitability and performance for the intended

purpose. Determine assay sensitivity and report the results.

MICROBIOLOGY

37. With regard to the validation of [redacted], provide a bioburden data summary to justify this [redacted].

38. For the [redacted] Lyophilizer, provide summary data from three consecutive successful [redacted] runs with acceptable [redacted] results.

[redacted]

39. Provide validation summary reports for sterility and bacterial endotoxin test methods.

LABELING

40. We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
   - Present tabulations of the new safety data combined with the original NDA data.
   - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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

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
02/24/2011