เอกสารกำกับยาภาษาอังกฤษ (ฉบับใหม่)

Cerezyme™

imiglucerase for injection

400 UNITS

DESCRIPTION

Cerezyme™ (imiglucerase for injection) is an analogue of the human enzyme β-glucocerebrosidase, produced by recombinant DNA technology. β- Glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase, E.C.3.2.1.45) is a lysosomal glycoprotein enzyme which catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

Cerezyme™ is produced by recombinant DNA technology using mammalian cell culture (Chinese hamster ovary). Purified imiglucerade is a monomeric glycoprotein of 497 amino acids, containing 4 N-linked glycosylation sites (Mr = 60,430) imiglucerase differs from placental glucocerbrosidase by one amino acid at position 495, where histidine is substituted for arginine. The oligosaccharide chains at the glycosylation sites have been modified to terminate in mannose sugars. The modified carbohydrate structures on imiglucerase are somewhat different from those on placental glucocerebrosidase. These mannose-terminated oligosaccharide chains of imiglucerase are specifically recognized by endocytic carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease.

Cerezyme™ is supplied as a sterile, non-pyrogenic, to off-white lyophilized product. The quantitative composition of the lyophilized drug is provided in the following table:

Ingredient	400 Unit Vial
Imiglucerase (total amount) *	424 units
Mannitol	340 mg
Sodium Citrates (Trisodium Citrate) (Disodium Hydrogen Citrate)	140 mg (104 mg unit) (36 mg)
Polysorbate 80, NF	1.06 mg
Citric Acid and/or Sodium Hydroxide may have been added at the time of manufacture to adjust pH.	

*This provides a withdrawal dose of 400 units of imiglucerase

An enzyme unit (U) is defined as the amount of enzyme that catalyzes the hydrolysis of 1 micromole of the synthetic substrate para-nitrophenyl-β-D-glucopyranoside (pNP-Glc) per minute at 37 °C. The product is stored at 2-8 °C (36-46 °F). After reconstitution with Sterile Water for Injection, USP, the imiglucerase concentration is 40 U/mL (see **DOSAGE AND ADMINISTRATION** for final concentrations and volumes). Reconstituted solutions have a pH of approximately 6.1.

CLINICAL PHARMCOLOGY

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

Mechanism of Action/Pharmacodynamics

Gaucher disease is characterized by a deficiency of β-glucocerebrosidase activity, resulting in accumulation of glucocerebroside in tissue macrophages which become engorged and are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney, and intestine. Secondary hematologic sequelae include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly, skeletal complications, including osteonecrosis and osteopenia with osteopenia with secondary pathological fractures. **Cerezyme™** (imiglucerase for injection) catalyzes the hydrolysis of glucocerebroside to glucose and ceramide. In clinical trials, **Cerezyme™** improved anemia and thrombocytopenia, reduced spleen and liver size, and decreased cachexia to degree similar to that observed with Ceredase™ (alglucerase injection).

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 et al, 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).

Pharmacokinetics
During one-hour intravenous infusions of four doses (7.5, 15, 30, 60, U/Kg) of **Cerezyme™** (imiglucerase for injection), 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. The pharmacokinetics of **Cerezyme™** do not appear to be different from placental-derived alglucerase (Ceredase™).

In patients who developed IgG antibody to **Cerezyme™**, an apparent effect on serum enzyme levels resulted in diminished volume of distribution and clearance and increased elimination half-life compared to patients without antibody (see **WARNINGS**).

INDICATIONS AND USAGE

Cerezyme™ (imiglucerase for injection) is indicated for long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of Non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease and who exhibit one or more of the following clinical significant non-neurological manifestations of the disease:

a) anemia
b) thrombocytopenia
c) bone disease
d) hepatomegaly or splenomegaly

CONTRAINDICATIONS

There are no known contraindications to the use of **Cerezyme™** (imiglucerase for injection). Treatment with **Cerezyme™** should be carefully re-evaluated if there is significant clinical evidence of hypersensitivity to the product.

WARNINGS

Approximately 15% of patients treated and tested to date have developed IgG antibody to **Cerezyme™** (imiglucerase for injection) during the first year of therapy. Patients who developed IgG antibody did so largely within 6 months of treatment and rarely developed antibodies to **Cerezyme™** after 12 months of therapy. Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity.

Patients with antibody to **Cerezyme™** have a higher risk of hypersensitivity reaction. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody. It is suggested that patients be monitored periodically for IgG antibody formation during the first year of treatment.

Hypersensitivity reactions, including anaphylaxis and anaphylactic shock have been reported. Treatment with **Cerezyme™** should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the product. Consider using pre-medication in patients with prior history of hypersensitivity with **Cerezyme™**.
If hypersensitivity occurs, consider temporarily stopping or slowing the infusion and/or administering appropriate medication. [See **ADVERSE REACTIONS**.]

If a severe hypersensitivity reaction occurs, stop administration of **Cerezyme™** and initiate appropriate medical treatment. The risks and benefits of re-administering **Cerezyme™** following a severe hypersensitivity or anaphylactic reaction should be considered.

Most patients have successfully continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and /or corticosteroids.

PRECAUTIONS

General
In less than 1% of the patient population, pulmonary hypertension and pneumonia have also been observed during treatment with **Cerezyme™** (imiglucerase for injection). Pulmonary hypertension and pneumonia are known complications of Gaucher disease and have been observed both in patients receiving and not receiving **Cerezyme™.** No causal Relationship with **Cerezyme™** has been established. Patients with respiratory symptoms in the absence of fever should be evaluated for the presence of pulmonary hypertension.

Therapy with **Cerezyme™** should be directed by physicians knowledgeable in the management of patients with Gaucher disease.

Caution may be advisable in administration of **Cerezyme™** to patients previously treated with Ceredase™ (alglucerase injection) and who have developed antibody to Ceredase™ or who have exhibited symptoms of hypersensitivity to Ceredase™.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies have not been conducted in either animals or humans to assess the potential effects of **Cerezyme™** (imiglucerase for injection) on carcinogenesis, mutagenesis, or impairment of fertility.

Teratogenic Effects: Pregnancy Category C
Animal reproduction studies have not been conducted with **Cerezyme™** (imiglucerase for injection). It is also not known whether **Cerezyme™** can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. **Cerezyme™** should not be administered during pregnancy except when the indication and need are clear and the potential benefit is judged by the physician to substantially justify the risk.

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.

Nursing Mothers
It is not known whether this drug is excreted in human milk, however, the enzyme is likely to be digested in the child's gastrointestinal tract. Because many drugs are excreted in human milk, caution should be exercised when **Cerezyme™** (imiglucerase for Injection) is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of **Cerezyme™** (imiglucerase for injection) have been established in patients between 2 and 16 years of age. Use of **Cerezyme™** in this age group is supported by evidence from adequate and well-controlled studies of **Cerezyme™** and Ceredase™ (alglucerase injection) in adults and pediatric patients, with addit6ional data obtained from the medical literature and from long-term postmarketing experience. **Cerezyme™** has been administered to patients younger than 2 years of age, however the safety and effectiveness in patients younger than 2 have not been established.

Interaction with Other Medicinal Products and other Forms of Interaction:
Interaction with **Cerezyme™** and other medicinal products have not been studied. Other forms of interactions such as with food are unlikely.

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

ADVERSE REACTIONS
Since the approval of **Cerezyme™** (imiglucerase for injection) in May 1994, Genzyme has maintained a worldwide post –marketing database of spontaneously adverse events and adverse events discussed in the medical literature. The percentage of events for each reported adverse reaction term has been calculated using the number of patients from these sources as the denominator for total patient exposure to **Cerezyme™** since 1994. Actual patient exposure is difficult to obtain due to the voluntary nature of the database and the continuous accrual and loss of patients over that span of time. The Actual number of patients exposed to **Cerezyme™** since 1994 is likely to be greater than estimated from these voluntary sources and, therefore, the percentages calculated for the frequencies of adverse reactions are most likely greater than the actual incidences.

Experience in patients treated with **Cerezyme™** has revealed that approximately 13.8% of patients experienced adverse events which were judged to be related to **Cerezyme™** administration and which occurred with an increase in frequency. Some of the adverse events were related to the route of administration. These include discomfort, pruritus, burning, swelling or sterile abscess at the site of venipuncture. Each of these events was found to occur in < 1% of the total patient population.

Hypersensitivity reactions, including anaphylaxis and anaphylactic shock, have been reported. Onset of such symptoms has occurred during or shortly after infusions; these symptoms include pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension (see **WARNINGS**). Each of these events was found to occur in < 1.5% of the total patient population. Pre-treatment with antihistamines and/or corticosteroids and reduced rate of Infusion have allowed continued of **Cerezyme™** in most patients.

Additional adverse reactions that have been reported in approximately 6.5% of patients treated with **Cerezyme™** include: nausea, abdominal pain, vomiting, diarrhea, rash, fatigue, headache, fever,

dizziness, chills, backache, and tachycardia. Each of these events was found to occur in < 1.5% of the total patient population.

Incidence rates cannot be calculated from the spontaneously reported adverse events in the post-marketing database. From this database, the most commonly reported adverse events in children (defined as ages 2-12 years) included dyspnea, fever, nausea, flushing, vomiting, and coughing, whereas in adolescents (> 12-16 years) and in adults (> 16 years) the most commonly reported events included headache, pruritis, and rash.

In addition to the adverse reactions that have been observed in patients treated with **Cerezyme™**, transient peripheral edema has been reported for this therapeutic class of drug.

OVERDOSE

Experience with doses up to 240 U/Kg every 2 weeks have been reported. At that dose there have been no reports of obvious toxicity.

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.

Cerezyme™ should be stored at 2-8˚C (36-46 ˚F). 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 unalterd.

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.

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

400 Units per Vial

Store at 2-8 ˚C (36-46˚F).

Rx only

Cerezyme™ (imiglucerase for injection) is manufactured by:
Genzyme Ireland Ltd,
Old Kilmeadan Road, Waterford, Ireland

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