PRODUCT MONOGRAPH

[Pr]ELELYSO®

Taliglucerase alfa for injection
(recombinant human glucocerebrosidase analogue)

Lyophilized Powder
200 units / vial

Enzyme Replacement Therapy

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, Qc
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[Pr] ELELYSO®

Taliglucerase alfa for injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion (IV)	Lyophilized powder for reconstitution and intravenous infusion 200 units	There are no clinically relevant non medicinal ingredients. For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.

ELELYSO is dosed by units. An enzyme unit is defined as the amount of enzyme that catalyses the hydrolysis of one micromole of the synthetic substrate para-nitrophenol-β-D-glucopyranoside (pNP-Glc) per minute at 37ºC.

DESCRIPTION

Taliglucerase alfa is a recombinant form of human glucocerebrosidase, expressed in genetically modified carrot cells, which catalyzes the degradation of the glycolipid glucocerebrosides and reduces its accumulation in organs and tissues.

INDICATIONS AND CLINICAL USE

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

ELELYSO may also be used in pediatric patients with a confirmed diagnosis of Type 1 Gaucher disease, and for the haematological manifestations in pediatric patients with a confirmed diagnosis of Type 3 Gaucher disease. Clinical data in pediatric patients, ages 2 to 17, is limited (see CLINICAL TRIALS).

CONTRAINDICATIONS

Patients who have severe allergic reactions to taliglucerase alfa or any of the excipients in the

formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph (See WARNINGS and PRECAUTIONS).

WARNINGS AND PRECAUTIONS

General

Treatment with ELELYSO should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the active ingredient, excipients or to other glucocerebrosidase enzymes (See Immune heading below and ADVERSE REACTIONS).

As dizziness has been reported in clinical trials with taliglucerase alfa, patients should be aware of how they react to ELELYSO before driving or operating machinery (See ADVERSE REACTION).

Excipients

This medicinal product contains sodium citrate and is administered in sodium chloride (0.9%) solution for injection. This should be taken into consideration when administering to patients on a controlled sodium diet.

Immune

Antibody response

As with all therapeutic proteins, some patients have developed anti-drug antibodies (ADA) to taliglucerase alfa in the clinical studies with Gaucher disease subjects. The relevance of anti-taliglucerase alfa antibodies to adverse events is currently unclear given the small number of patients thus far evaluated in the clinical program. However, an analysis for the presence of anti-taliglucerase antibodies with adverse events that might be related to hypersensitivity (acute events) showed that more events were observed in patients who tested positive for anti-taliglucerase alfa ADA than in patients who tested negative for anti-taliglucerase ADA. -In clinical trials, not all ADA observed were neutralizing ADA (See ADVERSE REACTIONS; See CLINICAL STUDIES).

Patients who develop infusion or immune reactions with taliglucerase alfa treatment should be monitored for anti-drug antibodies to taliglucerase alfa. Additionally, patients with immune reactions to other enzyme replacement therapies who are switching to taliglucerase alfa should be monitored for anti-drug antibodies to taliglucerase alfa.

Adverse reactions related to infusion and hypersensitivity

Serious hypersensitivity reactions, including anaphylaxis, have occurred in some patients treated with ELELYSO. Appropriate medical support should be readily available when taliglucerase alfa is administered. -Infusion reactions (i.e., defined as reactions occurring during or within 24 hours of infusion) and hypersensitivity reactions have been reported with taliglucerase alfa. If a severe allergic reaction occurs, immediate discontinuation of the taliglucerase alfa infusion is recommended. Patients who experience adverse reactions related to infusion or hypersensitivity can however usually be managed successfully and have therapy continued by slowing the

infusion rate, treating with medicinal products such as antihistamines, antipyretics and/or corticosteroids, and/or stopping and resuming treatment with decreased infusion rate. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions (See ADVERSE REACTIONS).

If anaphylaxis occurs, ELELYSO should be immediately discontinued, and appropriate medical treatment should be initiated.

Allergy to carrots
The occurrence of allergic reactions in those with known carrot allergies is currently not known and has not been studied in clinical trials therefore caution should be exercised in treating patients. If adverse reactions related to infusion or hypersensitivity occur, patients should be managed as described above.

Carcinogenesis and Mutagenesis
See part II: Scientific Information, Toxicology

Hepatic/Biliary/Pancreatic
No studies have been performed in patients with hepatic impairment.

Renal
No studies have been performed in patients with renal impairment.

Sexual Function/Reproduction
Pregnancy
Reproduction studies of taliglucerase alfa have been performed in pregnant rats and rabbits at doses up to 5 times the recommended human dose of 60 units/kg based on the body surface area and have revealed no 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 (See TOXICOLOGY).

Fertility
In animal studies, taliglucerase alfa did not affect fertility or reproductive performance or sperm characteristics (See TOXICOLOGY).

Special Populations
Pregnant Women
There are no adequate and well controlled studies in pregnant women. It is not known whether ELELYSO would cause fetal harm when administered to a pregnant woman or would affect reproductive capacity (See TOXICOLOGY).

Nursing Women
There are no data from studies in lactating women. It is not known whether taliglucerase alfa is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when taliglucerase alfa is administered to nursing women.

Pediatrics (2 to 17 years old)
ELELYSO has been administered to a limited number of children aged from 2 to 17 years in clinical trials. Studies performed to date have shown similar results with regards to both effectiveness of therapy and with the types and frequencies of adverse events in adult patients, with the exception that vomiting and abdominal pain were seen more commonly in pediatric patients. Overall comparison of common adverse events between adults and children is difficult due to the low number of subjects in the treatment groups (See ADVERSE REACTIONS and CLINICAL TRIALS).

Geriatrics
Overall, 8 elderly subjects (≥65 years) were enrolled in the clinical program. The sample size is small, but there does not appear to be a major difference in frequency or severity of events in these subjects compared to adult subjects aged 18 to <65 years old.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

A total of 132 subjects, adults and children, were exposed to taliglucerase alfa in clinical trials.

Patients were between 2 years and 85 years old at the time of their first treatment with taliglucerase alfa and included both treatment-naïve patients and those previously treated with imiglucerase.

Group	Number of subjects	Duration of exposure accrued to **ELELYSO** in patient-months	**ELELYSO** Dosing regimens
Adult	116	3121 months	30 units/kg or 60 units/kg
Pediatric	16	519.8 months	30 units/kg or 60 units/kg

The most serious adverse reactions in patients in controlled clinical trials were immune-mediated adverse events of Type 1 hypersensitivity.

The most common adverse reactions in controlled clinical studies were infusion-related reactions occurring within 24 hours of the infusion. The most commonly observed symptoms of infusion-related reactions were arthralgia, headache, infusion related reaction, vomiting, hypersensitivity, flushing, pruritus, pain in extremity and pulmonary hypertension. Other infusion reactions included diarrhea, chest discomfort, feeling hot, muscle spasms, tremor, throat irritation, erythema, rash and infusion site pain.

The safety of taliglucerase alfa has been established in pediatric patients from 2 years to 17 years of age. One treatment-related serious adverse event was reported in pediatric clinical trials; an 8 year-old pediatric patient experienced a serious adverse reaction (gastroenteritis). There does not appear to be a major difference in frequency of adverse reactions in pediatric patients compared

to adult patients, with the exception that vomiting and abdominal pain were seen more commonly in pediatric patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse drug reactions (ADR) are listed in **Table 1**. Information is presented by system organ class and frequency (very common ≥10%; common ≥1% and <10%, frequency is determined using the number of all causality events for each ADR). Within each frequency grouping, undesirable effects are presented by preferred term in order of decreasing seriousness.

Table 1 - Adverse Drug Reactions Reported with ELELYSO in Patients with Gaucher Disease

System Organ Class Incidence Category	**Adverse Drug Reaction (Preferred Term)**
Immune system disorders	
Common	Hypersensitivity
Nervous system disorders	
Very common	Headache
Common	Dizziness
Vascular disorders	
Common	Flushing
Respiratory, thoracic and Mediastinal disorders	
Common	Throat irritation
Gastrointestinal disorders	
Very common	Vomiting, Abdominal pain[#]
Common	Nausea
Skin and subcutaneous tissue disorders	
Very common	Pruritus*
Common	Erythema, Rash
Musculoskeletal and connective tissue disorders	
Very common	Pain in extremity, Arthralgia, Back pain
Common	Bone pain
General disorders and administration site conditions	
Very common	Fatigue
Common	Infusion site pain, Oedema peripheral
Injury, poisoning and procedural complications	
Common	Infusion related reaction
Investigations	

Common	Weight increased

*# Includes abdominal pain lower and upper;*Pruritus includes Pruritus generalized*

The data described reflect exposure of 132 patients (adults and children) with Gaucher disease who received ELELYSO at doses ranging from 9 to 78 units/kg every other week, for lengths of treatment up to 60 months in 7 clinical studies. Fifty (50) patients were naïve to ERT and 82 patients switched from imiglucerase to ELELYSO. Patients were between 2 and 85 years old at the time of first treatment with ELELYSO, and included 73 male and 59 female patients.
In the clinical program hypersensitivity reactions have occurred as early as the first infusion.

Adverse drug reactions to ELELYSO are shown in **Table 2** (frequency is determined using the number of all causality events for each ADR).

Table 2 - Adverse Drug Reactions Reported in Patients with Gaucher Disease Treated With ELELYSO During Clinical Trials

System Organ Class Preferred Term	**Naïve to ELELYSO n= 50 (%)**	**Switched from imiglucerase to ELELYSO n= 82 (%)**
Gastrointestinal disorders		
Vomiting	8 (16)	7 (9)
Abdominal pain	12 (24)	6 (7)
Nausea	3 (6)	2 (2)
General disorders and administration site conditions		
Fatigue	5 (10)	11 (13)
Infusion site pain	2 (4)	2 (2)
Oedema peripheral	2 (4)	8 (10)
Immune system disorders		
Hypersensitivity	4 (8)	1 (1)
Injury, poisoning and procedural complications		
Infusion related reaction	2 (4)	7 (9)
Investigations		
Weight increase	0	3 (4)
Musculoskeletal and connective tissue disorders		
Arthralgia	15 (30)	18 (22)

Back pain	7 (14)	9 (11)
Bone pain	3 (6)	5 (6)
Pain in extremity	13 (26)	11 (13)
Nervous system disorders		
Dizziness	8 (16)	3(4)
Headache	15 (30)	19 (23)
Respiratory, thoracic and Mediastinal disorders		
Throat irritation	2 (4)	2 (2)
Skin and subcutaneous tissue disorders		
Erythema	3 (6)	3 (4)
Pruritus	4 (8)	9 (11)
Rash	3 (6)	5 (6)
Vascular disorders		
Flushing	2 (4)	3 (4)

Adult ERT-naïve patient population
The safety of ELELYSO at doses of either 30 units/kg or 60 units/kg was assessed in 39 adult ERT-naïve patients with Gaucher disease over a 60-month period. Adverse drug reactions reported in ≥10% of patients were Arthralgia (n=14; 36%), Headache (n=12; 31%), Pain in extremity (n=8; 21%), Abdominal pain (n=7; 18%), Back pain (n=7; 18%), Dizziness (n=6; 15%), Fatigue (n=5; 13%), Hypersensitivity (n=4; 10%), and Pruritus (n=4; 10%).

Pediatric ERT-naïve patient population
The safety of ELELYSO at doses of either 30 units/kg or 60 units/kg was assessed in 11 pediatric ERT-naïve patients with Gaucher disease over a 36-month period. Adverse drug reactions reported in ≥10% of patients were Vomiting (n=5; 45%), Abdominal pain (n=5; 45%), Pain in extremity (n=5; 45%), Headache (n=3; 27%), Dizziness (n=2; 18%) and Rash (n=2; 18%).

ERT-experienced patient population
The safety of ELELYSO at doses of either 30 units/kg or 60 units/kg was assessed in 82 ERT-experienced patients (77 adults and 5 pediatrics) with Gaucher disease over a 36-month period. Adverse drug reactions reported in ≥10% of patients were Headache (n=19; 23%), Arthralgia (n=18; 22%), Fatigue (n=11; 13%), Pain in extremity (n =11; 13%), Back pain (n=9; 11%), Pruritus (n=9; 11%) and Oedema peripheral (n=8; 10%).

Immunogenicity

As with all therapeutic proteins, patients may develop anti-drug antibodies (ADA) to ELELYSO.

In clinical trials of treatment-naïve adults, 17 (53%) of 32 patients developed ADA during treatment with ELELYSO, and 2 (6%) of 32 patients tested positive for ADA at baseline prior to ELELYSO treatment. Of the 17 patients who developed ADA during ELELYSO treatment, 6 patients (35%) developed hypersensitivity reactions, 2 of whom met criteria for anaphylaxis. Two of the 17 patients who developed ADA during ELELYSO treatment discontinued treatment due to hypersensitivity reactions, one of whom had met criteria for anaphylaxis. Of the 2 patients who tested positive for ADA prior to initiation of ELELYSO treatment, one patient developed a hypersensitivity reaction during the first dose of ELELYSO and withdrew from the study. The second patient did not experience a hypersensitivity reaction.

In a clinical trial of treatment-naïve pediatric patients, 2 (22%) of 9 patients developed ADA during treatment with ELELYSO, and one of 9 patients was ADA-positive prior to initiation of ELELYSO. Two of these 3 patients experienced hypersensitivity reactions (1 who developed ADA during treatment and became negative after Week 12 and 1 who was ADA-positive at baseline and became ADA negative after Week 8) and continued treatment with ELELYSO. The third patient who developed ADA during treatment and continued to be ADA-positive until study completion at Week 52 did not experience a hypersensitivity reaction.

In clinical trials of 31 patients (26 adult and 5 pediatric patients) who switched from imiglucerase to ELELYSO treatment, 5 adults (16% of patients) developed ADA during treatment with ELELYSO. Four additional patients (13%, 2 adults and 2 children) tested positive for ADA at baseline but became ADA-negative after the switch to ELELYSO; one of these adult patients subsequently developed ADA to ELELYSO. Two adult patients (1 patient who developed ADA after the switch and 1 who was ADA positive at baseline) experienced hypersensitivity reactions. Both patients continued treatment with ELELYSO.

In total, 31 adult and pediatric patients tested positive for the taliglucerase alfa ADA. The relationship between ADA and hypersensitivity reactions is not fully understood. Monitoring for ADA to ELELYSO may be useful in ADA positive patients or in patients who have experienced hypersensitivity reactions to ELELYSO or other enzyme replacement therapies.

Thirty of 31 adult and pediatric patients, who previously tested positive for the anti-taliglucerase alfa ADA, were also evaluated for the presence of neutralizing antibodies in the mannose receptor binding and enzyme activity assays. Nineteen (63%) of the 30 patients were positive for the neutralizing antibodies capable of inhibiting mannose receptor binding of taliglucerase alfa. Eight of these 19 patients were also positive for neutralizing antibodies capable of inhibiting the enzymatic activity of taliglucerase alfa. Due to limited available data, it is not possible to determine a relationship between the presence of neutralizing antibodies and therapeutic response with 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.

Abnormal Hematologic and Clinical Chemistry Findings

No evidence of an adverse effect of taliglucerase alfa on laboratory test parameters was observed in clinical studies. The majority of the laboratory haematology and biochemistry parameters remained at normal levels from screening or improved to normal levels by the end of study. Elevations in ALT or AST levels observed in the current dataset are mild and could be explainable, either due to concomitant medication or illness in most Gaucher disease patients. All subjects that reported liver function test abnormalities showed either clinical improvement or clinical stability while on taliglucerase alfa treatment.

Post-Market Adverse Drug Reactions

The following adverse events were reported during POST-MARKETING SURVEILLANCE:

Immune system disorders: Anaphylactic reaction
Skin and subcutaneous tissue disorders: Urticaria, Angioedema

DRUG INTERACTIONS

Drug-Drug Interactions: Interactions with other drugs have not been established.

Drug-Food Interactions: Interactions with food have not been established.

Drug-Herb Interactions: Interactions with herbal products have not been established.

Drug-Laboratory Interactions: Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

ELELYSO treatment should be supervised by a physician experienced in the management of patients with Gaucher disease. Home administration under the supervision of a healthcare professional may be considered only for those patients who have been tolerating their infusion well (See WARNINGS AND PRECAUTIONS).

Due to the heterogeneity and the multi-systemic nature of Gaucher disease, dosage adjustments should be made on an individual basis. Dose requirements may increase or decrease, based on each patient's therapeutic response as assessed by routine comprehensive evaluations of the patient's manifestations.

A multi-center, open-label, single arm study was carried out in clinically stable adult and pediatric Gaucher disease patients treated with imiglucerase and switched to ELELYSO at the same dose as the previous imiglucerase dose. Patients remained stable with regards to the main

disease parameters. Results (see CLINICAL TRIALS) should be considered under the study design and safety consideration limitations imposed by this particular target population and time at which the study was performed. When considering patients for a switch to ELELYSO, the limitations of this single study should be taken into consideration.

Recommended Dose and Dosage Adjustment

Dosage should be individualized to each patient. Administer ELELYSO by intravenous infusion over 1-2 hours, every 2 weeks. Duration of infusion may be adjusted as tolerated by the patient. Initial doses of taliglucerase alfa range from 30 units/kg to 60 units/kg of body weight, depending upon the clinical assessment of the treating physician. Clinical studies have evaluated dose ranges from 9 units/kg to 67 units/kg every other week.

A post hoc analysis demonstrated that after 9 and 12 months of treatment with taliglucerase alfa, a 60 units/kg dose resulted in a statistically better response than 30 units/kg dose for spleen volume and platelet count in patients with Gaucher disease. No such similar discrimination between doses for liver volume, haemoglobin, or chitotriosidase activity was observed. The difference between the efficacy endpoints in whether they showed a dose response may be because of patient selection differences. Subjects were enrolled into the PB-06-001 study with splenomegaly (> 8 times normal) and thrombocytopenia (platelet count < 120,000/mm^3), but hepatomegaly and anemia were not required for study entry.

Based on the spleen volume and platelet count, taliglucerase alfa 60 units/kg dose provides a better clinical response than 30 units/kg.

Renal or hepatic impairment:
Studies of taliglucerase alfa in patients with Gaucher disease with renal or hepatic dysfunction have not been conducted.

Elderly (≥ 65 years old):
During clinical studies, 8 patients aged 65 and older were treated with ELELYSO. This limited data set does not indicate a need for a dose adjustment in this age group.

Pediatric population:
The safety and effectiveness of ELELYSO has been established in pediatric patients, ELELYSO has been administered to children aged 2 to 17 years in clinical trials. Studies performed to date have shown similar results with regard to both effectiveness of therapy and with the types and frequencies of adverse events in adult patients, with the exception that vomiting and abdominal pain were seen more commonly in pediatric patients.

Neuronopathic Gauchers disease:
Patients with severe neurological symptoms other than longstanding oculomotor gaze palsy were excluded from clinical studies. Two pediatric patients were diagnosed with neuronopathic disease and one additonal child had a genotype characteristic of Type 3 Gaucher disease.

Administration

Reconstitution:

Reconstitute each vial for injection with 5.1 mL Water for Injection (WFI). The reconstitution and dilution steps must be completed using aseptic techniques. Do not heat or microwave these vials. Water for injection should be added slowly by directing the flow along the side of the vial to assure proper mixing of the product. The reconstituted volume is 5.3 mL. Mix vials gently. Do not shake. The solution is a clear and colorless liquid. Do not use if the solution is discolored or if foreign particulate matter is present. ELELYSO contains no preservatives, thus, the product should be used immediately upon reconstitution. If immediate use is not possible, the reconstituted product has been shown to be stable when stored for up to 12 hours at room temperature OR for up to 24 hours at 2 to 8°C. Do not freeze. Protect from light. Discard any unused product.

The final concentrations and administration volumes are provided below:

	200 Unit Vial
Sterile water for reconstitution	5.1 mL
Final volume of reconstituted product	5.3 mL
Concentration after reconstitution	40 units/mL
Withdrawal volume	5.0 mL
Units of enzyme within final withdrawn volume	200 units

Dilution:

A 5.0 mL of reconstituted enzyme is withdrawn from each vial. The appropriate amount of ELELYSO for each patient is diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 100 to 200 mL. Mix gently. Do not shake. Since this is a protein solution, slight flocculation occurs occasionally after dilution. The diluted solution should be filtered through an in-line low protein-binding 0.2 μm filter during administration.

It is recommended that the diluted solution be administered as soon as possible after dilution. The product diluted in 0.9% sodium chloride intravenous solution may be stored up to 24 hours at 2°C to 8°C.

OVERDOSAGE

There is no experience with overdose of taliglucerase alfa. The maximum dose of taliglucerase alfa in clinical studies was 78 units/kg body weight.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Gaucher disease is a rare genetic disorder characterized by a functional deficiency of β-glucocerebrosidase activity. This results from a heterogeneous group of mutations in the gene mapped to chromosome 1 q21-q31, the glucocerebrosidase gene. Classification of GD is based on the absence (non-neuronopathic GD [NNGD]) or presence (neuronopathic GD [NGD]) of complex neurological symptoms. ERT addresses peripheral disease. The protein cannot cross the blood brain barrier; therefore it is of no benefit for the neurological symptoms of the neuronopathic disease.

β-glucocerebrosidase is naturally active in lysosomes and catalyses the hydrolysis of the glycolipid glucocerebroside into ceramide and glucose; there are no alternative degradative pathways. The accumulation of excessive glucocerebrosides in lysosomal compartments of monocyte/macrophage-derived cells gives rise to the characteristic Gaucher cell. It is the accumulation of these lipid-laden macrophages that results in the pathology. Accumulation of these Gaucher cells causes enlargement of the liver and spleen, which can be massive. Splenomegaly is associated with thrombocytopenia. Bone involvement results in abnormal bone remodeling, bone infarcts, avascular necrosis and bone pain including episodes of excruciating bone pain ("bone crises").

In clinical trials, ELELYSO reduced spleen and liver size, and improved anemia and thrombocytopenia.

Pharmacodynamics

Taliglucerase alfa is produced in genetically modified carrot cells by recombinant DNA technology. Glucocerebrosidase utilized for ERT must have exposed mannose sugars for entry into the macrophage, the site of action. Expression of taliglucerase alfa is targeted in the plant cell to the storage vacuoles using a plant specific C-terminal sorting signal that dictates the formation of the desired mannose structure in vivo. This targeting to the vacuoles takes advantage of the terminal residues in complex N-glycans in vacuolar glycoproteins being removed, resulting in paucimannosidic type N-glycans that constitute a consensus 'vacuoletype' glycan, with exposed mannose on all glycan structures. This process results in exposed mannose without glycan remodeling.

Taliglucerase alfa and imiglucerase exhibited similar enzyme kinetics towards a fluorescent short-chain analogue of the natural substrate, glucosylceramide, N-[6-[(7-nitrobenzo-2-oxa-1,3-diazol-4-yl) amino] hexanoyl]-glucosylsphingosine (C6-NBD-GlcCer). Taliglucerase alfa displayed a Vmax of 0.47 mmol C6-NBD-Cer formed/min/mg and a Km of 20.7 mM.

Taliglucerase alfa was taken up by mouse and human peritoneal macrophages, and maintained enzymatic activity after internalisation. Uptake of taliglucerase alfa was inhibited by yeast mannan, a specific ligand for mannose (Man/GlcNac) receptors. Macrophages from rats, rabbits, humans and monkeys were incubated with taliglucerase alfa in vitro. Concentration-dependent

uptake of taliglucerase alfa was observed in all of these species. Furthermore, mannan produced an inhibition of uptake ranging from 50 to 90%.

Pharmacokinetics

Adult population

The pharmacokinetics of ELELYSO has been studied in 6 healthy volunteers and 31 patients with Gaucher disease. Taking into account that the infusion rates were different between the two studies, exposures appeared to be lower in Gaucher disease patients than in healthy subjects.

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.

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.

Pediatric Population

The pharmacokinetics of taliglucerase alfa were evaluated in 9 pediatric patients 4 to 17 years of age with Type 1 Gaucher disease who were treated with ELELYSO for 10 to 27 months. Six of the 9 patients were treatment naïve, and 3 patients were switched from imiglucerase. In both the 30 units/kg and 60 units/kg dose groups, clearance values in pediatric patients were similar to those in adult patients. AUC values in pediatric patients were lower than AUC values in adult patients, due to weight-based dosing of taliglucerase alfa and lower body weights in pediatric patients.

Table 3: Taliglucerase Alfa Pharmacokinetic Parameters after Repeated Dosing in Adult and Pediatric Patients with Type 1 Gaucher Disease

	Pediatric Patients (N=9) Median (Range)		**Adult Patients at Week 38 (N=29) Median (Range)**	
	30 units/kg n = 5	**60 units/kg n = 4**	**30 units/kg n = 14**	**60 units/kg n = 15**
Age (years)	15 (10, 17)	11 (4, 16)	35 (19, 74)	33 (19, 58)
Weight (kg)	44.3 (22.8, 71.0)	28.6 (16.5, 50.4)	72.5 (51.5, 99.5)	73.5 (58.5, 87.0)[a]
$AUC_{0-\infty}$ (ng*h/mL)[b]	1416 (535, 1969)	2984 (1606, 4273)	2007 (1007, 10092)	6459 (2548, 21020)[a]
$T_{1/2}$ (min)	37.1 (22.5, 56.8)	32.5 (18.0, 42.9)	18.9 (9.20, 57.9)	28.7 (11.3, 104)[a]
CL (L/h)	30.5 (17.4, 37.8)	15.8 (11.7, 24.9)	30.5 (6.79, 68.0)	18.5 (6.20, 37.9)[a]
V_{ss} (L)	14.9 (10.1, 35.6)	8.80 (3.75, 21.4)	11.7 (2.3, 22.7)	10.7 (1.4, 18.5)[a]

[a] n = 14

[b] Values were derived from concentration data expressed in ng/mL

STORAGE AND STABILITY

Lyophilized vial:
Store ELELYSO at 2° - 8 °C and protect vials from light.

Reconstituted and diluted solution for infusion:
After reconstitution, promptly dilute vial.

The reconstituted solution may be stored for up to 12 hours at room temperature OR for up to 24 hours at 2 to 8°C, protected from light. The diluted solution may be stored for up to 24 hours at 2 to 8°C, protected from light.

The medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

SPECIAL HANDLING INSTRUCTIONS

Each vial of ELELYSO is for single use only. ELELYSO should be administered over a period from 2 hours to a minimum of 1 hour. Duration of the infusion may be adjusted as tolerated by the patient.

Store in a refrigerator (2°-8°C) and transport refrigerated (2°-8°C). Protect from light. Keep the vial in the outer carton.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ELELYSO (taliglucerase alfa), is supplied as a sterile, non-pyrogenic, white to off-white lyophilized product for intravenous infusion.

The quantitative composition of the lyophilized drug product is as follows:

- a 200 unit vial is composed of taliglucerase alfa (212 units, which allows for a withdrawal of 200 units), mannitol (206.7 mg), sodium citrate (30.4 mg) and Polysorbate 80 (0.56 mg). Citric acid anhydrous to adjust pH.

ELELYSO is supplied in Type 1 glass vials packaged in single vial cartons.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: taliglucerase alfa

Chemical name: recombinant human β-glucocerebrosidase

Molecular formula: $C_{2742}H_{4184}N_{684}O_{852}S_{16}$

Molecular mass (major isoform): 60,876.2 Da (electrospray mass spectrometry)
Structural formula: Taliglucerase alfa is an analogue of a known human enzyme, β-glucocerebrosidase, which includes the substitution of arginine by histidine at position 495 of the human sequence (position 497 in taliglucerase alfa). The predicted amino acid sequence of taliglucerase alfa is shown below. This sequence differs from the glucocerebrosidase sequence by the addition of amino acids at the N-terminal and C-terminal of the protein, which are introduced by the plant expression cassette. Hence, the complete amino acid sequence of taliglucerase alfa is predicted to have two additional amino acids at the N-terminal (E and F) and up to seven additional amino acids at the C-terminal (DLLVDTM), bolded.

Predicted Amino Acid Sequence for taliglucerase alfa:

	1	11	21	31	41	51
1	**EF**ARPCIPKS	FGYSSVVCVC	NATYCDSFDP	PTFPALGTFS	RYESTRSGRR	MELSMGPIQA
61	NHTGTGLLLT	LQPEQKFQKV	KGFGGAMTDA	AALNILALSP	PAQNLLLKSY	FSEEGIGYNI
121	IRVPMASCDF	SIRTYTYADT	PDDFQLHNFS	LPEEDTKLKI	PLIHRALQLA	QRPVSLLASP
181	WTSPTWLKTN	GAVNGKGSLK	GQPGDIYHQT	WARYFVKFLD	AYAEHKLQFW	AVTAENEPSA
241	GLLSGYPFQC	LGFTPEHQRD	FIARDLGPTL	ANSTHHNVRL	LMLDDQRLLL	PHWAKVVLTD
301	PEAAKYVHGI	AVHWYLDFLA	PAKATLGETH	RLFPNTMLFA	SEACVGSKFW	EQSVRLGSWD
361	RGMQYSHSII	TNLLYHVVGW	TDWNLALNPE	GGPNWVRNFV	DSPIIVDITK	DTFYKQPMFY
421	HLGHFSKFIP	EGSQRVGLVA	SQKNDLDAVA	LMHPDGSAVV	VVLNRSSKDV	PLTIKDPAVG
481	FLETISPGYS	IHTYLWHRQ**D**	**LLVDTM**			

Solubility:
Solubility (water) > 10 mg/mL

Product characteristics:
The recombinant human glucocerebrosidase drug product is supplied as sterile, non-pyrogenic, white to off-white lyophilized powder. The lyophilized powder, that may form a cake is reconstituted with Water for Injection and further diluted with a saline solution for intravenous infusion.

Taliglucerase alfa is produced in genetically modified carrot cells by recombinant DNA technology and processed in a controlled system. Testing for bioburden of the system is

performed. The presence of adventitious agents is not relevant for plant derived cell lines since mammalian viruses do not replicate in plant cells, and it is well established that there is no cross-infection of humans with plant viruses.

CLINICAL TRIALS

Study demographics and trial design

Table 4 - Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
PB-06-001 Pivotal Trial	Phase III, Multicenter, randomized, double blind, parallel group, dose ranging	30 units/kg every 2 weeks, 60 units/kg every 2 weeks IV infusion 38 weeks	16 (30 units/kg) 16 (60 units/kg)	36.2 (19-74)	Male and Female
PB-06-002	Phase III, Multicenter, open label	Dose equivalent to prior imiglucerase dose every 2 weeks IV infusion 38 weeks	31	41.6 (6-66) years	Male and Female
PB-06-003 Extension to PB-06-001 and PB-06-002	PB-06-001 : Multicenter, randomized, double blind, parallel group, dose ranging PB-06-002: Multicenter, open label	Same dose as previous studies (PB-06-001 and PB-06-002) IV infusion 15 to 30 months	44 12 From PB-06-001 (30 u/kg) 14 From PB-06-001 (60u/kg) 18 From PB-06-002 (same dose as end of PB-06-002)	38.9 (24-74) years 35.6 (19-58) years 45.4 (18-66) years	Male and Female
PB-06-005	Phase III, Multicenter, randomized, double blind	30 units/kg every 2 weeks, 60 units/kg every 2 weeks IV infusion 12 months	6 5	9.5 (3-14) years 6.6 (2-10) years	Male and Female

PB-06-006	Extended safety and efficacy for pediatric patients completing PB-06-005 or PB-06-002	PB-06-005 randomized to 30 U/kg or 60 U/kg every 2 weeks PB-06-002 continue same dose as previous study every 2 weeks 24 months	15 (10 from PB-06-005 and 5 from PB-06-002)	5 (3 -11) years 5 (3 -11) years 5 (6 -16) years	Male and Female
PB-06-007	Extended safety and efficacy for treatment-naive adult patients completing PB-06-001 and PB-06-003	PB-06-001/PB-06-003 randomized to 30 U/kg or 60 U/kg every 2 weeks 21 months	19	8 (36-77) years 9 (23-57) years 2 (38-39) years	Male and Female

PB-06-004 is an open-label expanded access trial of taliglucerase alfa in patients with Gaucher disease.

Clinical studies

Clinical Trials of ELELYSO as Initial Therapy

Clinical Trial in Patients 19 Years and Older

The safety and efficacy of ELELYSO were assessed in 31 adult patients with Type 1 Gaucher disease. The trial was a 9-month, multi-center, double-blind, randomized trial in patients with Gaucher disease-related enlarged spleens (>8 times normal) and thrombocytopenia (<120,000 /mm^3). 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 trial. Patients were 19 to 74 years of age (mean age 36 years), and 48% were male. Patients were randomized to receive ELELYSO at a dosage of either 30 units/kg (n=15) or 60 units/kg (n=16) every other week. The recommended dosage in treatment-naïve adult patients is 60 units/kg every other week. ELELYSO 30 units/kg every other week is not a recommended dosage (see DOSAGE AND ADMINISTRATION).

Table 4 shows the baseline values and mean (SD) changes in clinical parameters (spleen volume, liver volume, platelet count, and hemoglobin) after 9 months of treatment with ELELYSO. For all clinical trials, liver and spleen volumes were measured by MRI and are reported as percentage of body weight (%BW) and multiples of normal (MN). The observed change from baseline in the primary endpoint, reduction in spleen volume, was considered to be clinically meaningful in light of the natural history of untreated Gaucher disease.

Table 5: Mean (SD) Changes in Clinical Parameters from Baseline to 9 Months in Treatment-Naïve Adults with Type 1 Gaucher Disease Initiating Therapy with ELELYSO (N=31)**

	Clinical Parameter	30 units/kg* (n=15) Mean (SD)	60 units/kg (n=16) Mean (SD)
Spleen Volume (%BW♮)	Baseline	3.1 (1.5)	3.3 (2.7)
	Month 9	2.2 (1.3)	2.1 (1.9)
	Change	-0.9 (0.4)	-1.3 (1.1)
Spleen Volume (MN♯)	Baseline	15.4 (7.7)	16.7 (13.4)
	Month 9	11.1 (6.3)	10.4 (9.4)
	Change	-4.5 (2.1)	-6.6 (5.4)
Liver Volume (%BW)	Baseline	4.2 (0.9)	3.8 (1.0)
	Month 9	3.6 (0.7)	3.1 (0.7)
	Change	-0.6 (0.5)	-0.6 (0.4)
Liver Volume (MN)	Baseline	1.7 (0.4)	1.5 (0.4)
	Month 9	1.4 (0.3)	1.2 (0.3)
	Change	-0.2 (0.2)	-0.3 (0.2)
Platelet Count (mm^3)	Baseline	75,320 (40,861)	65,038 (28,668)
	Month 9	86,747 (50,989)	106,531 (53,212)
	Change	11,427 (20,214)	41,494 (47,063)
Hemoglobin (g/dl)	Baseline	12.2 (1.7)	11.4 (2.6)
	Month 9	14.0 (1.4)	13.6 (2.0)
	Change	1.6 (1.4)	2.2 (1.4)

*The recommended ELELYSO dosage in treatment-naïve adult patients is 60 units/kg every other week. ELELYSO 30 units/kg every other week is not a recommended dosage. *(see DOSAGE AND ADMINISTRATION)*

** *SD = standard deviation*

♮ *%BW = percentage of body weight*

♯ *MN = multiples of normal*

Twenty-six of the 31 patients in this 9-month clinical trial continued blinded treatment with ELELYSO in an extension trial for a total treatment duration of 24 months. The following data are the changes in clinical parameters from baseline to Month 24 for the 30 units/kg (n=12) and 60 units/kg (n=14) dose groups, respectively: mean (SD) spleen volume (%BW) decreased by 1.4 (0.6) and 2.0 (2.0), in MN by 6.8 (3.0) and 10.2 (9.8); hemoglobin increased by 1.3 (1.7) g/dL and 2.4 (2.3) g/dL; liver volume (%BW) decreased by 1.1 (0.5) and 1.0 (0.7), in MN by 0.4 (0.2) and 0.4 (0.3 and platelet count increased 28,433 (31,996) /mm^3 and 72,029 (68,157) /mm^3. Twenty-three of the 26 patients who continued open-label treatment with ELELYSO for additional 12 months demonstrated stability in these clinical parameters.

Clinical Trial in Patients 16 years and Younger

The safety and efficacy of ELELYSO were assessed in 9 pediatric patients with Type 1 Gaucher disease. The trial was a 12-month, multi-center, double-blind, randomized study in treatment-naïve patients. Patients were 2 to 13 years of age (mean age 8.1 years), and 67% were male. Patients were randomized to receive ELELYSO at a dosage of either 30 units/kg (n=4) or 60 units/kg (n=5) every other week. The recommended ELELYSO dosage in treatment-naïve pediatric patients is 60 units/kg every other week. ELELYSO 30 units/kg every other week is not a recommended dosage (see DOSAGE AND ADMINISTRATION).

The following data are the changes [median (Q1, Q3)] in clinical parameters from baseline to Month 12 for the 60 units/kg dose group (n=5): spleen volume decreased from 18.4 (14.2, 35.1) MN to 11.0 (8.3, 14.5) MN; hemoglobin increased from 11.1 (9.2, 11.3) g/dL to 11.7 (11.5, 12.9) g/dL; liver volume decreased from 2.1 (2.0, 2.3) MN to 1.6 (1.5, 1.9) MN; platelet count increased from 80,000 (79,000, 87,000)/mm^3 to 131,000 (119,000, 215,000)/mm^3.

Nine pediatric patients in the 12-month clinical trial continued blinded treatment with ELELYSO in an extension trial for a total treatment duration of 24 months. The following data are the changes [median (Q1, Q3)] in clinical parameters from baseline to Month 24 for the 60 units/kg dose group (n=5): spleen volume decreased by 19.0 (8.3, 41.2) MN; hemoglobin increased by 2.5 (1.9, 3.0) g/dL; liver volume decreased by 0.8 (0.6, 1.1) MN; and platelet count increased by 76,000 (67,000, 100,000)/mm^3.

In addition to the patients with Type 1 Gaucher disease, two pediatric patients were diagnosed with neuronopathic disease and one additional child had a genotype characteristic of Type 3 Gaucher disease.

Clinical Trial in Patients Switching from Imiglucerase Treatment to ELELYSO

The safety and efficacy of ELELYSO were assessed in 31 patients (26 adult and 5 pediatric patients) 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 dosages ranging from 9.5 units/kg to 60 units/kg every other week for a minimum of 2 years. Patients were required to be clinically stable and have a stable biweekly dose of imiglucerase for at least 6 months prior to enrollment. Patients were 6 to 66 years of age (mean age 42 years, including pediatric patients), and 55% 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. If needed, adjustment of dosage was allowed during the study in order to maintain stability of clinical parameters (i.e., spleen volume, liver volume, platelet count, and hemoglobin).

Mean (SD) organ volumes and hematologic values remained stable through 9 months of ELELYSO treatment. At baseline, spleen volume was 5.2 (4.5) MN, liver volume was 1.0 (0.3) MN, platelet count was 161,137 (73,387)/mm^3, and hemoglobin was 13.5 (1.4) g/dL. After 9 months of ELELYSO treatment, spleen volume was 4.8 (4.6) MN, liver volume was 1.0 (0.2) MN, platelet count was 161,167 (80,820)/mm^3, and hemoglobin was 13.4 (1.5) g/dL. ELELYSO dose remained unchanged in 30 of 31 patients. One patient required a dose increase at Week 24 (from 9.5 units/kg to 19 units/kg) for a platelet count of 92,000/mm^3 at Week 22, which subsequently increased to 170,000/mm^3 at Month 9.

Eighteen of the 26 adult patients who completed the 9-month clinical trial continued treatment with ELELYSO in an open-label extension trial for additional 27 months (total treatment 36 months). Patients maintained stability in clinical parameters (spleen volume, liver volume, platelet count and hemoglobin); however only 10 of 18 adult patients completed 27 months of ELELYSO treatment in the extension trial and only 7 patients had their spleen and liver volumes assessed at 36 months.

Five pediatric patients in the 9-month clinical trial who continued open-label treatment with ELELYSO for additional 24 months demonstrated stability in these clinical parameters.

Geriatric population

Clinical studies of taliglucerase alfa did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Comparative Bioavailability Studies

Taliglucerase alfa is administered IV infusion, such that 100% of administered drug is

immediately present in circulation, thus bioavailability studies are not applicable to this drug.

Antidrug Antibody and Efficacy
Analyses of anti-taliglucerase alfa antibody development and potential clinical sequelae were performed using the clinical development database. A correlative relationship between subject antibody status and PK has not been observed. The relevance of antidrug antibody (ADA) to therapeutic response is unclear as the four main clinical parameters showed no consistent relationship to subject antibody status; regardless of ADA status improvement was seen in the clinical parameters. Although clinically manageable, the occurrence of all-causality, pooled, immune-mediated type 1 hypersensitivity events was more frequent in subjects with treatment-induced ADA. However, because of the limited size of the database a clear association between subject antibody status and the risk of hypersensitivity reaction has not been established.

Assessment of Neutralizing Antibody on Efficacy
Thirty of 31 adult and pediatric patients, who previously tested positive for the anti-taliglucerase alfa ADA, were also evaluated for the presence of neutralizing antibodies in the mannose receptor binding and enzyme activity assays. Nineteen (63%) of the 30 patients were positive for the neutralizing antibodies capable of inhibiting mannose receptor binding of taliglucerase alfa. Eight of these 19 patients were also positive for neutralizing antibodies capable of inhibiting the enzymatic activity of taliglucerase alfa. The significance of these findings is unknown at this time.

DETAILED PHARMACOLOGY

Taliglucerase alfa is a recombinant active form of the human lysosomal enzyme, β-glucocerebrosidase that catalyses the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

The pharmacology program consisted of a series of in vitro studies to evaluate primary pharmacodynamics of taliglucerase alfa. The activity of taliglucerase alfa was compared with the approved product imiglucerase (Cerezyme) in some of these studies. In addition, the uptake of taliglucerase alfa by rat, rabbit, human and monkey macrophages was evaluated. Potential adverse effects on Central Nervous System (CNS), respiratory and cardiovascular systems were evaluated by monitoring of clinical signs and recording of electrocardiograms (ECG) in single and/or repeat-dose toxicity studies. Taliglucerase alfa and imiglucerase exhibited similar enzyme kinetics towards a fluorescent short-chain analogue of the natural substrate. Taliglucerase alfa and imiglucerase were taken up by mouse and human peritoneal macrophages, and maintained enzymatic activity after internalisation. Uptake of taliglucerase alfa tended to be higher than the uptake of imiglucerase. Uptake of both products was inhibited by yeast mannan, a specific ligand for mannose (Man/GlcNac) receptors.

Macrophages from rats, rabbits, humans and monkeys were incubated with taliglucerase alfa *in vitro*. Concentration-dependent uptake of taliglucerase alfa was observed in all of these species. Furthermore, mannan produced an inhibition of uptake ranging from 50 to 90%. These data confirmed that the species used in the non-clinical toxicology programme (mice, rats, monkeys,

and rabbits) were relevant and, therefore, the safety data can be considered relevant for assessing the risk for potential adverse effects in humans.

TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on data analysis from studies of safety pharmacology, single, repeated dose toxicity and toxicity to reproduction and development. Pre and post-natal development studies have not been conducted with taliglucerase alfa.

Nonclinical toxicology studies to establish the safety of taliglucerase alfa included single-dose toxicity studies in mice and monkeys, repeat-dose toxicity studies in marmoset and cynomolgus monkeys, and reproductive toxicity studies in rats and rabbits. In these studies, taliglucerase alfa was dosed by IV administration, the intended clinical route.

Single dose toxicity:
A single IV bolus injection of taliglucerase alfa to male and female mice at dose levels of 1.8, 9 or 18 mg/kg did not result in mortality or test article-related clinical signs. No effect was noted on body weight. Gross necropsy revealed no noteworthy findings. The lack of systemic toxicity at 18 mg/kg was confirmed in a second (non-GLP compliant) study in mice, with evaluations extended to clinical pathology and istopathology of liver, kidney and spleen.

Repeat-dose toxicity:
The repeat-dose studies were conducted in monkeys up to a dose level of 5 times the maximum clinical dose of taliglucerase alfa (60 units/kg) on a mg/m^2 basis and up to a duration of 39 weeks with twice monthly dosing. The latter regimen mimicked the proposed clinical treatment regimen and took into account the chronic indication. Repeat-dose toxicity studies with taliglucerase alfa provided no indication of target organs subject to age-related development. The repeat-dose studies also included evaluations of local tolerance and immunogenicity.

Carcinogenicity and Genotoxicity:
Genotoxicity and carcinogenicity studies were not considered necessary for taliglucerase alfa, based on the ICH S6 Guideline. In addition, based on its protein nature, its well understood pharmacological mechanism of action, data from the 39-week toxicity study and the clinical history of ERT in Gaucher's disease, there was not a cause for concern regarding carcinogenicity.

Reproductive and Developmental toxicity:
To assess the potential reproductive and developmental effects of taliglucerase alfa, a rat fertility and early embryonic development study was conducted along with embryo-foetal development studies in rats and rabbits.

In the rat fertility and early embryonic development study, male and female rats received taliglucerase alfa at dose levels of 11 or 55 mg/kg by slow bolus injection once every 3 or 4 days.

Taliglucerase alfa did not affect fertility or reproductive performance indices. The only observation was swollen limbs/paws and/or swollen face or muzzle at 55 mg/kg/dose, during the 30-90 minute post dose examination.

The NOAEL was determined to be 55 mg/kg/dose for reproductive toxicity and 11 mg/kg/dose for parental toxicity.

Embryo-foetal development studies were conducted in rats and rabbits. Pregnant rats received taliglucerase alfa by slow bolus injection at dose levels of 11 and 55 mg/kg. The NOAEL was at least 55 mg/kg/dose for developmental toxicity and 11 mg/kg/dose for maternal toxicity in pregnant rats. Pregnant rabbits were given taliglucerase alfa by slow bolus injection at dose levels of 5.6 and 27.8 mg/kg. In rats, maternal effects were limited to clinical signs (swollen limbs/paws, and/or swollen face or muzzle which resolved between doses), primarily occurring on treatment days at 55 mg/kg/dose. No test article-related maternal effects were recorded in rabbits. The NOAEL was at least 27.8 mg/kg/dose for both developmental and maternal toxicity in pregnant rabbits.

The NOAELs from these two embryo-foetal development studies correspond to a 5-fold multiple of the proposed maximum human dose of 66 mg/m^2 (equivalent to 60 units/kg).

Local tolerance:
Local injection site changes were noted in the repeat-dose studies. Microscopic changes at the injection site occurred and primarily included haemorrhage and inflammation.

Other toxicity:
To evaluate possible immune effects, antibody assessments were performed in the 4-week marmoset monkey study, the 4-week cynomolgus monkey study and the 39-week cynomolgus monkey study. None of the antibodies detected in any of these studies was neutralizing. The pattern of antibody response observed in the repeat-dose toxicity studies indicates that taliglucerase alfa has a low potential for immunogenicity. There was no consistency in the dose, gender, and time responses to treatment.

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PART III: CONSUMER INFORMATION

Pr ELELYSO ®
Taliglucerase alfa

This leaflet is part III of a three-part "Product Monograph" published when ELELYSO was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ELELYSO. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
ELELYSO is an enzyme replacement therapy for pediatric and adult patients with Gaucher disease.

What it does:
Gaucher disease is a genetic disorder caused by a missing or defective enzyme name glucocerebrosidase. When this enzyme is missing or does not work properly, a substance called glucocerebroside builds up inside cells in the body. The build-up of this substance causes the signs and symptoms found in Gaucher disease.

Signs of the disease are one or more of the following:
- Spleen or liver enlargement
- A low number of red blood cells (anaemia)
- A tendency to bleed easily caused by a low blood platelet count
- Bone disease

When it should not be used:
Do not use ELELYSO if you are allergic to taliglucerase alfa or to any ingredient in the formulation or component of the container.

What the medicinal ingredient is:
Taliglucerase alfa

What the important nonmedicinal ingredients are:
Citric acid anhydrous, Mannitol, Polysorbate 80, Sodium citrate.

What dosage forms it comes in:
ELELYSO 200 units is presented as a powder for solution for infusion. ELELYSO is supplied in a 13.5mL vial.

WARNINGS AND PRECAUTIONS

BEFORE you use ELELYSO talk to your doctor or pharmacist if:
- You have previously experienced an adverse reaction related to the infusion or allergic reaction with another enzyme replacement therapy for Gaucher disease
- You have allergies to this drug or its ingredients or components of the container; or if you are allergic to carrots
- You are pregnant or plan to become pregnant or are breast-feeding

INTERACTIONS WITH THIS MEDICATION

No interaction studies have been performed. Please inform your doctor if you are using any other medicinal products.

PROPER USE OF THIS MEDICATION

Usual dose:
Dosage is individualized for each patient. ELELYSO is only used under the supervision of a health care professional. If you are tolerating your infusions well in the clinic, your doctor may suggest that the infusion be administered at home by a health care professional.

The initial doses of ELELYSO range from 30 units/kg to 60 units/kg of body weight.

ELELYSO is given once every two weeks.

Overdose:
There is no experience with overdose of taliglucerase alfa with doses over 78 units/kg.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you have missed an ELELYSO infusion, please contact your doctor.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ELELYSO can cause side effects, although not everybody gets them.

Most side effects are mild to moderate and generally are associated with the infusion however side effects may be serious and may need treatment.

Very common side effect (these are likely to affect more than 10 in every 100 people):
- Headache
- Abdominal pain
- Pain in extremity, Joint pain
- Fatigue
- Vomiting
- Back pain
- Itching

Common side effects (these are likely to affect between 1 and 10 in every 100 people):
- Allergic reactions
- Dizziness
- Flushing
- Throat irritation
- Nausea

- Redness
- Rash
- Bone pain
- Infusion related reaction
- Infusion site pain
- Swelling
- Weight increase

If you experience any of these symptoms, please tell your doctor immediately.

The most serious adverse reactions seen were allergic reactions. If you have an allergic reaction following administration of ELELYSO, contact your doctor immediately. If a severe allergic reaction occurs, immediately discontinue ELELYSO. If you experience an allergic reaction your doctor or nurse may continue treatment by slowing the infusion rate and/or giving you medicines such as antihistamines, antipyretics or corticosteroids. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions.

HOW TO STORE IT

Keep out of reach and sight of children.

Unopened vial: store under refrigeration (2°-8°C). Keep the vial in the outer carton in order to protect from light. Do not use after the expiry date printed on the label.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

$ Report online at www.healthcanada.gc.ca/medeffect

$ Call toll-free at 1-866-234-2345

$ Complete a Canada Vigilance Reporting Form and:

- Fax toll-free to 1-866-678-6789, or

- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 1908C
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.Pfizer.ca or by contacting the sponsor, Pfizer Canada Inc., at: 1-800-463-6001

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