

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**022458Orig1s000**

**SUMMARY REVIEW**

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 1, 2012

FROM: Julie Beitz, MD

SUBJECT: Office Director Memo

TO: NDA 022458 Elelyso (taliglucerase alfa) for injection  
Protalix Ltd.

**Summary**

Gaucher disease is the most common of the lysosomal storage diseases. An autosomal recessive inherited disorder, Gaucher disease results in a deficiency of the lysosomal enzyme glucocerebrosidase (GCB) and causes an accumulation of glucocerebroside within macrophages (Gaucher cells). This leads to multi-organ dysfunction involving the liver, spleen, and bone marrow. In a minority of patients, central nervous system (CNS) involvement leads to progressive neurological decline. Of the three clinical types of Gaucher disease, Type 1 accounts for more than 90% of all cases. The prevalence of Type 1 Gaucher disease is 1:40,000 to 60,000 in the general population and 1:500 to 800 among Ashkenazi Jews. Typical manifestations of Type 1 Gaucher disease which may range from mild to severe include hepatomegaly, splenomegaly, thrombocytopenia, bleeding tendencies, anemia, hypermetabolism, bone pain and fractures, growth retardation, and pulmonary disease. Type 1 disease does not involve the CNS.

Enzyme replacement therapy (ERT) designed to compensate for the underlying enzymatic defect has been the cornerstone of treatment for Gaucher disease. ERT has been shown to reduce organomegaly and improve hematological parameters. Although there is some evidence that ERT improves the bone-related complications of Gaucher disease, longstanding osseous complications of Gaucher disease may remain refractory to ERT. Since ERT has not been shown to pass the blood brain barrier, it has limited effects on CNS manifestations.

ERT has been commercially available since 1991 with the approval of Genzyme Corporation's Ceredase (alglucerase), a placentally-derived GCB. This product was eventually replaced by Genzyme's recombinant product, Cerezyme (imiglucerase), approved in 1994. Shire Human Genetics Therapies' VPRIV (velaglucerase alfa) is a GCB produced by gene activation technology in a human fibroblast cell line; it differs from imiglucerase by one amino acid, and has an identical amino acid sequence to alglucerase. VPRIV was approved on February 26, 2010.

The subject of this NDA, Elelyso (taliglucerase alfa), is a hydrolytic lysosomal glucocerebroside-specific enzyme expressed in genetically modified carrot plant root cells in a disposable bioreactor system. Its amino acid sequence differs from that of human GCB by two and seven amino acids at the N- and C-terminals, respectively. This memo documents my concurrence with the Division of Gastroenterology and Inborn Error Products' (DGIEP's) approval recommendation for Elelyso (taliglucerase alfa) for the treatment of adults with Type 1 Gaucher disease.

**Dosing**

Taliglucerase alfa is available as a lyophilized powder (in 200 Unit single-use vials) to be reconstituted and diluted for infusion. The recommended dose of taliglucerase alfa is 60 Units/kg administered as a 1-2 hour intravenous infusion every other week. Dosage adjustments can be made based on achievement and maintenance of each patient's therapeutic goals. Patients currently treated with imiglucerase for Gaucher

disease can be switched to taliglucerase alfa; patients previously receiving a stable dose of imiglucerase may begin treatment with taliglucerase alfa at the same dose.

### **Regulatory History**

Protalix Ltd. submitted IND 069703 on June 15, 2005, received on June 16, 2005, for plant cell expressed recombinant human glucocerebrosidase (taliglucerase alfa). On March 28, 2007, the sponsor submitted a special protocol assessment request for Trial PB-06-001, a proposed phase 3 clinical trial evaluating two doses of taliglucerase alfa in adult patients with Gaucher disease. In a written response dated May 11, 2007, DGIEP requested clarification regarding the proposed method of analyzing MRI images to assess liver and spleen volumes. In a subsequent written response dated August 22, 2007, DGIEP indicated that the applicant's proposal to expand clinical development of taliglucerase alfa to pediatric patients and to patients switched from imiglucerase was acceptable. Further discussion of the evaluation of MRI images and the sponsor's proposed statistical analysis plan for PB-06-001 occurred during a Type C meeting held on April 14, 2008. Additional comments regarding MRI evaluations were provided at the pre-NDA meeting held on May 21, 2009.

A treatment protocol (PB-06-004) was submitted and allowed to proceed on August 14, 2009 that provided U.S. patients with Gaucher disease access to ERT at a time when supplies of imiglucerase were compromised by manufacturing problems. On August 24, 2009, a Fast Track designation was granted for the investigation of taliglucerase alfa for the treatment of Type 1 Gaucher disease. Taliglucerase alfa received orphan designation for the treatment of Type 1 Gaucher disease on September 3, 2009.

NDA 022458 was submitted on April 26, 2010 and granted a standard review. A Complete Response letter was issued on February 24, 2011, citing deficiencies involving 1) clinical, 2) clinical pharmacology, 3) immunogenicity, 4) product quality, and 5) microbiology issues. Discussions regarding the product label were deferred to the next review cycle.

A Class 2 resubmission dated July 31, 2011 was received on August 1, 2011. A solicited major amendment received on November 15, 2011 extended the review clock to May 1, 2012. The application was not discussed before an FDA advisory committee because it did not raise significant safety or efficacy issues that were unexpected for a drug in this class.

All previously identified approvability issues have been adequately addressed by the NDA applicant. Negotiations regarding labeling, and postmarketing requirements and commitments have been satisfactorily concluded. There are no deficiencies related to the inspection of manufacturing facilities that preclude approval.

### **Product Quality Considerations**

While use of a carrot root cell expression system has the advantage that growth media is devoid of serum or any other mammalian-derived products, several deficiencies involving product quality were identified during the first review cycle that precluded approval. In the complete response, the applicant satisfactorily addressed deficiencies relating to: 1) particulate testing and appearance testing on reconstituted drug product; 2) the stability of drug product lots that are manufactured from drug substance (b) (4), 3) the need for a potency assay that quantitatively measures specific receptor binding and/or high affinity internalization into cells, 4) the need for head-to-head comparisons of three drug substance lots (b) (4) of taliglucerase alfa, and 5) the need for process validation with drug product vials placed on (b) (4) to confirm consistency of the lyophilization process.

At this time there are no product quality issues that preclude approval of taliglucerase alfa, however, the applicant has agreed to the following post-approval commitments: 1) to revise the cellular uptake potency assay release and stability acceptance criteria, 2) to revise Experion automated electrophoresis release and stability acceptance criteria, 3) 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, and 4) to perform biochemical characterization of the (b) (4) detected in the imaging capillary electrophoresis assay, and evaluate the impact of this heterogeneity on product quality.

### **Microbiology**

In the complete response, the applicant satisfactorily addressed the identified deficiencies by providing information 1) regarding bioburden, to justify the hold time between the (b) (4); and 2) to demonstrate successful sterilization of the lyophilizer. At this time, there are no microbiology deficiencies that preclude approval.

### **Clinical Pharmacology Considerations**

Pharmacokinetic (PK) assessments were performed in Trial PB-06-001 at Day 1 and Week 38 (Month 9) in 31 treatment-naïve patients with Gaucher disease receiving either 30 Units/kg or 60 Units/kg every other week. The median  $C_{max}$  and area under the concentration-time curve ( $AUC_{last}$  or  $AUC_{\infty}$ ) of taliglucerase alfa were approximately 3-fold higher in patients receiving 60 Units/kg compared to patients receiving 30 Units/kg, which is greater than the expected 2-fold increase assuming dose proportionality. Thus, the PK of taliglucerase alfa appears to be nonlinear with a greater than dose-proportional increase in exposure at the doses studied.

No drug-drug interaction trials have been performed. The effects of age, gender, or presence of hepatic or renal impairment on the pharmacokinetics of taliglucerase alfa have not been studied. A thorough QT trial was not performed.

### **Efficacy**

The efficacy of taliglucerase alfa was assessed in 31 adult patients with treatment-naïve Type 1 Gaucher disease (PB-06-001), and in 25 Gaucher disease patients previously treated with imiglucerase who received open label taliglucerase alfa for 9 months (PB-06-002).

**Treatment-naïve Type 1 Gaucher disease.** Trial PB-06-001 was a 9-month, randomized, double-blind, controlled trial in 32 treatment-naïve patients. Enrollees were required to have Gaucher disease-related splenomegaly ( $>8$  times normal by MRI) and thrombocytopenia (platelet count  $<120,000/mm^3$ ). Patients were randomized to receive taliglucerase alfa at a dose of either 30 Units/kg or 60 Units/kg every other week. Thirty-one patients aged 19 to 74 years (mean age 36 years) were evaluable for efficacy. After nine months of therapy, patients in both dose groups showed a decrease from baseline in mean spleen volume (the primary efficacy endpoint): a 29% decrease among 15 patients receiving 30 Units/kg and a 40% decrease among 16 patients receiving 60 Units/kg. These changes are considered to be clinically meaningful in light of the natural history of untreated Gaucher disease.<sup>1</sup> Both dose groups also demonstrated reductions in liver volume, and improvements in hemoglobin levels and platelet counts.

Twenty-six patients previously enrolled in Trial PB-06-001 continued treatment with taliglucerase alfa in a blinded fashion in an extension trial, PB-06-003 (12 patients on 30 Units/kg and 14 patients on 60 Units/kg). At 24 months, continued modest reductions were noted in spleen and liver volume, and hemoglobin levels and platelet counts stabilized or improved. In general, the greatest improvements in clinical and laboratory parameters were noted in patients dosed at 60 Units/kg who were negative for anti-taliglucerase alfa antibodies.

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<sup>1</sup> In written correspondence to Protalix Ltd. dated August 22, 2007, the Division stated that a 20% mean improvement in spleen volume from baseline would represent a clinically relevant improvement. Spleen volumes were reported as mean multiples of normal (MN) volume. In Trial PB-06-001, the mean MN volume at baseline was 15.4 and 16.7 in the 30 Units/kg and 60 Units/kg groups, respectively; after nine months of taliglucerase alfa treatment, the mean MN volume was reduced to 10.9 and 10.1 in the two groups, respectively.

**Treatment of patients switching from imiglucerase to taliglucerase alfa.** Trial PB-06-002 was a 9-month, open-label, single arm trial in 28 patients who had been receiving treatment with imiglucerase at doses ranging from 11 to 60 Units/kg for a minimum of two years. Enrolled patients were required to have stable disease on imiglucerase for at least six months. Imiglucerase treatment was stopped and taliglucerase alfa initiated at the same dose every two weeks. Interim results from 25 evaluable patients enrolled on this trial demonstrate that spleen and liver volumes, hemoglobin levels and platelet counts remained stable through 9 months of treatment with taliglucerase alfa. The mean age of enrollees was 45 years (range 13-66 years, including two pediatric patients).

Eighteen patients previously enrolled in Trial PB-06-002 continued taliglucerase alfa treatment in the extension trial (PB-06-003) and received doses ranging from 11 to 60 Units/kg. At 24 months, there was only limited information available on patients who rolled over from Trial PB-06-002.

### **Safety**

The safety of taliglucerase alfa was assessed in 121 patients with Type 1 Gaucher disease who were dosed at 11 to 73 Units/kg every other week in clinical trials. As of the cut-off date (May 1, 2011), safety information was available on 32 patients in Trial PB-06-001, on 28 patients in Trial PB-06-002, on 50 patients in the applicant's treatment protocol, PB-06-004, and on 11 patients in the applicant's dedicated pediatric trial, PB-06-005. Safety information was also available for 44 patients who rolled over from Trials PB-06-001 and PB-06-002 into the extension trial, PB-06-003. Of the 121 patients, 59 have received taliglucerase alfa treatment for 12 months.

As with any intravenous protein product, severe allergic reactions are possible. Anaphylaxis was reported in three of 32 (9%) treatment-naïve patients treated with taliglucerase alfa on Trial PB-06-001. Three additional patients developed anaphylaxis: one on the extension trial, PB-06-003, and two on the treatment protocol, PB-06-004. The *Warnings and Precautions* section of the product label will recommend that if anaphylaxis occurs, taliglucerase alfa should be immediately discontinued and appropriate medical treatment initiated. In patients who have experienced anaphylaxis during infusion with taliglucerase alfa or with other enzyme replacement therapy, caution should be exercised upon retreatment; appropriate medical support should be readily available.

Infusion reactions (including allergic reactions) occurring within 24 hours of the infusion were the most commonly reported reactions in patients treated with taliglucerase alfa in clinical trials. These reactions were reported in nearly half of patients and most were mild and did not require intervention. The *Warnings and Precautions* section of the product label will recommend that such reactions may be managed by decreasing the infusion rate, or administering antihistamines and antipyretics, depending upon the type and severity of the reaction.

### **Immunogenicity**

In the complete response, the applicant satisfactorily addressed the identified immunogenicity deficiencies and made further enhancements to the IgG anti-taliglucerase alfa antibody assay. Using new cut-points, the incidence of IgG anti-taliglucerase alfa antibodies in Trial PB-06-001 was 53% (17/32) in treatment naïve patients; the incidence was higher in patients dosed with 60 Units/kg than in patients dosed with 30 Units/kg. Two additional patients were antibody positive at baseline; one patient withdrew after developing an allergic reaction with the first dose of taliglucerase alfa and the second patient had increasing antibody titers with continued treatment. In the switch-over trial, PB-06-002, 14% (4/28) of patients who switched to taliglucerase alfa from imiglucerase developed anti-taliglucerase alfa antibodies. One additional patient who switched from imiglucerase was antibody positive at baseline but did not develop increased titers after initiating taliglucerase alfa treatment.

Assessment of differences in taliglucerase alfa PK, PD, efficacy or safety parameters in patients developing anti-taliglucerase alfa antibodies compared to those who do not cannot be completed at this time. Product labeling will recommend that patients who develop infusion or immune reactions with taliglucerase alfa be monitored for anti-taliglucerase alfa antibodies. Additionally, patients with an immune reaction to other

enzyme replacement therapies who are switching to taliglucerase alfa should be monitored for anti-taliglucerase alfa antibodies.

Although there are no immunogenicity deficiencies that preclude approval, two concerns will need to be addressed post-approval. First, the applicant's assays for neutralizing antibodies to enzyme activity and cellular uptake are not sufficiently sensitive. Second, antibodies to plant-specific sugars found on taliglucerase alfa were detected in healthy subjects who were naïve to drug. The applicant will be required to develop validated, sensitive and accurate assays for neutralizing anti-drug antibodies and antibodies to plant-specific sugars. Once validated assays are developed, the applicant will be required to assess neutralizing anti-drug antibody levels, cellular uptake inhibition by cell surface mannose receptors (due to the presence of neutralizing anti-drug antibodies), and plant-specific sugar antibody levels in archived samples from patients enrolled in phase 3 trials (i.e., PB-06-001, PB-06-002, PB-06-003, and the ongoing pediatric trial, PB-06-005). These studies will allow further assessment of the impact of immunogenicity rates and patient titers on taliglucerase alfa PK, PD, efficacy and safety parameters.

### **Pediatric Considerations**

**Pediatric Use.** The safety and effectiveness of taliglucerase alfa have not yet been established. The applicant will be required to complete the ongoing pediatric clinical trial, PB-06-005, evaluating two dose levels of taliglucerase alfa in accordance with Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA). This is a 12-month randomized, double-blind, parallel-dose group trial in treatment-naïve pediatric patients. As of the May 1, 2011 cut-off date, eleven patients (ages 2 to 14 years) have been randomized to receive treatment with either 30 Units/kg or 60 Units/kg of taliglucerase alfa. Follow-up of patients will extend up to 5 years on treatment. Assessment of immunogenicity status, including development of neutralizing anti-drug antibodies, will be performed.

**Required Pediatric Assessments.** Because taliglucerase alfa for this indication has an orphan drug designation, Protalix Ltd. is exempt from conducting required pediatric studies under the Pediatric Research Equity Act (21 U.S.C. 355c).

### **Tradename Review**

The Division of Medication Error Prevention and Analysis (DMEPA), in consultation with the Office of Prescription Drug Products (formerly the Division of Drug Marketing, Advertising, and Communications), has concluded that the applicant's proposed tradename "Elelyso" is acceptable. In a letter dated February 1, 2011, Protalix Ltd. was notified that the proposed tradename was acceptable but that it will be re-reviewed 90 days prior to the approval of the NDA. Re-evaluation of the proposed name "Elelyso" did not identify any vulnerabilities that would result in medication errors with other names.

### **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.

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, or unexpected serious adverse effects on 1) pregnancy outcomes, 2) fetal outcomes (teratogenicity), or 3) outcomes in newborns and infants exposed to Elelyso 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, the applicant will be required:

1. To develop a validated, sensitive, and accurate assay for the detection of neutralizing antibodies to Elelyso 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.
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 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.
3. To develop a validated, sensitive, and accurate assay for the detection of antibodies to plant-specific sugars in Elelyso 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.
4. To conduct an assessment of neutralizing anti-drug antibody (ADA) response and presence of antibodies against plant-specific sugars in Elelyso in patient plasma samples. Validated assays (developed under PMR 1, PMR 2 and PMR 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, pharmacodynamics, and efficacy of Elelyso where data are available.
5. To evaluate the long-term safety and efficacy of Elelyso in a registry of Gaucher disease patients being treated with Elelyso. Detailed clinical status information will be collected at study entry and on an annual basis for at least 10 years. An interim report will be submitted after completion of the first 5 years of the study.
6. To evaluate the effect of Elelyso on pregnancy and fetal outcomes, and to collect detailed clinical status information on newborns and infants whose mothers are treated with Elelyso during lactation. This study may be completed as a sub-study within the registry (see PMR 5). An interim report will be submitted after completion of the first 5 years of the study.

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 in adult and pediatric patients with type 1 Gaucher disease treated with Elelyso.

Therefore, based on appropriate scientific data, the applicant will be required:

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.

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.

Although not a postmarketing requirement under Section 505(o)(3), the applicant has also agreed to submit a detailed analysis of available effectiveness and safety information for taliglucerase alfa through 36 months of treatment compared with information available for other approved enzyme replacement therapies for Gaucher disease.

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JULIE G BEITZ  
05/01/2012