ELELYSO®
Taliglucerase alfa

1. NAME OF THE MEDICINAL PRODUCT

Elelyso® powder for concentrate for solution for infusion 200 units/vial.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

**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 contains 0.3 mmol sodium.

For a full list of excipients, see section **6.1. List of excipients**.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

Taliglucerase alfa is a white to off-white lyophilized powder that may form a cake.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Taliglucerase alfa for infusion is a hydrolytic lysosomal glucocerebroside-specific enzyme indicated for long-term enzyme replacement therapy for adult and pediatric patients with a confirmed diagnosis of Type 1 Gaucher disease associated with at least one of the following: splenomegaly, hepatomegaly, anemia, thrombocytopenia.

4.2. Posology and method of administration

Treatment with taliglucerase alfa 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 infusions (see section **4.8. Undesirable effects**).

Posology

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 achievement of therapeutic goals, as assessed by regular comprehensive evaluations of the patient's clinical manifestations.

Adult dosing

Initial doses of taliglucerase alfa in adult subjects range from 30 units/kg to 60 units/kg of body weight once every 2 weeks, depending upon the clinical assessment of the treating physician. Clinical studies have evaluated median dose ranges from 9 units/kg to 67 units/kg every other week.

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

Pediatric dosing

Initial doses of taliglucerase alfa in pediatric subjects range from 30 units/kg to 60 units/kg of body weight once every 2 weeks, depending upon the clinical assessment of the treating physician. Clinical studies have evaluated dose ranges from 26 units/kg to 78 units/kg every other week (see section **4.9. Overdose**).

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

The safety and efficacy of taliglucerase alfa in children less than 2 years of age have not yet been established. No data are available.

Method of administration

After reconstitution and dilution, the total volume of prepared solution is administered intravenously by infusion over a period of 60 to 120 minutes (see section **4.4. Special warnings and precautions for use**). For pediatric patients with weights less than 30 kg, an infusion rate of no greater than 1 mL/minute should be used. For pediatric patients with weights more than 30 kg, after an initial infusion rate of 1 mL/minute and after tolerability to taliglucerase alfa is established, the infusion rate may be increased to 2 mL/minute. For adult patients, after an initial infusion rate of 1.2 mL/minute and after tolerability to taliglucerase alfa is established, the infusion rate may be increased to a maximum of 2.2 mL/minute. The duration of infusion may be adjusted as tolerated by the patient. The diluted solution should be filtered through an in-line low protein-binding 0.2 μm filter during administration.

The number of taliglucerase alfa vials necessary for the patient at the recommended dose is reconstituted in Sterile Water for Injection, as instructed. The reconstituted medicinal product

is pooled, and the volume of infusion is adjusted with sodium chloride 9 mg/mL (0.9%) solution for injection to a total volume of 100 to 200 mL (see section **6.6. Special precautions for disposal and other handling**).

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

For instructions on reconstitution and dilution of taliglucerase alfa, see section **6.6. Special precautions for disposal and other handling**.

Renal or hepatic impairment

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

Elderly (≥65 years old)

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

4.3. Contraindications

Severe allergic reactions to taliglucerase alfa or any of the excipients listed in section **6.1. List of excipients**.

4.4. Special warnings and precautions for use

Antibody response

Patients have developed immunoglobulin G (IgG) antibodies to taliglucerase alfa. 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 (see section **4.4. Special warnings and precautions for use**: Infusion-related reactions and 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 IgG antibodies. Four treatment-naïve patients (3 adults and 1 pediatric patient) and one adult patient switched from imiglucerase were determined to be positive for neutralizing activity in an *in vitro* assay (see section **4.8. Undesirable effects**).

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

Infusion-related reactions and hypersensitivity

Hypersensitivity reactions, including anaphylaxis, are possible; therefore, appropriate medical support should be readily available when taliglucerase alfa is administered. Infusion-related reactions (defined as reaction occurring within 24 hours of the infusion) and allergic 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 infusion-related reactions or hypersensitivity can usually be managed successfully and continued 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 decreased infusion rate. Pre-treatment with antihistamines and/or corticosteroids may prevent subsequent reactions.

Allergy to carrots

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

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6. Fertility, pregnancy and lactation

Pregnancy

Reproduction studies of taliglucerase alfa have been performed in rats and rabbits at doses up to 5 times the maximum human dose, on a mg/m² basis, and have revealed no evidence of impaired fertility or harm to the fetus due to taliglucerase alfa administration (see section **5.3. Preclinical safety data**). 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.

Breast-feeding

It is not known whether taliglucerase alfa is excreted in human milk. Because many medicinal products are excreted in human milk, caution should be exercised when taliglucerase alfa is administered to a breast-feeding woman.

Fertility

In animal studies, taliglucerase alfa did not affect fertility, reproductive performance or sperm characteristics (see section **5.3. Preclinical safety data**).

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

Summary of the safety profile

The safety of taliglucerase alfa 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). Taliglucerase alfa was administered in median doses of 9 units/kg to 78 units/kg body weight every other week, for lengths of treatment up to 60 months.

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.

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

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 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 16 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.

Tabulated list of adverse reactions

The adverse reactions reported in patients with Gaucher disease are listed in Table 1 (adult and pediatric subjects).

Table 1: ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC (adult and pediatric subjects).

System Organ Class	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	Frequency Not Known (Cannot be Estimated from the Available Data)
Immune system disorders		Hypersensitivity				Anaphylactic reaction*
Nervous system disorders	Headache, Dizziness					
Vascular disorders		Flushing				
Respiratory, thoracic and mediastinal disorders		Throat irritation				

System Organ Class	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	Frequency Not Known (Cannot be Estimated from the Available Data)
Gastrointestinal disorders	Vomiting, Abdominal pain[†]	Nausea				
Skin and subcutaneous tissue disorders		Erythema, Rash, Pruritus[**]				Urticaria[*], Angioedema[a,*]
Musculoskeletal and connective tissue disorders	Arthralgia, Pain in extremity, Back pain	Bone pain				
General disorders and administration site conditions		Edema peripheral, Fatigue, Infusion site pain				
Investigations		Weight increased				
Injury, poisoning and procedural complications		Infusion-related reactions				

[*] ADR identified post-marketing
[**] Pruritus includes Pruritus generalized
[†] Abdominal pain includes MedDRA preferred terms of Abdominal pain, Abdominal pain lower and Abdominal pain upper
[a] Angioedema includes Eyelid edema, Angioedema, Lip edema, Swelling face, Conjunctival edema, Eye swelling, Lip swelling, Edema mouth, Swollen tongue and Laryngeal edema

In the clinical program, hypersensitivity reactions have occurred as early as the first infusion (see section **4.4. Special warnings and precautions for use**).

Immunogenicity

As with all therapeutic proteins, patients have developed IgG ADA to taliglucerase alfa.

In a study in enzyme replacement therapy (ERT)-naïve adult patients, 17 of 32 patients (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 treatment and remained negative thereafter with continued treatment. In ERT-naïve pediatric patients, 2 of 11 (18%) patients developed ADA. One ERT-naïve pediatric patient was ADA-positive at baseline but became ADA-negative following treatment with taliglucerase alfa.

In a study in ERT-experienced adult and pediatric patients (N=31; 26 adult patients and 5 pediatric 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 pediatric patients developed ADA after switching from imiglucerase treatment to taliglucerase alfa treatment. In the ERT-experienced population, two adult and two pediatric patients who switched from imiglucerase were ADA-positive at

baseline but ADA-negative following taliglucerase alfa treatment. One of these ERT-experienced adults subsequently became ADA-positive following continued treatment. In total, 31 adult and pediatric patients tested positive for the taliglucerase alfa ADA. The relevance of ADA to adverse events is currently unclear (see also section **5.1. Pharmacodynamic properties**). Thirty (30) 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 (19) of the 30 patients (63%) were positive for the neutralizing antibodies capable of inhibiting mannose receptor binding of taliglucerase alfa. Eight (8) 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.

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 taliglucerase alfa with the incidence of antibodies to other products may be misleading.

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Clinical studies

Neuronopathic Gaucher disease

Patients with severe and complex neurological symptoms were excluded from clinical studies; pediatric patients with longstanding oculomotor gaze palsy and/or mutations suggestive of neuronopathic disease were included in the clinical trial program.

Adult population

Study in adult patients naïve to enzyme replacement therapy

The efficacy of taliglucerase alfa was evaluated in one study conducted in 31 patients, aged 18 years and older, with Gaucher disease.

One pivotal, multi-center, double-blind, randomized Phase III study of 30 units/kg or 60 units/kg was conducted in adult patients with Gaucher disease who were naïve to enzyme

replacement therapy. Intravenous infusions were administered every 2 weeks for 9 months (38 weeks). Thirty-one (31) patients treated with 30 units/kg (n=15) or 60 units/kg (n=16) were evaluated for efficacy. Fifteen (15) patients were male. The average age was 36.1 years, with a range of 19 to 74 years.

Both dosage groups demonstrated a statistically significant reduction in spleen volume at the Month 6 visit and Month 9 visit compared to baseline (30 units/kg, 22.21%; 60 units/kg, 29.94%; both $p<0.0001$) and (30 units/kg, 26.91%; 60 units/kg, 38.01%; both $p<0.0001$), respectively. Similar effects were observed for hemoglobin increase, liver volume decrease and platelet count increase, as noted in Table 2.

Table 2: Mean change from baseline to 9 months for clinical parameters in treatment-naïve adult patients with Type 1 Gaucher disease initiating therapy with taliglucerase alfa (mean with standard deviation)

Clinical Parameter	Time Point	30 units/kg (N=15)	60 units/kg (N=16)
		Mean (SD)^	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)
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)
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 (per 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)

* %BW = Percent Body Weight
** MN = Multiple of Normal
# g/dL = Grams per Deciliter
^ SD = Standard Deviation

Bone marrow involvement was assessed pre-treatment and at 9 months in a subset of 8 treatment-naïve patients using the Quantitative Chemical Shift Imaging technique that measures bone marrow fat fraction (Ff). Improvement was observed in all patients. Additionally, 3 of 5 patients with low baseline measurements below 0.23 (the threshold associated with an increased risk for bone complications), improved to levels that correlate with reduced risk.

Twenty-six (26) 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 (26) 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: mean (SD) spleen volume expressed as %BW decreased 1.4 (0.6) and 2.0 (2.0), and as MN decreased 6.8 (3.0) and 10.2 (9.8); hemoglobin increased 1.3 (1.7) g/dL and 2.4 (2.3) g/dL; liver volume expressed as %BW decreased 1.1 (0.5) and 1.0 (0.7), and decreased 0.4 (0.2) and 0.4 (0.3) MN; and platelet count increased 28,433 (31,996)/mm^3 and 72,029 (68,157)/mm^3. Patients in the open-label portion of the extension trials demonstrated continued improvements in these clinical parameters through 60 months total treatment.

Study in adult patients switching from imiglucerase to taliglucerase alfa

A multi-center, open-label, single-arm study was conducted in clinically stable Gaucher disease patients treated with imiglucerase and switched to taliglucerase alfa at the same dose as the previous imiglucerase dose. Twenty-six (26) adult patients were enrolled and 25 completed 9 months of treatment with taliglucerase alfa infusions every 2 weeks. Doses ranged from 9 units/kg to 60 units/kg with a mean of 28.8 units/kg. The age range was 18 to 66 years; 14 patients were male and 12 were female. Organ volumes remained stable. Mean spleen volume was 822 mL at baseline and 749 mL at Month 9, corresponding to spleen volumes of 5.5 MN at baseline and 5.1 MN at Month 9. Median spleen volume was 814 mL at baseline and 697 mL after 9 months, corresponding to median spleen volumes of 4.3 MN at baseline and 3.5 MN at Month 9. Mean liver volumes were 1,857 mL at baseline and 1,786 mL after 9 months, corresponding to liver volumes of 1.0 MN at baseline and 0.9 MN at Month 9. Median liver volumes were 1,816 mL and 1,801 mL at baseline and 9 months, corresponding to liver volumes of 0.9 MN at baseline and 0.9 MN at Month 9. Hematological parameters were also stable. Mean hemoglobin was 13.5 g/dL at baseline and 13.3 g/dL after 9 months, and mean platelet counts were 160,447/mm^3 at baseline and 157,920/mm^3 after 9 months. Median hemoglobin levels were 13.6 g/dL at both baseline and after 9 months, and median platelet counts were 163,167/mm^3 and 159,000/mm^3 at baseline and after 9 months, respectively.

Eighteen (18) of the 26 adult patients who completed the 9-month clinical trial continued treatment with taliglucerase alfa in an extension trial. The 5 pediatric patients continued into a separate extension study. Ten (10) 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 hemoglobin -0.2 (0.9) g/dL.

Combined adult and pediatric data in patients switching from imiglucerase to taliglucerase alfa

A multi-center, open-label, single-arm study was conducted in clinically stable Gaucher disease patients treated with imiglucerase and switched to taliglucerase alfa at the same dose as the previous imiglucerase dose. Twenty-six (26) adult and 5 pediatric patients were enrolled and 30 of these completed 9 months of treatment with taliglucerase alfa infusions every 2 weeks. Doses ranged from 9 units/kg to 60 units/kg with a mean of 31 units/kg. The age range was 6 to 66 years; 17 patients were male and 14 were female. Organ volumes remained stable. Mean spleen volume was 721 mL at baseline and 655 mL at Month 9,

corresponding to spleen volumes of 5.2 MN at baseline and 4.8 MN at Month 9. Median spleen volume was 534 mL at baseline and 433 mL after 9 months, corresponding to median spleen volumes of 4.1 MN at baseline and 3.5 MN at Month 9. Mean liver volumes were 1,766 mL at baseline and 1,716 mL after 9 months, corresponding to liver volumes of 1.0 MN at baseline and 1.0 MN at Month 9. Median liver volumes were 1,689 mL and 1,721 mL at baseline and Month 9, corresponding to liver volumes of 1.0 MN at baseline and 0.9 MN at Month 9. Hematological parameters were also stable. Mean hemoglobin was 13.5 g/dL at baseline and 13.4 g/dL after 9 months, and mean platelet counts were 161,137/mm^3 at baseline and 161,167/mm^3 after 9 months. Median hemoglobin levels were 13.6 g/dL at baseline and 13.7 g/dL after 9 months, and median platelet counts were 161,917/mm^3 and 169,500/mm^3 at baseline and after 9 months, respectively.

Pediatric population

The efficacy of taliglucerase alfa has been established in patients from 2 to 16 years of age. Use of taliglucerase alfa in this age group is supported by evidence from adequate and well-controlled studies of taliglucerase alfa in 16 pediatric patients: 11 patients were treatment-naïve patients and 5 patients switched from imiglucerase to taliglucerase alfa.

Study in pediatric patients switching from imiglucerase to taliglucerase alfa

Five (5) pediatric patients were enrolled and completed a study in patients switching from imiglucerase to taliglucerase alfa. 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. Mean spleen volumes were 313 mL and 4.1 MN at baseline and 276 mL and 3.3 MN at 9 months (Median spleen values were 324 mL and 3.1 MN at baseline, and 256 mL and 2.5 MN at 9 months). Mean liver volumes were 1,346 mL and 1.3 MN at baseline and 1,393 mL and 1.2 MN at 9 months; median liver values were 1,243 mL and 1.1 MN at baseline, and 1,305 mL and 1.1 MN at 9 months. Hematological parameters were also stable. Mean hemoglobin was 13.5 g/dL at baseline and 13.9 g/dL after 9 months; median values were 13.4 g/dL and 14.3 g/dL at baseline and 9 months, respectively. Mean platelet counts were 164,587/mm^3 at baseline and 177,400/mm^3 after 9 months; median values were 146,500/mm^3 and 200,000/mm^3 at baseline and 9 months, respectively.

All 5 pediatric 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 5 patients completed 24 months and 2 patients completed 33 months. The following data are the changes 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; hemoglobin 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.

Study in pediatric patients naïve to enzyme replacement therapy

One pivotal, multi-center, double blind, randomized Phase III study of 30 or 60 units/kg was conducted in pediatric patients with Gaucher disease who were naïve to enzyme replacement therapy. Intravenous infusions were administered every 2 weeks for 12 months. Eleven (11) patients were enrolled and all 11 completed the study; treated with 30 units/kg (n=6) or 60 units/kg (n=5) and were evaluated for efficacy. Eight (8) patients were male, and the age ranged from 2 years to 14 years.

Both dosage groups demonstrated a statistically significant increase in hemoglobin from baseline (taliglucerase alfa 30 units/kg, 11.3 g/dL; taliglucerase alfa 60 units/kg, 10.6 g/dL) at Month 12 (taliglucerase alfa 30 units/kg, 12.7 g/dL, increase 13.8%; 60 units/kg, 12.2 g/dL, increase 15.8%). Hemoglobin rose 19.4% (taliglucerase alfa 30 units/kg) and 16.9% (taliglucerase alfa 60 units/kg) in those subjects anemic 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: Mean change from baseline to 12 months for clinical parameters in treatment-naïve pediatric patients with Gaucher disease initiating therapy with taliglucerase alfa (mean with standard deviation)

Clinical Parameter	**Time Point**	**30 units/kg (N=6)**	**60 units/kg (N=5)**
		Mean (SD)[^]	**Mean (SD)**
Hemoglobin (g/dL)[#]	Baseline	11.3 (1.7)	10.6 (1.4)
	Month 12	12.7 (1.2)	12.2 (1.1)
	Change	1.4 (1.3)	1.6 (0.7)
Platelet Count (per mm^3)	Baseline	162,667 (71,838)	99,600 (42,899)
	Month 12	208,167 (90,747)	172,200 (89,290)
	Change	45,500 (52,884)	72,600 (59,197)
Spleen Volume (%BW)[*]	Baseline	4.4 (2.4)	5.9 (4.9)
	Month 12	2.8 (1.7)	2.6 (1.4)
	Change	-1.6 (1.3)	-3.3 (3.4)
Spleen Volume (MN)[**]	Baseline	22.2 (12.1)	29.4 (24.3)
	Month 12	14.0 (8.6)	12.9 (7.2)
	Change	-8.2 (6.4)	-16.5 (17.1)
Liver Volume (%BW)	Baseline	4.5 (1.4)	5.6 (1.2)
	Month 12	3.8 (1.0)	4.2 (0.6)
	Change	-0.7 (0.4)	-1.4 (0.7)
Liver Volume (MN)	Baseline	1.8 (0.5)	2.2 (0.5)
	Month 12	1.5 (0.4)	1.7 (0.3)
	Change	-0.3 (0.2)	-0.6 (0.3)

[*] %BW = Percent Body Weight
[**] MN = Multiple of Normal
[#] g/dL = Grams per Deciliter
[^] SD = Standard Deviation

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

Table 4: Pediatric auxological data (mean with standard deviation)

Clinical Parameter	Time Point	30 units/kg (N=6)	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 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)

* SD = Standard Deviation

Ten (10) of the 11 pediatric 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 10 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 unit/kg (n=5) and 60 units/kg dose groups (n=5), respectively: mean (SD) spleen volume expressed as %BW decreased 3.3 (1.0) and 5.0 (4.5), and as MN decreased 16.5 (4.9) and 24.8 (22.7); hemoglobin increased 1.9 (0.9) and 2.2 (1.4) g/dL; liver volume expressed as %BW decreased 1.5 (0.5) and 2.1 (0.9) and decreased 0.6 (0.2) and 0.8 (0.3) MN; and platelet count increased 25,600 (38,253)/mm^3 and 93,200 (38,206)/mm^3. Patients in the open-label portion demonstrated continued improvements in these clinical parameters through 36 months total treatment.

Pediatric patients with Type 3 Gaucher disease

The taliglucerase alfa clinical development program included 3 children with Type 3 Gaucher disease (two children classified by their physician as having Type 3 Gaucher disease and one additional child presumptively classified by the sponsor as having Type 3 Gaucher disease based on his mutation analysis). Efficacy results in the taliglucerase alfa clinical program demonstrated improvement for these children with Type 3 Gaucher disease, consistent with that seen in the children with Type 1 Gaucher disease. Because the number of pediatric patients was relatively small, it is difficult to determine whether the differences observed in the adverse event frequencies between pediatric patients with Type 1 Gaucher disease (n=13) and pediatric patients with Type 3 Gaucher disease (n=3) had any relevance to the safety profile.

Geriatric population

Clinical studies of taliglucerase alfa did not include sufficient numbers of subjects aged 65 and older to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Impact of antidrug antibodies on efficacy

The relevance of ADA to therapeutic response is currently unclear (see also section **4.8. Undesirable effects**).

5.2. Pharmacokinetic properties

Clinical pharmacokinetics

Adult population

In patients with Gaucher disease, taliglucerase alfa is rapidly eliminated following intravenous infusion. After intravenous infusion over 60 to 120 minutes at doses of 30 units/kg and 60 units/kg, the median elimination half-life is about 18.9 to 28.7 minutes, respectively. After continued once bi-weekly dosing, there was no clear indication of accumulation. At steady state, the median AUC_{0-t} (exposure) is 1,989 ng.h/mL and 6,751 ng.h/mL, respectively, following 30 units/kg and 60 units/kg doses at Week 38, that appears to suggest a more than dose proportional increase in AUC_{0-t}. There were no observed clinically relevant gender related differences in exposure.

After single dose the median systemic clearance (CL) values were approximately 30.5 L/hr and 18.5 L/hr for 30 units/kg and 60 units/kg doses, respectively. The median volume of distribution values during the elimination phase (V_z) range from 12.6 L to 13.9 L. The median volume of distribution at steady state (V_{ss}) ranged from 7.30 L to 11.7 L for both dose groups.

Pediatric population

Pharmacokinetics of taliglucerase alfa were evaluated in pediatric subjects with Gaucher disease. Following repeated dose IV infusion of 30 units/kg and 60 units/kg taliglucerase alfa in about 100 minutes in pediatric subjects, 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.

The observed median elimination half-life values of taliglucerase alfa following repeated administrations in pediatric patients appear similar to those in adults (i.e., median: 18.9 minutes with a range of 9.20 to 57.9 at Week 38 for 30 units/kg, and 28.7 minutes with a range of 11.3 to 104 at Week 38 for 60 units/kg). The median systemic CL after repeated administrations in pediatric patients also appeared similar to those in adults (i.e., median: 30.5 L/hr with a range of 6.79 to 68.0 at Week 38 for 30 units/kg, and 18.5 L/hr with a range of 6.25 to 37.9 at Week 38 for 60 units/kg). AUC_{0-t} values in pediatric 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 with a 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 pediatric patients.

5.3. Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Mannitol
Sodium citrate
Polysorbate 80
Citric acid anhydrous

6.2. Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, except those mentioned in section **6.6. Special precautions for disposal and other handling**.

6.3. Shelf life

Unopened vials

Refer to outer carton for expiration date.

Reconstituted solution

As taliglucerase alfa contains no preservative, the product should be used immediately once reconstituted. Chemical and physical in-use stability of the reconstituted solution has been demonstrated for 4 hours at 20°C to 25°C without protection from light or for 24 hours at 2°C to 8°C under protection from light.

Diluted solution for infusion

Chemical and physical in-use stability of the diluted solution has been demonstrated for 24 hours at 2°C to 8°C under protection from light.

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

6.4. Special precautions for storage

Store and transport refrigerated (2°C to 8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions of the diluted medicinal product, see section **6.3. Shelf life**.

6.5. Nature and contents of container

Taliglucerase alfa powder is packaged in 13.5 mL (10 mL nominal) glass vials (Type 1) closed with rubber stoppers and aluminum crimp seals with flip off caps.

6.6. Special precautions for disposal and other handling

Each vial of taliglucerase alfa is for single use only.

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

The powder for concentrate for solution for infusion has to be reconstituted with Sterile 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. Do not leave these vials at room temperature longer than 24 hours prior to reconstitution.

Use aseptic technique.

Reconstitution

Reconstitute each vial for injection with 5.1 mL Sterile Water for Injection. Water for Injection should be added slowly to minimize formation of air bubbles and to assure proper mixing of the product. The reconstituted volume is 5.3 mL.

Mix vials gently. DO NOT SHAKE. After reconstitution, the solution is a clear and colorless 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 discoloration. Do not use vials that exhibit discoloration or contain foreign particulate matter.

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

Dilution

The reconstituted solution contains 40 units taliglucerase alfa per mL. The reconstituted volume allows accurate withdrawal of 5.0 mL (200 units) from each vial. 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, slight flocculation (described as translucent proteinaceous particles or fibers) 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 and infused as described in section **4.2. Posology and method of administration**. In-use stability parameters are described in section **6.3. Shelf life**.

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

7. PRODUCT OWNER

Pfizer Inc.
235 East 42nd Street
New York, NY 10017
United States

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