PRODUCT INFORMATION

NAME OF THE MEDICINE

ELELYSO® (taliglucerase alfa rpc) 200 units powder for injection

taliglucerase alfa recombinant plant carrot (rpc).

CAS Number: 37228-64-1.

DESCRIPTION

Taliglucerase alfa rpc is a glycosylated protein with approximately 7% of its molecular mass contributed by glycans. The glycans present in taliglucerase alfa rpc are typical of plant-expressed proteins. The most abundant glycan has terminal mannose, β-(1,2)-xylose, and α-(1,3)-fucose residues. The terminal mannose residues specifically bind the endocytic mannose receptors on macrophages, resulting in uptake of the enzyme into the macrophages, the cells that accumulate lipid in Gaucher disease and are the target cells for enzyme replacement therapy. The glycan structures β-(1,2)-xylose, and α-(1,3)-fucose residues are widely present in plant but not in mammalian glycoproteins.

Taliglucerase alfa rpc sequence contains seven cysteine residues that form two disulfide bonds between the first four cysteine residues (Cys6-Cys18, Cys20-Cys25) and three free sulfhydryls (thiols).

Predicted Amino Acid Sequence for taliglucerase alfa rpc:

	1	11	21	31	41	51
1	EFARPCIPKS	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	IHTYLWHRQD	LLVDTM			

Taliglucerase alfa rpc is a white to off-white lyophilised powder, that may form a cake.

Each vial of ELELYSO contains 200 units* of taliglucerase alfa rpc**, 195 mg mannitol, 28.7 mg sodium citrate and 0.53 mg polysorbate 80.

After reconstitution, the solution contains 40 units (approximately 1.2 mg) of taliglucerase alfa rpc 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 37ºC.

**Taliglucerase alfa rpc 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.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: alimentary tract and metabolism - enzymes.

Taliglucerase alfa rpc 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, remodeling failure and bone crises. The oligosaccharide chains at taliglucerase alfa rpc glycosylation sites have terminal mannose sugars that are necessary for interaction with mannose receptors present on macrophages. Taliglucerase alfa rpc uptake by macrophages was shown, in *in vitro* studies with both mouse and human cells, to be in large part mediated by mannose receptors.

Pharmacokinetics

Clinical pharmacokinetics

In healthy subjects, after a single dose by intravenous infusion over 90 minutes, taliglucerase alfa rpc is rapidly eliminated with a mean elimination half-life of 8 minutes at a dose of 30 units/kg and 17 minutes at a dose of 60 units/kg. The mean AUCt is 3,608 ng.hr/mL at 30 units/kg and 13474 ng.hr/mL at 60 units/kg, and the increase in AUCt appears more than proportional to the dose. The mean clearance was 3.2 mL/min/kg at 30 units/kg dose and 1.9 mL/min/kg at 60 units/kg dose with the observed mean steady state volume of distribution (Vss) of 68 to 71 mL/kg. No gender differences in exposure were observed.

In patients with Gaucher disease, taliglucerase alfa rpc is rapidly eliminated. After a single dose by intravenous infusion over 1 to 2 hours at a dose of 30 units/kg and 60 units/kg, the mean elimination half-life is about 25 minutes. Single dose data indicate that exposure is substantially lower in patients compared to healthy subjects. After continued biweekly dosing there was no clear indication of accumulation, although for the 60 units/kg dose a trend was observed towards higher values, but this was not reflected in the clearance or elimination half-life. At steady state at week 38, the mean AUCt (exposure) is 2654 ng.hr/mL at 30 units/kg dose, and 7665 ng.hr/mL at 60 units/kg dose, and this appears to suggest a more than dose proportional increase in AUCt.

After a single dose and at steady state AUC was observed, and the mean clearance was about 30 L/h at 30 units/kg dose and 20 L/h at 60 units/kg dose. The mean volume of distribution during the elimination phase (Vz) ranged from about 11.7 to 17.5 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.

CLINICAL TRIALS

Clinical studies

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

The safety and efficacy of ELELYSO 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.

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) where 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 minteral density, were evaluated as tertiary endpoints.

Intravenous infusions were administered every 2 weeks for 9 months (ie 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 1.

Table 1: 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		ELELYSO 30 units/kg n=15	ELELYSO 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)**	11427 (20214)	41494 (47063)	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 (11427/mm^3, p=0.0460), but did not meet the prespecified alpha level of 0.025.

As tertiary and exploratory 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 adult patients who were previously treatment naïve continued to be treated with ELELYSO in an extension of this study (PB-06-003) in a blinded manner for a total treatment duration of 24 months, and showed continued improvement in efficacy. For the respective 30 units/kg and 60 units/kg dose groups, mean±SD spleen volume decreased 40.5 ± 9.6% and 54.9 ± 12.8%; haemoglobin increased 1.3 ± 1.7 g/dL and 2.4 ± 2.3 g/dL; liver volume decreased 20.6 ± 6.9% and 17.5 ± 13.3%; and platelet count increased 28433 ± 31966/mm^3 and 72029 ± 68157/mm^3.

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). Elibility 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, 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). Increases in haemoglobin were noted by 4 weeks. Haemoglobin rose 19.4% (30 units/kg) and 16.9% (60 units/kg) in those patients anaemic at baseline. Similar effects were observed for spleen volume decrease, liver volume decrease and platelet count increase as noted in Table 2 below.

Table 2: 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	ELELYSO 30 units/kg (n=6) Mean (SD)	ELELYSO 60 units/kg (n=5) Mean (SD)
Spleen Volume % Change	-28.6 (21.5)	-41.1 (13.8)
Haemoglobin g/dL Change	1.4 (1.3)	1.6 (0.7)
Liver Volume % Change	-6.3 (8.5)	-14.0 (9.0)
Platelet Count /mm^3 Change	45500 (52884)	72600 (59197)

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 3.

Table 3: Paediatric Auxological Data for Study PB-06-005

Clinical Parameter	Time Point	ELELYSO 30 units/kg (n=6)	ELELYSO 60 units/kg (n=5)
Height (cm)	**Baseline (Mean (SE))**	129.3 (8.9)	107.8 (6.4)
	Month 12 (Mean (SE))	134.4 (8.5)	115.7 (6.2)
	% Change (SE)	4.2 (0.9)	7.6 (1.0)
Height Velocity (cm/yr)	**Month 12 (Mean (SE))**	5.1 (0.9)	8.0 (0.6)
Weight (kg)	**Baseline (Mean (SE))**	27.9 (4.3)	17.7 (2.1)
	Month 12 (Mean (SE))	30.3 (4.3)	20.4 (2.7)
	% Change (SE)	9.6 (2.9)	14.7 (2.5)

Study in patients switching from Imiglucerase to ELELYSO (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 ELELYSO 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 enrollment. 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 ELELYSO was administered every 2 weeks. Adjustment of dose was allowed by study criteria if needed in order 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 92000/mm^3 at week 22, and responded with a platelet count of 170000mm^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 11 to 60 units/kg with a mean of 29.2 units/kg. The age range was 18 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 1816.5 mL at baseline and 1800.6 mL at 9 months. Haematological parameters were also stable. Median haemoglobin was 13.6 g/dL at both baseline and after 9 months, and median platelet counts were 163167/mm^3 at baseline and 159000/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 1243 mL at baseline and 1305 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 146500/mm^3 and 200000/mm^3 at baseline and 9 months, respectively.

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.

CONTRAINDICATIONS

Severe allergic reactions to taliglucerase alfa rpc, any excipient components of the product, or other similar glucocerebrosidase enzymes (See PRECAUTIONS).

PRECAUTIONS

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

Antibody response

Patients have developed immunoglobulin G (IgG) antibodies to taliglucerase alfa rpc. The relevance of anti-taliglucerase alfa antibodies to adverse events is currently unclear, given the small numbers of patients thus far evaluated in the clinical program. However, an analysis of the presence of anti-taliglucerase antibodies with adverse events that might be related to hypersensitivity showed that more events were observed in patients who tested positive for anti-taliglucerase alfa IgG antibodies than in patients who tested negative for anti-taliglucerase alfa IgG antibodies. Two of the 26 treatment naïve patients and one patient switched from imiglucerase were determined to be positive for neutralising antibody activity in an *in vitro* assay; these three patients tested negative in a cell-based assay. There has been no demonstrated association between positive neutralising antibody assay results and therapeutic response.

In the adult treatment naïve study (PB-06-001), 17 out of 32 (53%) treatment naïve patients who were administered ELELYSO every two weeks developed ADA post-treatment (defined as ADA positive at one or more post-treatment time points). Two additional patients were antibody positive at baseline; the first patient withdrew after developing an allergic reaction with the first dose of ELELYSO and the second patient had increasing antibody titers with continued treatment.

In the switch study from imiglucerase to taliglucerase alfa once every two weeks (PB-06-002), 4 out of 28 (14%) patients developed ADA after the switch. One additional patient who switched from imiglucerase in this was positive at baseline but did not develop increased ADA titers after ELELYSO treatment. The relevance of ADA to therapeutic response and adverse events is currently unclear.

In a retrospective study across all clinical studies, 8 out of 71 (11%) clinical trial patients were considered to have antibodies to the plant specific glycans on taliglucerase alfa rpc. The presence of these antibodies was not associated with treatment related adverse events; nor was there a relationship demonstrated with efficacy outcomes.

Since it is unknown if antibodies play a role in adverse reactions or therapeutic response to taliglucerase alfa rpc, consideration should be given to the testing for the presence of anti-taliglucerase antibodies in cases of severe infusion-related reactions, hypersensitivity reactions or in cases of lack of or loss of effect.

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.

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 (defined as reaction occurring within 24 hours of the infusion), and allergic hypersensitivity reactions have been reported with ELELYSO. Patients who experience infusion-related reactions or hypersensitivity can usually be managed successfully and continue on therapy by slowing the

infusion rate; treating with medicinal products such as antihistamines, antipyretics and/or corticosteroids; and/or stopping and resuming treatment with a decreased infusion rate. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions.

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.

Allergy to carrots

The occurrence of allergic reactions to taliglucerase alfa rpc in patients with known carrot allergies is currently unknown and has not been studied in clinical trials; therefore, caution should be exercised in treating such patients. If infusion-related reactions or hypersentivity occurs, patients should be managed as described above.

Sodium

This medicinal product contains sodium and when 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.

Effect on Fertility

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

Use in Pregnancy

Category B1

Reproductive toxicity studies using pregnant rats and rabbits given high doses of taliglucerase alfa rpc revealed no evidence of harm to the fetus. 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.

Use in Lactation

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.

Paediatric Use

The safety and efficacy profiles were similar between adult and paediatric patients.

Use in the Elderly

Clinical studies of ELELYSO did not include sufficient numbers of patients aged 65 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 drug therapy in this patient group.

Genotoxicity

Tests for genotoxic activity were not performed. Given that taliglucerase alfa rpc is degraded to peptides and amino acids and that the products of its enzymic action are glucose and ceramide, it 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 rpc (i.e. lysosomal glucocerebrosidase) and the products of its enzymic action (i.e. glucose and ceramide), ELELYSO is unlikely to pose a carcinogenic risk.

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 possesses the homozygote L444P genotype. There is no clinical experience with the use of ELELYSO in patients with Type 2 Gaucher disease.

Use in Renal and Hepatic Impairment

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

Effects on Ability to Drive and Use of 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.

INTERACTIONS WITH OTHER MEDICINES

In the absence of compatibility studies, ELELYSO should not be mixed with other medicinal products, except those mentioned in the DOSAGE AND ADMINISTRATION section.

ADVERSE EFFECTS

Summary of the safety profile

The safety of ELELYSO has been evaluated in over 130 patients with Gaucher disease. ELELYSO was administered in doses of 11 to 73 units/kg of body weight every 2 weeks, for treatment durations of up to 39 months.

Patients were between 2 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 PRECAUTIONS).

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, infusion-related reactions, 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 and rash.

The safety of ELELYSO has been established in paediatric patients from 2 to 17 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 list of adverse reactions

The adverse reactions reported in patients with Gaucher disease are listed in Table 4 (all adult and paediatric patients). Information is presented by system organ class and frequency according to MedDRA convention. Frequency is defined as very common (³ 1/10) or common (³ 1/100 to <1/10). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4: Adverse Reactions Reported in Phase 3 Clinical Studies*

System Organ Class	Adverse Reaction	
	Very Common	**Common**
Immune system disorders		Hypersensitivity
Nervous system disorders	Headache	Dizziness
Vascular disorders		Flushing
Respiratory, thoracic and mediastinal disorders		Throat irritation
Gastrointestinal disorders	Vomiting, Abdominal pain[a]	Nausea
Skin and subcutaneous tissue disorders		Pruritus, Erythema, Rash
Musculoskeletal and connective tissue disorders	Arthralgia, Pain in extremity	Bone pain, Back pain
General disorders and administration site conditions		Infusion site pain, Fatigue, Oedema peripheral
Injury, poisoning and procedural complications		Infusion-related reaction
Investigations		Weight increased

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

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

A tabulated summary of adverse events providing percentages for each reaction observed (preferred term) with a frequency of ≥ 1% is provided in Table 5.

Table 5: Number (%) of Patients with Treatment Related Adverse Events Occuring with a Frequency of ≥ 1%

System Organ Class/Preferred Term	n = 132
Immune system disorders	
Hypersensititivity	5 (3.8%)
Injury, poisoning and procedural complications	
Infusion-related reaction	7 (5.3%)
Nervous system disorders	
Dizziness	2 (1.5%)
Headache	8 (6.1%)
Paraesthesia	2 (1.5%)
Eye disorders	
Eye pruritus	2 (1.5%)
Eye swelling	2 (1.5%)
Lacrimation increased	2 (1.5%)
Vascular disorders	
Flushing	3 (2.3%)
Respiratory, thoracic and mediastinal disorders	
Rhinorrhoea	3 (2.3%)
Sneezing	3 (2.3%)
Throat irritation	3 (2.3%)
Gastrointestinal disorders	
Abdominal pain	2 (1.5%)
Nausea	4 (3.0%)
Skin and subcutaneous tissue disorders	
Erythema	3 (2.3%)
Pruritus	7 (5.3%)
Rash	2 (1.5%)
Musculoskeletal and connective tissue disorders	
Arthralgia	2 (1.5%)
Back pain	2 (1.5%)
Pain in extremity	2 (1.5%)
General disorders and administration site conditions	2 (1.5%)
Fatigue	2 (1.5%)
Infusion site pain	2 (1.5%)
Oedema peripheral	
Investigations	
Alanine aminotransferase increased	2 (1.5%)
Weight increased	3 (2.3%)

Post-Marketing Experience

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

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

Immune system disorders: Anaphylactic reaction.

DOSAGE AND ADMINISTRATION

Treatment with ELELYSO should be supervised by a physician 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 physician may be considered only for those patients who have been tolerating their infusions.

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.

Dosing

Initial doses of ELELYSO in adult and paediatric (2 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 physician. Clinical studies have evaluated dose ranges from 11 units/kg to 73 units/kg every 2 weeks.

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

Method of administration

After reconstitution and dilution, the preparation is administered by intravenous infusion over a period from 60 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.

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

Paediatrics (2 to 17 years of age)

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

Elderly (>65 years of age)

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.

Instructions for reconstitution, dilution and disposal

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

The powder for injection needs to be reconstituted with Water for Injections, 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 maybe 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 rpc 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 Injections. Water for Injections should be added slowly to minimise the formation of air bubbles and to assure proper mixing of the product with Water for Injections. 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 to 200 mL. Mix the infusion solution gently. Since this is a protein solution, a few translucent particles or fibers 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 adminstered as soon a possible after dilution.

Disposal

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

OVERDOSAGE

There is no experience with overdose of ELELYSO. The maximum dose of ELELYSO in clinical studies was 73 units/kg body weight.

PRESENTATION AND STORAGE CONDITIONS

ELELYSO powder for injection is packaged in a 13.5 mL Type 1 borosilicate glass vial. Available as single vial packs.

Storage conditions

Unopened vials: Store and transport at 2ºC to 8ºC. (Refrigerate. Do not freeze). Keep the vial within the outer carton in order to protect from light.

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 2ºC to 8ºC under protection from light after the initial reconstitution step.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (Schedule 4).

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

21 May 2014.