SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ELELYSO® 200 units/vial powder for solution for intravenous infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of ELELYSO contains 200 units* of taliglucerase alfa**.

Contains sugar (mannitol).

After reconstitution, the solution contains 40 units (approximately 1,2 mg) of taliglucerase alfa per mL (200 units/5 mL).

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

**Taliglucerase alfa is a recombinant form of human glucocerebrosidase expressed in genetically modified carrot plant cells in suspension that naturally bears terminal mannose structures for targeting macrophages.

Excipients with known effect

One vial of ELELYSO contains 0,3 mmol sodium and 206,7 mg of mannitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion

A white to off-white lyophilised powder that may form a cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ELELYSO is indicated for long-term enzyme replacement therapy for adult and paediatric patients with a confirmed diagnosis of Type 1 Gaucher disease associated with at least one of the following: splenomegaly, hepatomegaly, anaemia, thrombocytopenia.

4.2 Posology and method of administration

Treatment with ELELYSO should be supervised by a medical practitioner experienced in the management of patients with Gaucher disease. Home administration under the supervision of a healthcare professional trained in recognising and medically managing serious infusion-related reactions under the direction of a practising medical practitioner may be considered only for those patients who have been tolerating their infusions.

Posology

ELELYSO must be administered by intravenous infusion over a period from 60 to 120 minutes. Due to the heterogeneity and the multi-systemic nature of Gaucher disease, dosage must be individualised to each patient. Dose requirements may increase or decrease, based on achievement of therapeutic goals, as assessed by regular comprehensive evaluations of the patient's clinical manifestations.

Initial doses of ELELYSO in adult and paediatric (2 years to 17 years of age) patients range from 30 units/kg to 60 units/kg of body weight once every 2 weeks, depending on the clinical assessment of the treating medical practitioner.

Patients currently being treated with imiglucerase for Gaucher disease can be switched to ELELYSO. It is recommended that patients previously treated on a stable dose of imiglucerase begin treatment with ELELYSO at the same dose as imiglucerase when they switch from imiglucerase to ELELYSO.

Special populations

Elderly population

During clinical studies, 8 patients 65 years of age or older were treated with ELELYSO. This limited data set does not indicate the need for dose adjustment in this age group.

Paediatric population

During clinical studies, 16 patients 2 years to 17 years of age were treated with ELELYSO. The safety and efficacy profiles were similar between adult and paediatric patients.

Method of administration

After reconstitution and dilution, the preparation is administered by intravenous infusion over a period from 60 minutes to 120 minutes. The duration of infusion may be adjusted as tolerated by the patient. The total volume of the infusion solution should be delivered over a period of no less than 60 minutes (see section 6.6).

Each vial of ELELYSO is for single use only in one patient only.

4.3 Contraindications

ELELYSO is contraindicated:

- in patients who have known severe allergic reactions to taliglucerase alfa, other similar glucocerebrosidase enzymes or to any of the excipients of ELELYSO (see sections 4.4 and 6.1).
- in patients who have a known allergy to carrots.

4.4 Special warnings and precautions for use

Infusion-related reactions and hypersensitivity

As with any intravenous protein product, infusion-related reactions and hypersensitivity reactions, including anaphylaxis, are possible, therefore appropriate medical support should be readily available when ELELYSO is administered. Infusion-related reactions and allergic hypersensitivity reactions have been reported with ELELYSO.

Infusion-related reactions usually represent symptoms occurring within 24 hours of the infusion and are not necessarily linked to anaphylaxis or hypersensitivity. They may include symptoms such as arthralgia,

headache, vomiting, flushing, pruritus, pain in extremity, diarrhoea, chest discomfort, feeling hot, muscle spasms, tremor and throat irritation. They can usually be managed successfully by decreasing the infusion rate, temporarily stopping the infusion or administering antihistamines and/or analgesics/antipyretics.

Anaphylaxis has been observed in some patients treated with ELELYSO. If anaphylaxis occurs, immediately discontinue the infusion and initiate appropriate treatment.

Hypersensitivity (which may include anaphylaxis) is characterised by hypotension, bronchospasm, laryngeal oedema, wheezing and urticaria. Patients who experience hypersensitivity can usually be treated with medicines such as antihistamines, antipyretics and/or corticosteroids. Hypersensitivity may contraindicate further treatment, however, pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions. Hypersensitivity events occur more commonly within the first 3 months of starting treatment, however, they may occur at any time therefore ongoing monitoring is required.

If a severe allergic reaction occurs, current medical standards for emergency treatment should be followed and the immediate discontinuation of the ELELYSO infusion is recommended.

Antibody response/immunogenicity

As with other therapeutic proteins, the development of immunoglobulin G (IgG) anti-drug antibodies (ADA) to ELELYSO has been described. Hypersensitivity reactions occur in patients with and without ADA but are more common among those with ADA, some of whom experience anaphylactic reactions.

In a study in enzyme replacement therapy (ERT)-naïve adult patients, seventeen of thirty-two patients (17 of 32; 53 %) who were administered taliglucerase alfa every two weeks developed ADA post-treatment (defined as ADA-positive at one or more post-treatment time points). Two additional patients were ADA-positive at baseline; one patient withdrew after developing an allergic reaction with the first dose of taliglucerase alfa, and the second patient became ADA-negative at 21 months of treatment and remained negative thereafter with continued treatment. In ERT-naïve paediatric patients, 2 of 11 (18 %) patients developed ADA. One ERT-naïve paediatric patient was ADA-positive at baseline but became

ADA-negative following treatment with taliglucerase alfa. In a study in ERT-experienced adult and paediatric patients (N=31; 26 adult patients and 5 paediatric patients), 5 adult patients (16 % of all patients) who switched from imiglucerase treatment to taliglucerase alfa treatment once every two weeks developed ADA after the switch. None of the ERT-experienced paediatric patients developed ADA after switching from imiglucerase treatment to taliglucerase alfa treatment. In the ERT-experienced population, two adult and two paediatric patients who switched from imiglucerase were ADA-positive at baseline but ADA-negative following ELELYSO treatment. One of these ERT-experienced adults subsequently became ADA-positive following continued treatment. The relevance of ADA to adverse events is currently unclear.

Using neutralising antibody assays of limited sensitivity, the following patients were determined to be positive for neutralising activity in an *in vitro* enzyme inhibition assay.

- three treatment-naïve adult patients (one patient initially tested positive at 18 months, one at 21 months and one at 42 months of ELELYSO treatment)
- one adult patient switched from imiglucerase (initially tested positive at 9 months of ELELYSO treatment)
- one treatment naïve paediatric patient (initially tested positive at 36 months of ELELYSO treatment)

The significance of these findings is unknown at this time.

There has been no demonstrated consistent association between positive neutralising antibody assay results and therapeutic response, however, in three patients with anti-neutralising antibodies, there was a tendency to lower haematological response. It may be useful for medical practitioners to measure neutralising antibodies in patients where there is a lack of therapeutic response at a reasonable dose.

Testing for anti-taliglucerase antibodies should be considered in cases of severe infusion-related reactions or hypersensitivity. High or rising titres or the presence of neutralising antibodies would be of concern.

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.

Pulmonary hypertension

Pulmonary hypertension is a known complication of Gaucher disease. Patients with respiratory symptoms should be evaluated for the presence of pulmonary hypertension.

Routine evaluation to detect the presence of pulmonary hypertension after diagnosis of Gaucher disease and over time is recommended. Patients diagnosed with pulmonary hypertension should receive adequate doses of ELELYSO to ensure control of underlying Gaucher disease as well as be evaluated for the need of additional pulmonary hypertension specific treatments.

Allergy to carrots

The occurrence of allergic reactions to ELELYSO in patients with known carrot allergies has not been studied in clinical trials and is currently unknown (see section 4.3). If infusion-related reactions or hypersensitivity occurs, patients should be managed as described above.

Neuronopathic Gaucher disease

Patients with severe and complex neurological symptoms were excluded from clinical studies; paediatric patients with longstanding oculomotor gaze palsy and/or mutations suggestive of neuronopathic disease were permitted to enrol. Two out of 11 (18 %) patients in the paediatric study (PB-06-005) for patients naïve to enzyme replacement therapy were diagnosed with Type 3c disease and one child in the switch trial possessed the homozygote L444P genotype. There is no clinical experience with the use of ELELYSO in patients with Type 2 Gaucher disease.

Special populations

Use in renal and hepatic impairment

Studies of ELELYSO in patients with Gaucher disease with renal or hepatic impairment have not been conducted.

Use in the elderly

Clinical studies of ELELYSO did not include sufficient numbers of patients 65 years of age and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient requires caution, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other medicine therapy in this patient group.

Effects on laboratory tests

No data available.

Paediatric population

ELELYSO safety and efficacy profiles were similar between adult and paediatric patients. However, the number of children involved in the clinical trials is small.

Excipients with known effect

Sodium

This medicine contains sodium and is administered in 9 mg/mL (0,9 %) sodium chloride intravenous solution. This should be taken into consideration when administered to patients on a controlled sodium diet.

Mannitol

ELELYSO contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

In the absence of compatibility studies, ELELYSO should not be mixed with other medicines, except those mentioned in section 6.6.

4.6 Fertility, pregnancy and lactation

Pregnancy

Reproductive toxicity studies using pregnant rats and rabbits given high doses of taliglucerase alfa revealed no evidence of harm to the foetus. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, caution should be exercised when prescribing to pregnant women and this medicine should only be used during pregnancy if the potential benefit justifies the risk.

Breastfeeding

It is unknown whether ELELYSO is excreted in animal or human breast milk. Because many medicines are excreted in human milk, caution should be exercised when ELELYSO is administered to a breastfeeding woman.

Fertility

Taliglucerase alfa did not affect fertility or reproductive performance in male and female rats.

4.7 Effects on ability to drive and use machines

Patients should be aware of how they react to ELELYSO before driving or operating machinery as dizziness has been reported in clinical trials with ELELYSO.

4.8 Undesirable effects

Summary of the safety profile

The safety of ELELYSO has been evaluated in over 130 patients with Gaucher disease; data from 74 patients in controlled clinical trials were used to determine the frequency of adverse drug reactions (Table 1). ELELYSO was administered in median doses of 9 units/kg to 78 units/kg of body weight every 2 weeks, for treatment durations of up to 60 months.

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

The most serious adverse reactions in patients in clinical trials were immune-mediated adverse events of Type 1 hypersensitivity reactions (see section 4.4).

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

The safety of ELELYSO has been established in paediatric patients from 2 to 16 years of age. One treatment-related serious adverse event was reported in paediatric clinical trials; an 8-year-old patient experienced a serious adverse reaction (gastroenteritis). There does not appear to be a major difference in frequency of adverse reactions in paediatric patients compared to adult patients, with the exception that vomiting and abdominal pain were seen more commonly in paediatric patients.

Tabulated summary of adverse reactions

The adverse reactions reported in patients with Gaucher disease are listed in Table 1 (all adult and paediatric patients). The adverse event terms in clinical studies were categorised utilising the incidence rate as follows: very common ≥ 1/10; common ≥ 1/100 to < 1/10; uncommon ≥ 1/1 000 to < 1/100; rare ≥ 1/10 000 to < 1/1 000; very rare < 1/10 000. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

*Table 1: Adverse reactions reported in Phase 3 clinical studies**

System organ class	Frequency	Side effect
Immune system disorders	Common	Hypersensitivity

Nervous system disorders	Very common	Headache Dizziness
Vascular disorders	Common	Flushing
Respiratory, thoracic and mediastinal disorders	Common	Throat irritation
Gastrointestinal disorders	Very common	Vomiting Abdominal pain [a]
	Common	Nausea
Skin and subcutaneous tissue disorders	Common	Pruritus Erythema Rash
	Frequency not known (cannot be estimated from the available data)	Angioedema [b]
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Pain in extremity
	Common	Bone pain Back pain
General disorders and administration site conditions	Common	Infusion site pain Fatigue Peripheral oedema
Injury, poisoning and procedural complications	Common	Infusion-related reaction
Investigations	Common	Increased weight

[a] Abdominal pain includes upper abdominal pain and lower abdominal pain.

[b] Angioedema includes eyelid oedema, angioedema, lip oedema, face swelling, conjunctival oedema, eye swelling, lip swelling, mouth oedema, swollen tongue, and laryngeal oedema.

* Frequency of adverse drug reactions was calculated from all causality adverse event data.

Post-marketing experience

The limited post-marketing experience with ELELYSO is consistent with the above profile.

The following adverse events were reported during post-marketing surveillance:

Immune system disorders: anaphylactic reaction

Skin and subcutaneous tissue disorders: urticaria

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alimentary tract and metabolism - enzymes.

ATC code: A16AB11

Mechanism of action

Taliglucerase alfa is a recombinant active form of the human lysosomal enzyme, β-Glucocerebrosidase, expressed in genetically modified carrot plant root cells. β-Glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase, E.C. 3.2.1.45) is a lysosomal glycoprotein enzyme that catalyses the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

Gaucher disease is caused by point mutations in the human glucocerebrosidase (hGCD) gene, which result in a less active endogenous enzyme resulting in the accumulation of glucocerebroside in the lysosomes of macrophages.

The characteristic glycolipid-laden macrophages, called Gaucher cells, are found in liver, spleen and bone marrow. The associated clinical systemic symptoms include severe hepatosplenomegaly as well as anaemia, thrombocytopenia and skeletal deterioration in the form of osteonecrosis, pathological fractures associated with osteopaenia, remodelling failure and bone crises. The oligosaccharide chains at taliglucerase alfa glycosylation sites have terminal mannose sugars that are necessary for interaction with mannose receptors present on macrophages. Taliglucerase alfa uptake by macrophages was shown, in *in vitro* studies with both mouse and human cells, to be in large part mediated by mannose receptors.

Clinical trials

Study in adult patients naïve to enzyme replacement therapy (PB-06-001)

The safety and efficacy of taliglucerase alfa was evaluated in a pivotal, multi-centre, double-blind, randomised Phase III study investigating two dose groups, 30 units/kg and 60 units/kg. The study was conducted in 31 adult patients, aged 18 years of age and above, with Gaucher disease (PB-06-001) who were treatment naïve to enzyme replacement therapy (ERT).

Patients with a confirmed diagnosis of Gaucher disease (leukocyte GCD activity level ≤ 3 nmol/mg*hr (≤ 30 % of the mean activity of the reference range), enlarged spleens (> 8 times normal) and thrombocytopenia (< 120 000/mm^3) were eligible. Patients could not have received ERT in the past or for at least 12 months prior to study entry and must have had a negative anti-glucocerebrosidase antibody test result at screening. Patients must not have received substrate reduction therapy (SRT) in the past

12 months. Bone disease was not part of the inclusion criteria. Patients with severe neurological symptoms were excluded from the study.

The primary endpoint was percent change from baseline in spleen volume measured by MRI at month 9. Major secondary endpoints included change from baseline in haemoglobin, liver volume (percent change) and platelet count. Change from baseline in Quantitative Chemical Shift Imaging (QCSI) technique, which measures bone marrow fat fraction (Ff) and Dual-Energy X-ray Absorptiometry (DEXA), which measures mineral density, were evaluated as tertiary endpoints.

Intravenous infusions were administered every 2 weeks for 9 months (i.e., 38 weeks). Thirty-one (31) patients treated with 30 units/kg (n=15) and 60 units/kg (n=16) were evaluated for efficacy. Patient age ranged from 19 to 74 years of age (mean age 36 years), of these 48 % (15/31) were male. Sixteen (16) patients had enlarged livers and 10 patients had anaemia at baseline. All patients were naïve to ERT.

Both dose groups, 30 units/kg and 60 units/kg, demonstrated a statistically significant reduction in spleen volume compared with baseline at the month 6 visit (22,21 % and 29,94 % respectively; both *p*<0,0001) and month 9 visit (26,91 % and 38,01 % respectively; both *p*<0,0001). Similar effects were observed for haemoglobin increase, liver volume decrease and platelet count increase as noted in Table 2.

Table 2: Summary of clinical parameters: mean change from baseline to 9 months and comparison between dose groups in study PB-06-001 (n=31; intention-to-treat population)

Clinical Parameters		Taliglucerase alfa 30 units/kg n=15	Taliglucerase alfa 60 units/kg n=16	Comparison between dose groups 30 vs. 60 units/kg
Spleen volume % change	Mean (SD)	-26,91 (7,79)	-38,01 (9,38)	NA
	p value	<0,0001	<0,0001	0,060
Haemoglobin g/dL change	Mean (SD)	1,6 (1,4)	2,2 (1,4)	NA
	p value	0,0010	<0,0001	0,719

Liver volume % change	Mean (SD)	-10,48 (11,27)	-11,11 (6,68)	NA
	p value	0,0041	<0,0001	0,349
Platelet count /mm^3 change	Mean (SD)	11 427 (20 214)	41 494 (47 063)	NA
	p value	0,0460*	0,0031	0,042

SD: standard deviation; NA: not applicable.

*Clinically relevant improvement in platelet count at month 9 was also observed for the taliglucerase alfa 30 units/kg dose group (11 427/mm^3, p=0,0460), but did not meet the pre-specified alpha level of 0,025.

As tertiary endpoints, bone involvement was assessed pre-treatment and at 9 months in a subset of 8 out of 31 (26 %) treatment naïve patients using the QCSI technique and DEXA. A trend in improvement of the mean change of T and Z score for lumbar spine and femoral neck were observed after 9 months treatment in both dose groups.

Twenty-six of the 31 patients in the 9-month clinical trial continued treatment with taliglucerase alfa in extension trials. Total combined study duration with taliglucerase alfa was 60 months, the first 24 months of which were conducted as a double-blind trial and the remaining 36 months as open-label. Twenty-six patients completed 24 months, 23 completed 36 months and 17 completed 60 months. The following data are the changes in clinical parameters for the double-blind portion of the extension trial (from baseline to Month 24) for the 30 units/kg (n=12) and 60 units/kg (n=14) dose groups, respectively: median (range) spleen volume expressed as % BW decreased 1,4 (0,7; 2,7) and 1,3 (0,6; 8,0), and as multiples of normal (MN) decreased 7,1 (3,3; 13,3) and 6,6 (3,0; 39,9); haemoglobin increased 1,2 (-1,2; 5,0) g/dL and 1,6 (-1,5; 7,3) g/dL; liver volume expressed as % BW decreased 0,9 (0,4; 2,6) and 1,0 (-0,2; 2,8), and decreased 0,4 (0,2; 1,0) and 0,4 (-0,1; 1,1) MN; and platelet count increased 15 350 (-14 000, 87 000)/mm^3 and 49 000 (-10 000, 202 000)/mm^3. Patients in the open-label portion of the extension trials demonstrated median improvements from baseline that were generally maintained across the measurement time points of the open label period for these outcomes.

Study in patients switching from imiglucerase to taliglucerase alfa (PB-06-002)

A multi-centre, open-label, single arm 9-month study in clinically stable adult and paediatric Gaucher disease patients (2 years of age or above) treated with imiglucerase and switched to taliglucerase alfa at the same dose as the previous imiglucerase dose was performed (PB-06-002).

Patients were required to be clinically stable and to have a stable biweekly dose of imiglucerase for at least 6 months prior to enrolment. Patient age ranged from 13 to 66 years of age (mean 45 years of age), 46 % were male. Imiglucerase therapy was stopped, and treatment with taliglucerase alfa was administered every 2 weeks. Adjustment of dose was allowed by study criteria if needed to maintain clinical parameters (i.e., haemoglobin, platelet count, spleen volume, and liver volume). One patient required a dose increase (from 9,5 units/kg to 19 units/kg at week 24) for a platelet count of 92 000/mm^3 at week 22 and responded with a platelet count of 170 000/mm^3 at month 9.

Primary efficacy endpoints included platelet count, haemoglobin, spleen volume, liver volume and biomarkers (chitotriosidase and PARC/CCL18). Secondary endpoints for paediatric patients included: height and weight for growth evaluation; Tanner Stage for sexual development; and bone age by X-ray of left hand and wrist.

Twenty-six clinically stable adult patients were enrolled and 25 completed 9 months of treatment. Doses ranged from 9 units/kg to 60 units/kg with a mean of 28,8 units/kg. The age range was 18 years to 66 years and 14 patients were male and 12 were female.

Organ volumes remained stable. Median spleen volume was 814,2 mL at baseline and 697,3 mL after 9 months, and the respective median liver volumes were 1 816,5 mL at baseline and 1 800,6 mL at 9 months. Haematological parameters were also stable. Median haemoglobin levels were 13,6 g/dL at both baseline and after 9 months, and median platelet counts were 163 167/mm^3 at baseline and 159 000/mm^3 after 9 months.

Five paediatric patients were enrolled and completed the trial. Median doses ranged from 26 units/kg to 60 units/kg. The age range was 6 years to 16 years; 3 patients were male and 2 were female. Organ

volumes remained stable. Median spleen values were 324 mL at baseline and 256 mL at 9 months. Median liver values were 1 243 mL at baseline and 1 305 mL at 9 months. Haematological parameters were also stable. Median haemoglobin was 13,4 g/dL and 14,3 g/dL at baseline and 9 months, respectively. Median platelet count was 146 500/mm^3 and 200 000/mm^3 at baseline and 9 months, respectively.

All five paediatric patients in the 9-month clinical trial continued treatment with taliglucerase alfa in an extension trial for a total treatment duration of 33 months. All five patients completed 24 months and 2 patients completed 33 months. The following data are the changes from baseline in clinical parameters at month 33 (n=2): mean (SD) spleen volume expressed as % BW was stable 0,0 (0,0), and decreased 0,1 (0,0) MN; haemoglobin increased 0,5 (0,5) g/dL; liver volume expressed as % BW decreased 0,2 (0,0), and decreased 0,1 (0,0) MN; and platelet count increased 4 700 (13 152)/mm^3.

Eighteen of the 26 adult patients who completed the 9-month clinical trial continued treatment with taliglucerase alfa in an extension trial (PB-06-003). The five paediatric patients continued into a separate extension study (PB-06-006). Ten adult patients completed 36 months of treatment. At month 36, the changes in clinical parameters from baseline for adult patients were: mean (SD) spleen volume in % BW -0,3 (0,5), in MN -1,3 (2,3); liver volume in % BW 0,0 (0,4), in MN 0,0 (0,2); platelet count -3 800 (33 920)/mm^3; and haemoglobin -0,2 (0,9) g/dL.

Expanded access study (PB-06-004)

A multi-centre, open-label, expanded access trial was designed to assess the safety of taliglucerase alfa in patients with Gaucher disease who required ERT due to a shortage of imiglucerase product. Study duration was up to 33 months, or until marketing approval was obtained and taliglucerase alfa was available. Patients previously treated with imiglucerase were to receive the same dose as the previous imiglucerase dose, before dose reduction or discontinuation. Patient age ranged from 21 to 85 years of age (mean 46 years of age), 55 % were male.

The study was not comparative and no formal hypothesis testing for efficacy was planned or done. Nonetheless, the data from the efficacy population indicate that in patients previously treated with

imiglucerase, the mean haemoglobin concentration and platelet counts were stable during long term treatment with taliglucerase alfa.

Two patients withdrew from the study specifically because of adverse events (AE) which involved infusion-related reactions (periorbital swelling in one and chest discomfort in the other). These reactions were characterised as mild to moderate. A third patient had mild hypersensitivity reactions during many of the infusions but was able to continue receiving the study medicine and completed the study.

Most adverse events were mild or moderate and were not related to the study medicine. Thirty six of the 58 treated patients completed the study and most of the 22 patients who discontinued early voluntarily withdrew because taliglucerase alfa became commercially available in their country.

An extension study in adult patients who completed studies PB-06-001 or PB-06-002 (PB-06-003)

An open label, extension trial in patients with Gaucher disease, who completed nine months of treatment in Studies PB-06-001 or PB-06-002. Patients continued to receive the allocated dose from Study PB-06-001, or the same dose they received at the completion of Study PB-06-002. Forty-four (44) patients received treatment with taliglucerase alfa for at least 15 months and for a total of no more than 30 months.

The efficacy results provided evidence that taliglucerase alfa-maintained effectiveness for as long as 39 months. Continued improvement was observed in spleen and liver volumes and in haematological parameters in patients naïve to ERT.

Paediatric population

Study in paediatric patients naïve to enzyme replacement therapy (PB-06-005)

A pivotal, multi-centre, double-blind, randomised Phase III study of 30 units/kg or 60 units/kg was conducted in paediatric patients (2 to 17 years of age) with confirmed Gaucher disease (leukocyte acid β-Glucosidase activity level ≤ 30 % of the mean activity of the reference range for healthy patients) and who were naïve to ERT (PB-06-005). Eligibility criteria was as per study PB-06-001 (given above), with the additional exclusion criteria of patients with complex neuronopathic features other than longstanding oculomotor gaze palsy; unresolved anaemia due to iron, folic acid or vitamin B12 deficiency, a history of

allergy to carrots, HIV, HBsAg and/or hepatitis C infections.

The primary endpoint was measured by percent (%) change in haemoglobin. Secondary endpoints included chitotriosidase or CCL18, spleen and liver volume evaluated by MRI (or ultrasound), platelet count, change in growth and development (weight, height, Tanner Stage, bone age), bone disease and Quality of Life from baseline. The safety of taliglucerase alfa was assessed by clinical laboratory, physical examination, echocardiography and adverse events. Anti-taliglucerase alfa antibodies were also assessed.

Intravenous infusions were administered every 2 weeks for 12 months. Eleven patients treated with 30 units/kg (n=6) and 60 units/kg (n=5) were evaluated for efficacy, of these 8 (72 %) patients were male and ranged from 2 to 14 years of age.

Both dosage groups, 30 units/kg and 60 units/kg, demonstrated an increase in haemoglobin from baseline (11,3 g/dL and 10,6 g/dL, respectively) at Month 12 (12,7 g/dL, increase 13,8 % and 12,2 g/dL, increase 15,8 %, respectively). Haemoglobin rose 19,4 % (30 units/kg) and 16,9 % (60 units/kg) in those patient's anaemic at baseline. Similar effects were observed for spleen volume decrease, liver volume decrease and platelet count increase as noted in Table 3 below.

Table 3: Summary of clinical parameters: mean change from baseline to 12 months and comparison between dose groups in the paediatric naïve study PB-06-005 (n=11; intention-to-treat population)

Clinical parameters		Taliglucerase alfa 30 units/kg (n=6)	Taliglucerase alfa 60 units/kg (n=5)
Spleen volume (mL) % change	Mean (SD)	-28,6 (21,5)	-41,1 (13,8)
	Median	-32,2	-33,3
	Range	(-52; -1)	(-61; -30)
Spleen volume per body weight (% L/kg)	Mean (SD)	-34,1 (22,7)	-48,5 (12,3)
	Median	-37,2	-41,3
	Range	(-57,6; 1,5)	(-64,5; -37,5)
Haemoglobin	Mean	1,4 (1,3)	1,6 (0,7)

g/dL change	(SD)		
	Median	1,4	1,6
	Range	(0; 3)	(1; 2)
Liver volume % change	Mean (SD)	-6,3 (8,5)	-14,0 (9,0)
	Median	-10,2	-16,1
	Range	(-12; 11)	(-27; -5)
Liver volume per body weight (% L/kg)	Mean (SD)	-14,5 (6,5)	-19,2 (8,3)
	Median	-15,7	-22
	Range	(-21,6; -5,6)	(-33,9; -18,9)
Platelet count /mm^3 change	Mean (SD)	45 500 (52 884)	72 600 (59 197)
	Median	28 000	51 000
	Range	(-12 000; 120 000)	(1 000; 136 000)

SD: standard deviation

Auxological parameters for the paediatric cohort, including height, height velocity and weight, all improved on taliglucerase alfa therapy as shown in Table 4.

Table 4: Paediatric auxological data for study PB-06-005

Clinical parameter	Time point	Taliglucerase alfa 30 units/kg (n=6)	Taliglucerase alfa 60 units/kg (n=5)
Height (cm)	Baseline (mean (SD))	129,3 (21,7)	107,8 (14,3)
	Month 12 (mean (SD))	134,4 (20,8)	115,7 (13,9)
	% Change (SD)	4,2 (2,2)	7,6 (2,1)
Height SDS by chronologic age	Baseline (mean (SD))	-1,3 (1,3)	-2,5 (1,2)
	Month 12 (mean (SD))	-1,3 (1,5)	-2,0 (1,0)
	% Change (SD)	0,0 (0,3)	0,5 (0,2)

Height velocity (cm/yr)	Month 12 (mean (SD))	5,1 (2,2)	8,0 (1,3)
Weight (kg)	Baseline (mean (SD))	27,9 (10,5)	17,7 (4,8)
	Month 12 (mean (SD))	30,3 (10,5)	20,4 (6,0)
	% Change (SD)	9,6 (7,0)	14,7 (5,7)
Weight SDS by chronologic age	Baseline (mean (SD))	-0,8 (1,5)	-2,0 (1,8)
	Month 12 (mean (SD))	-0,8 (1,8)	-1,8 (1,8)
	% Change (SD)	0,0 (0,3)	0,2 (0,3)

SDS = standard deviation scores

Ten of the 11 paediatric patients in the 12-month clinical trial continued treatment with taliglucerase alfa in an extension trial for a total treatment duration of 36 months, the first 24 months of which were conducted as a double-blind trial, while the remaining 12 months were open-label. All ten patients completed 24 months and 9 of these completed 36 months. The following data are the changes in clinical parameters for the double-blind portion (from baseline to Month 24) for the 30 units/kg (n=5) and 60 units/kg dose groups (n=5), respectively: median (range) spleen volume expressed as % BW decreased 3,6 (2,0; 4,0) and 3,8 (1,0; 11,2), and as MN decreased 17,9 (9,8; 20,1) and 19,0 (5,1; 56,0); haemoglobin increased 1,7 (1,1; 3,3) g/dL and 2,5 (-0,1; 3,5) g/dL; liver volume expressed as % BW decreased 1,4 (1,1; 2,2) and 2,1 (1,1; 3,2) and decreased 0,6 (0,4; 0,9) and 0,8 (0,5; 1,3) MN; and platelet count increased 16 000 (-25 000, 76 000)/mm^3 and 76 000 (66 000, 157 000)/mm^3. Patients in the open-label portion of the extension trials demonstrated median improvements from baseline that were generally maintained across the measurement time points of the open label period for these outcomes.

5.2 Pharmacokinetic properties

Clinical Pharmacokinetics

Adult population

In 32 adult patients with Gaucher disease, taliglucerase alfa was rapidly eliminated. Patients received a single dose by intravenous infusion over 1 to 2 hours at a dose of 30 units/kg or 60 units/kg. After continued biweekly dosing there was no clear indication of accumulation. At steady state at week 38, the mean AUC_t (exposure) appears to suggest a more than dose proportional increase in AUC_t. There were no observed clinically relevant gender related differences in exposure (AUC).

Mean clearance was about 30 L/hr at 30 units/kg dose and 20 L/hr at 60 units/kg dose. The median volume of distribution values during the elimination phase (V_z) range from 12,6 L to 13,9 L.

The mean t_{max} on both day 1 and at week 38 is longer in the 60 units/kg dose group than in the 30 units/kg dose group, while the mean CL and the mean V_z are lower on day 1 and at week 38 in the 60 units/kg dose group compared with the 30 units/kg dose group. The mean $t_{1/2}$ is longer at week 38 in the 60 units/kg dose group compared with the 30 units/kg dose group. There are no notable differences in the mean t_{max}, $t_{1/2}$, CL or V_z on day 1 or at week 38 in either the 30 units/kg or the 60 units/kg dose groups.

Paediatric population

Pharmacokinetics of taliglucerase alfa were evaluated in 11 paediatric patients with Gaucher disease. Following repeated dose IV infusion of 30 units/kg and 60 units/kg taliglucerase alfa in about 100 minutes in paediatric patients, median elimination half-life of taliglucerase alfa was 31,9 minutes (range: 12,9 to 56,8) and 32,5 minutes (range: 18,0 to 42,9), respectively. Median systemic clearance (CL) were 27,4 L/hr (range: 10,9 to 37,8) for 30 units/kg, and 15,8 L/hr (range: 11,7 to 24,9) for 60 units/kg. The steady state median AUC_{0-t} was 1 491 ng.hr/mL (range: 527 to 1 932) for 30 units/kg and 2 969 ng.hr/mL (range: 1 593 to 4 256) for 60 units/kg. Dose normalised exposure (AUC_{0-t}) was 46,4 ± 24,6 [ng.hr/mL]/mg for 30 units/kg and 63,9 ± 21,1 [ng.hr/mL]/mg for 60 units/kg.

AUC_{0-t} values in paediatric patients were lower than those observed in adult patients (i.e., median AUC_{0-t} 1 989 ng.h/mL with a range of 1 002 to 9 546 at Week 38 for 30 units/kg and 6 751 ng.h/mL range of 2 545 to 20 496 at Week 38 for 60 units/kg), due to weight-based dosing of taliglucerase alfa and lower body weights in paediatric patients.

5.3 Preclinical safety data

Genotoxicity

Tests for genotoxic activity were not performed. Given that taliglucerase alfa is degraded to peptides and amino acids and that the products of its enzymic action are glucose and ceramide, taliglucerase alfa is unlikely to pose a genotoxic risk.

Carcinogenicity

Tests for carcinogenic activity were not performed. Given the nature and location of the enzymic activity of taliglucerase alfa (i.e., lysosomal glucocerebrosidase) and the products of its enzymic action (i.e., glucose and ceramide), taliglucerase alfa is unlikely to pose a carcinogenic risk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid, anhydrous (for pH adjustment)

Mannitol

Polysorbate 80

Sodium citrate (as tribasic dihydrate)

6.2 Incompatibilities

In the absence of compatibility studies, ELELYSO should not be mixed with other medicines, except those mentioned in section 6.6.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Unopened vials

Store and transport at 2 ºC to 8 ºC. Refrigerate. Do not freeze. Keep the vial within the outer carton to protect from light.

Keep out of the sight and reach of children.

Reconstituted and diluted solutions

ELELYSO should be reconstituted and diluted just before use and used immediately. If not used immediately, in-use storage times and conditions of the reconstituted solution and the diluted solution prior to use are the responsibility of the user.

The reconstituted vial and the diluted solution that is made from the reconstituted vial can be stored for a combined time of not more than 24 hours at 2 ºC to 8 ºC under protection from light after the initial reconstitution step.

6.5 Nature and contents of container

ELELYSO powder for injection is packaged in a 13,5 mL Type 1 borosilicate glass vial. The glass vial is enclosed in a cardboard carton. Available as single vial packs.

6.6 Special precautions for disposal and other handling

Instructions for reconstitution, dilution and disposal

To allow accurate dispensing of the medicine, each vial contains an overfill of 6 % (i.e., 12 units).

The powder for solution for infusion needs to be reconstituted with Water for Injection, diluted immediately with sodium chloride 9 mg/mL (0,9 %) solution for infusion and then administered by intravenous infusion.

The number of vials to be reconstituted should be determined based on the individual patient's body weight and dosage regimen. Occasionally, small dosage adjustments may be made to avoid discarding partially used vials. Dosage may be rounded to the nearest whole vial, as long as the monthly administered dosage remains substantially unaltered.

Use aseptic technique.

Reconstitution

The reconstituted solution contains 40 units of taliglucerase alfa per mL. The reconstituted volume allows accurate withdrawal of 5,0 mL (equal to 200 units) from each vial.

Reconstitute each vial for injection with 5,1 mL Water for Injection. Water for Injection should be added slowly to minimise the formation of air bubbles and to assure proper mixing of the medicine with Water for Injection. The reconstituted volume is 5,3 mL.

Mix vials gently. DO NOT SHAKE. After reconstitution the solution should be a clear and colourless liquid, essentially free of visible particles. The reconstituted solution must be further diluted. Before further dilution, visually inspect the reconstituted solution in each vial for foreign particulate matter and discolouration. Do not use vials that exhibit discolouration or contain foreign particulate matter.

After reconstitution, promptly dilute the reconstituted solution and discard the vial. Do not store unused vials for subsequent use.

Dilution

Withdraw 5,0 mL reconstituted solution from each vial and combine the withdrawn volumes into a sterile infusion bag.

Then dilute the combined volume with sodium chloride 9 mg/mL (0,9 %) solution for infusion to a total volume of 100 mL to 200 mL. Mix the infusion solution gently. Since this is a protein solution, a few translucent particles or fibres may be observed 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.

Disposal

Any unused product should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

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10. DATE OF REVISION OF THE TEXT

Manufacturer: Pharmacia & Upjohn Co. LLC, wholly owned subsidiary of Pfizer, Inc., Kalamazoo, MI, USA