Cerezyme
Imiglucerase for injection
400 Units

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 400 units* of imiglucerase**.
After reconstitution, the solution contains 40 units (approximately 1.0 mg) of imiglucerase per ml (400 U/10 ml).

* An enzyme unit (U) 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°C.
** Imiglucerase is a modified form of human acid β-glucosidase and is produced by recombinant DNA technology using a mammalian Chinese Hamster Ovary (CHO) cell culture, with mannose modification for targeting macrophages.

Excipients:
For a full list of excipients, see section *List of Excipients*.
This medicinal product contains sodium and is administered in 0.9% sodium chloride intravenous solution (see section *Dosage and Administration*). After reconstitution, the solution contains 1.24 mmol sodium (400 U/10 mL). To be taken into consideration by patients on a controlled sodium diet.

PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Cerezyme is a white to off-white powder.

CLINICAL PARTICULARS

Therapeutic Indications

Cerezyme (imiglucerase for injection) is indicated for use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease and who exhibit clinically significant non-neurological manifestations of the disease.

The non-neurological manifestations of Gaucher disease include one or more of the following conditions:

- anemia, after exclusion of other causes, such as iron deficiency
- thrombocytopenia
- bone disease, after exclusion of other causes, such as Vitamin D deficiency
- hepatomegaly or splenomegaly

Dosage and Administration

Cerezyme (imiglucerase for injection) is administered by intravenous infusion over 1-2 hours.
Dosage should be individualized to each patient. Initial dosages range from 2.5 U/kg of body weight 3 times a week to 60 U/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for which the most data are available. Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration. Dosage adjustments should be made on an individual basis and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations.

Paediatric population
No dose adjustment is necessary for the paediatric population.

The efficacy of Cerezyme on neurological symptoms of chronic neuronopathic Gaucher patients has not been established and no special dosage regimen can be recommended for these manifestations (see section P*harmacodynamic Properties*).

Method of Administration

After reconstitution and dilution, the preparation is administered by intravenous infusion. At initial infusions, Cerezyme should be administered at a rate not exceeding 0.5 unit per kg body weight per minute. At subsequent administrations, infusion rate may be increased but should not exceed 1 unit per kg body weight per minute. Infusion rate increases should occur under supervision of a health care professional.

Infusion of Cerezyme at home may be considered for patients who are tolerating their infusions well for several months. Decision to have patient move to home infusion should be made after evaluation and recommendation by the treating physician. Infusion of Cerezyme by the patient or caregiver at home requires training by a health care professional in a clinical setting. The patient or caregiver will be instructed in infusion technique and the keeping of a treatment diary. Patients experiencing adverse events during the infusion need to immediately **stop the infusion process and** seek the attention of a healthcare professional. Subsequent infusions may need to occur in a clinical setting. Dose and infusion rate should remain constant while at home, and not be changed without supervision of a health care professional.

Cerezyme should be stored at 2-8°C. After reconstitution, Cerezyme should be inspected visually before use. Because this is a protein solution, slight flocculation (described as thin translucent fibers) occurs occasionally after dilution. The diluted solution may be filtered through an in-line low protein-binding 0.2 µm filter during administration. Any vials exhibiting opaque particles or discoloration should not be used. DO NOT USE Cerezyme after the expiration date on the vial.

On the day of use, after the correct amount of Cerezyme to be administered to the patient has been determined, the appropriate number of vials are each reconstituted with Sterile Water for Injection, USP. The final concentrations and administration volumes are provided in the following table:

	400 Unit Vial
Sterile water for reconstitution	10.2 mL
Final volume of reconstituted product	10.6 mL
Concentration after reconstitution	40 U/mL
Withdrawal volume	10.0 mL
Units of enzyme within final volume	400 units

A nominal 10.0 mL for the 400 unit vial is withdrawn from each vial. The appropriate amount of Cerezyme for each patient is diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 100 – 200 mL. Cerezyme is administered by intravenous infusion over 1-2 hours. Aseptic techniques should be used when diluting the dose.

Since Cerezyme does not contain any preservative, after reconstitution, vials should be promptly diluted and not stored for subsequent use. Cerezyme, after reconstitution, has been shown to be stable for up to 12 hours when stored at room temperature (25°C) and at 2-8°C.
Cerezyme, when diluted, has been shown to be stable for up to 24 hours when stored at 2-8°C.

Relatively low toxicity, combined with the extended time course of response, allows small dosage adjustments to be made occasionally to avoid discarding partially used bottles. Thus, the dosage administered in individual infusions may be slightly increased or decreased to utilize fully each vial as long as the monthly administered dosage remains substantially unaltered.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Special Warnings and Precautions for Use

Hypersensitivity

Current data using a screening ELISA followed by a confirmatory radioimmunoprecipitation assay, suggest that, during the first year of therapy, IgG antibodies to imiglucerase are formed in approximately 15% of the treated patients. It appears that patients who will develop IgG antibody are most likely to do so within 6 months of treatment and will rarely develop antibodies to Cerezyme after 12 months of therapy. It is suggested that patients suspected of a decreased response to the treatment be monitored periodically for IgG antibody formation to imiglucerase.

Patients with antibody to imiglucerase have a higher risk of hypersensitivity reactions (see section *Undesirable Effects*). If a patient experiences a reaction suggestive of hypersensitivity, subsequent testing for imiglucerase antibodies is advised. As with any intravenous protein product, severe allergic-type hypersensitivity reactions are possible, but occur uncommonly. If these reactions occur, immediate discontinuation of the Cerezyme infusion is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment are to be observed.

Excipients

This medicinal product contains sodium and is administered in 0.9% sodium chloride intravenous solution (see section *Dosage and Administration*). To be taken into consideration by patients on a controlled sodium diet.

Interaction with Other Medicinal Products and Other Forms of Interaction

No interaction studies have been performed.

Fertility, Pregnancy and Lactation

Limited experience from 150 pregnancy outcomes (primarily based on spontaneous reporting and literature review) is available suggesting that use of Cerezyme is beneficial to control the underlying Gaucher disease in pregnancy. Furthermore, these data indicate no malformative toxicity for the foetus by Cerezyme, although the statistical evidence is low. Foetal demise has been reported rarely, although it is not clear whether this related to the use of Cerezyme or to the underlying Gaucher disease.

No animal studies have been carried out with respect to assessing the effects of Cerezyme on pregnancy, embryonal/foetal development, parturition and postnatal development. It is not known whether Cerezyme passes via the placenta to the developing foetus.

In pregnant Gaucher patients and those intending to become pregnant, a risk-benefit treatment assessment is required for each pregnancy. Patients who have Gaucher disease and become pregnant may experience a period of increased disease activity during pregnancy and the puerperium. This includes an increased risk of skeletal manifestations, exacerbation of cytopenia, haemorrhage, and an increased need for transfusion. Both pregnancy and lactation are known to stress maternal calcium homeostasis and to accelerate bone turnover. This may contribute to skeletal disease burden in Gaucher disease.

Treatment naïve women should be advised to consider commencing therapy prior to conception in order to attain optimal health. In women receiving Cerezyme treatment continuation throughout pregnancy should be considered. Close monitoring of the pregnancy and clinical manifestations of Gaucher disease is necessary for the individualization of dose according to the patient's needs and therapeutic response.

It is not known whether this active substance is excreted in human milk, however, the enzyme is likely to be digested in the child's gastrointestinal tract

Effects on Ability to Drive and Use Machines

Cerezyme has no or negligible influence on the ability to drive and use machines.

Undesirable Effects
Adverse drug reactions are listed by system organ class and frequency (common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000)) in the table below. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Nervous system disorders	Uncommon:	Dizziness, headache, paraesthesia*
Cardiac disorders	Uncommon:	Tachycardia*, cyanosis*
Vascular disorders	Uncommon:	Flushing*, hypotension*
Respiratory, thoracic and mediastinal disorders	Common:	Dyspnoea*, coughing*
Gastrointestinal disorders	Uncommon:	Vomiting, nausea, abdominal cramping, diarrhoea
Immune system disorders	Common:	Hypersensitivity reactions
	Rare :	Anaphylactoid reactions
Skin and subcutaneous tissue disorders	Common:	Urticaria/angioedema*, pruritus*, rash*
Musculoskeletal and connective tissue disorders	Uncommon:	Arthralgia, backache*
General disorders and administration site conditions	Uncommon:	Infusion site discomfort, infusion site burning, infusion site swelling, injection site sterile abscess, chest discomfort*, fever, rigors, fatigue

Symptoms suggestive of hypersensitivity (* marked in the table above) have been noted, overall in approximately 3% of the patients. Onset of such symptoms has occurred during or shortly after infusions. These symptoms generally respond to treatment with antihistamines and/or corticosteroids. Patients should be advised to discontinue infusion of the product and contact their physician if these symptoms occur.

Overdose
No case of overdose has been reported. In patients dosages up to 240 U/kg body weight once every two weeks have been used.

PHARMACOLOGICAL PROPERTIESPharmacodynamic Properties
Pharmacotherapeutic group: Enzymes-Imiglucerase (recombinant macrophage targeted β-glucocerebrosidase), ATC code: A16AB02

Gaucher disease is a rare recessively inherited metabolic disorder that results from a deficiency of the lysosomal enzyme acid β-glucosidase. This enzyme breaks down glucosylceramide, a key component of the lipid structure of cell membranes, into glucose and ceramide. In individuals with Gaucher disease, glucosylceramide degradation is insufficient, leading to accumulation of large quantities of this substrate within the lysosomes of macrophages (termed ‘Gaucher cells’), leading to widespread secondary pathology.

Gaucher cells are typically found in liver, spleen and bone marrow and occasionally in lung, kidney and intestine. Clinically, Gaucher disease is a heterogeneous phenotypic spectrum. The most frequent

disease manifestations are hepatosplenomegaly, thrombocytopenia, anaemia, and skeletal pathology, The skeletal abnormalities are frequently the most debilitating and disabling features of Gaucher disease. These skeletal manifestations include bone marrow infiltration, osteonecrosis, bone pain and bone crises, osteopenia and osteoporosis, pathological fractures, and growth impairment. Gaucher disease is associated with increased glucose production and increased resting energy expenditure rate, which may contribute to fatigue and cachexia. Patients with Gaucher disease may also have a low grade inflammatory profile. In addition, Gaucher disease has been associated with an increased risk of immunoglobulin abnormalities such as hyperimmunoglobulinemia, polyclonal gammopathy, monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma. The natural history of Gaucher disease usually shows progression, with the risk of irreversible complications arising in various organs over time. The clinical manifestations of Gaucher disease can adversely affect quality of life. Gaucher disease is associated with increased morbidity and early mortality.
Signs and symptoms presenting in childhood typically represent more severe Gaucher disease. In children, Gaucher disease can lead to growth retardation and delayed puberty.

Pulmonary hypertension is a known complication of Gaucher disease. Patients who have undergone a splenectomy have an increased risk of pulmonary hypertension. Cerezyme therapy reduces the requirement for splenectomy in most cases and early treatment with Cerezyme has been associated with a reduced risk 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, in particular, should receive adequate doses of Cerezyme to ensure control of underlying Gaucher disease as well as be evaluated for the need of additional pulmonary hypertension specific treatments.

Imiglucerase (recombinant macrophage targeted acid ß glucosidase) replaces the deficient enzyme activity, hydrolysing glucosylceramide, thus correcting initial pathophysiology and preventing secondary pathology. Cerezyme reduces spleen and liver size, improves or normalises thrombocytopenia and anaemia, improves or normalises bone mineral density and bone marrow burden, and reduces or eliminates bone pain and bone crises. Cerezyme reduces resting energy expenditure rate. Cerezyme has been shown to improve both mental and physical aspects in the quality of life of Gaucher disease. Cerezyme decreases chitotriosidase, a biomarker for glucosylceramide accumulation in macrophages and response to treatment. In children, Cerezyme has been shown to enable normal pubertal development, and to induce catch-up growth, leading to normal height and bone mineral density in adulthood.

The rate and extent of response to Cerezyme treatment is dose-dependent. Generally, improvements in organ systems with a faster turnover rate, such as the haematological, can be noted far more rapidly than in those with a slower turnover, such as the bone.
In an ICGG Gaucher Registry analysis of a large cohort of patients (n=528) with Gaucher disease type 1, a time- and dose-dependent effect for Cerezyme was observed for haematological and visceral parameters (platelet count, haemoglobin concentration, spleen and liver volume) within the dose range of 15, 30 and 60 U/kg body weight once every 2 weeks. Patients treated with 60 U/kg body weight every 2 weeks showed a faster improvement and a greater maximum treatment effect as compared to patients receiving the lower doses.

Similarly, in an ICGG Gaucher Registry analysis of bone mineral density using dual-energy X-ray absorptiometry (DXA) in 342 patients, after 8 years of treatment normal bone mineral density was achieved with a Cerezyme dose of 60 U/kg body weight once every 2 weeks, but not with lower doses of 15 and 30 U/kg body weight once every 2 weeks (Wenstrup et al, 2007).

In a study investigating 2 cohorts of patients treated with a median dose of 80 U/kg body weight every 4 weeks and a median dose of 30 U/kg body weight every 4 weeks, among the patients with bone marrow burden score ≥ 6, more patients in the higher dose cohort (33%; n=22) achieved a decrease in the score of 2 points after 24 months of Cerezyme treatment compared with patients in the lower dose cohort (10%; n=13) (de Fost, 2006).

Treatment with Cerezyme at a dose of 60 U/kg body weight once every 2 weeks, showed improvement in bone pain as early as 3 months, decrease in bone crises within 12 months, and improvement in bone mineral density after 24 months of treatment (Sims et al, 2008).

The usual frequency of infusion is once every 2 weeks (see section Dosage and Administration). Maintenance therapy every 4 weeks (Q4) at the same cumulative dose as the bi-weekly (Q2) dose has been studied in adult patients with stable residual Gaucher disease type 1. Changes from baseline in hemoglobin, platelets, liver and spleen volumes, bone crisis, and bone disease comprised a predefined composite endpoint; achievement or maintenance of established Gaucher disease therapeutic goals for the hematologic and visceral parameters comprised an additional endpoint. Sixty-three percent of Q4- and 81% of Q2-treated patients met the composite endpoint at Month 24; the difference was not statistically significant based on the 95% CI (-0.357, 0.058). Eighty-nine percent of Q4- and 100% of Q2-treated patients met the therapeutic goals-based endpoint; the difference was not statistically significant based on the 95% CI (-0.231, 0.060). A Q4 infusion regimen may be a therapeutic option for some adult patients with stable residual Gaucher disease type 1, but clinical data are limited.

No controlled clinical studies have been conducted on the efficacy of Cerezyme on neurological manifestations of the disease. Therefore no conclusions on the effect of enzyme replacement therapy on the neurological manifestations of the disease can be drawn.

Medical or healthcare professionals are encouraged to register Gaucher patients, including those with chronic neuronopathic manifestations of the disease, in the “ICGG Gaucher Registry”. Patient data will be anonymously collected in this Registry. The objectives of the “ICGG Gaucher Registry” are to enhance the understanding of Gaucher disease and to evaluate the effectiveness of enzyme replacement therapy, ultimately leading to improvement in the safe and efficacious use of Cerezyme.

Pharmacokinetic Properties
During one-hour intravenous infusions of four doses (7.5, 15, 30, 60 U/kg) of imiglucerase, steady-state enzymatic activity was achieved by 30 minutes. Following infusion, plasma enzymatic activity declined rapidly with a half-life ranging from 3.6 to 10.4 minutes. Plasma clearance ranged from 9.8 to 20.3 mL/min/kg (mean ± S.D., 14.5 ± 4.0 mL/min/kg). The volume of distribution corrected for weight ranged from 0.09 to 0.15 L/kg (0.12 ± 0.02 L/kg). These variables do not appear to be influenced by dose or duration of infusion, however, only one or two patients were studied at each dose level and infusion rate.

Preclinical Safety Data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, and genotoxicicty.

PHARMACEUTICAL PARTICULARS

List of Excipients
Mannitol, Sodium citrate (to adjust pH), Citric acid monohydrate (to adjust pH), Polysorbate 80

Incompatibilities
In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf-life
Unopened vials:
Do not use after the expiry date on vial.

Diluted solution:
From a microbiological safety point of view, the product should be used immediately. If not used immediately, in-use storage and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C - 8°C under protection from light.

Special precautions for storage
Store in a refrigerator (2°C – 8°C).
For storage conditions of the diluted medicinal product, see section *Shelf-life*

How Supplied
Cerezyme (imiglucerase for injection) is supplied as a sterile, non-pyrogenic, lyophilized product. It is available as follows:

400 Units per Vial

Cerezyme 400 Units (imiglucerase for injection) is manufactured by:
Genzyme Corporation
11 Forbes Road, Northborough,
MA 01532, USA

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