For the use only of Registered Medical Practitioners (Specialist in Medicine) or a Hospital or a Laboratory.

This package insert is continually updated: Please read carefully before using a new pack.

CEREZYME®
400 UNITS

1. Generic Name

IMIGLUCERASE POWDER FOR CONCENTRATE FOR SOLUTION FOR INFUSION

2. 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). Each vial must be further diluted before use (see section *Special Precautions for Disposal and Other Handling*).

* 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 with known effect:

Each vial contains 41 mg of sodium.

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

3. Dosage form and strength

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

4. Clinical particulars

4.1 Therapeutic indication

Cerezyme® 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 who exhibit clinically significant non-neurological manifestations of the disease.

4.2 Posology and method of administration

Disease management should be directed by physicians knowledgeable in the treatment of Gaucher disease.

Posology

Due to the heterogeneity and the multi-systemic nature of Gaucher disease, dosage should be individualised for each patient based on a comprehensive evaluation of all clinical manifestations of the disease. Once individual patient response for all relevant clinical manifestations is well-established, dosages and frequency of administration may be adjusted with the goal to either maintain already reached optimal parameters for all clinical manifestations or further improve those clinical parameters which have not yet been normalised.

A range of dosage regimens has proven effective towards some or all of the non-neurological manifestations of the disease. Initial doses of 60 U/kg of body weight once every 2 weeks have shown improvement in haematological and visceral parameters within 6 months of therapy and continued use has either stopped progression of or improved bone disease. Administration of doses as low as 15 U/kg of body weight once every 2 weeks has been shown to improve haematological parameters and organomegaly, but not bone parameters. The usual frequency of infusion is once every 2 weeks; this is the frequency of infusion for which the most data are available.

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 *Pharmacodynamic 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.

For instructions on reconstitution and dilution of the medicinal product before administration, see section *Special Precautions for Disposal and Other Handling*.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients (See section *Special Warning and Precautions for Use*).

4.4 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.

Patients who have developed antibodies or symptoms of hypersensitivity to Ceredase (alglucerase) should be treated with caution when administering Cerezyme (imiglucerase).

Sodium
This medicinal product contains 41 mg sodium per vial, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult. It is administered in 0.9% sodium chloride intravenous solution (see section *Special Precautions for Disposal and Other Handling*). To be taken into consideration by patients on a controlled sodium diet.

4.5 Drug Interactions

No interaction studies have been performed.

4.6 Use in special populations

Pregnancy
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.

Breast-Feeding
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.

4.7 Effects on ability to drive and use machines

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

4.8 Undersirable effects

Tabulated list of adverse reactions
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: Rare:	Hypersensitivity reactions 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.

4.9 Overdose

No case of overdose has been reported. In patients dosages up to 240 U/kg body weight once every 2 weeks have been used.

5. Pharmacological properties

5.1 Mechanism of action

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.

5.2 Pharmacodynamic Properties

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

Pharmacodynamic effects

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.

Clinical efficacy and safety

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 4.2). 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.

5.3 Pharmacokinetic properties
During 1 hour intravenous infusions of 4 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 (mean ± S.D. 0.12 ± 0.02 L/kg). These variables do not appear to be influenced by dose or duration of infusion, however, only 1 or 2 patients were studied at each dose level and infusion rate.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity, and genotoxicicty.

7. Description
Cerezyme® is supplied as a sterile, non-pyrogenic, lyophilized product. It is available as follows:
400 Units per Vial

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

8. Pharmaceutical particulars

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

8.2 Shelf Life

Unopened vials:
3 years.

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.

8.3 Packaging information

To provide sufficient volume to allow accurate dispensing, each vial is formulated to contain an overfill of 0.6 ml.

Pack sizes: 1, 5 or 25 ml vials per carton
Not all pack sizes may be marketed

8.4 Storage and handling instruction

Store in a refrigerator (2°C – 8°C).

For storage conditions of the diluted medicinal product, (see section Shelf Life).

Special Precautions for Disposal and Other Handling
Each vial of Cerezyme is for single use only.

The powder for concentrate for solution for infusion has to be reconstituted with water for injections, diluted with 0.9% sodium chloride intravenous solution and then administered by intravenous infusion.

Determine the number of vials to be reconstituted based on the individual patient's dosage regimen and remove the vials from the refrigerator.

Occasionally, small dosage adjustments may be made to avoid discarding partially used vials. Dosages may be rounded to the nearest full vial, as long as the monthly administered dosage remains substantially unaltered.

Use Aseptic Technique
Reconstitution
Reconstitute each vial with 10.2 ml water for injections; avoid forceful impact of water for injections on the powder and, by mixing gently, avoid foaming of the solution. The reconstituted volume is 10.6 ml. The pH of the reconstituted solution is approximately 6.2.

After reconstitution it is a clear, colourless liquid, free from foreign matter. The reconstituted solution must be further diluted. Before further dilution, visually inspect the reconstituted solution in each vial for foreign particles and discoloration. Do not use vials exhibiting foreign particles or discoloration. After reconstitution, promptly dilute vials and do not store for subsequent use.

Dilution
The reconstituted solution contains 40 units imiglucerase per ml. The reconstituted volume allows accurate withdrawal of 10.0 ml (equal to 400 units) from each vial. Withdraw 10.0 ml reconstituted solution from each vial and combine the withdrawn volumes. Then dilute the combined volumes with 0.9% sodium chloride intravenous solution to a total volume of 100 to 200 ml. Mix the

infusion solution gently.

Administration
It is recommended to administer the diluted solution through an in-line low protein-binding 0.2 µm filter to remove any protein particles. This will not lead to any loss of imiglucerase activity. It is recommended that the diluted solution be administered within 3 hours. The product diluted in 0.9% sodium chloride intravenous solution will retain chemical stability if stored up to 24 hours at 2°C and 8°C under protection from light; but microbiological safety will depend on the reconstitution and dilution having been performed aseptically.

Cerezyme contains no preservatives. Any unused product or waste material should be disposed of in accordance with local requirements.

9. Patient Counselling Information

Not applicable

10. Details of manufacturer

Manufactured by:
Genzyme Ireland Limited
IDA Industrial Park,
Old Kilmeaden Road,
Waterford, Ireland -X91 TP27(Manufacturing Site, Primary Packaging Site, Batch Release Site &Testing Site)

Packed By:
Genzyme Corporation
11 Forbes Road
Northborough, MA 01532 USA (Secondary Packaging Site)

Importer:
M/s. Sanofi Healthcare India Private Limited,
Gala No. 4, Ground Floor, Building No. B1,
Citylink Warehousing Complex, S No.121/10/A,121/10/B & 69, NH3, VADAPE,
Tal: BHIWANDI-16, (THANE-Z5),
State: Maharashtra, Pin: 421302

11. Details of permission or licence number with date
IMP -135/2016 dated 11 Aug 2016

12. Date of Revision-

Date of Update: May 2025

Source: EU Summary of Product Characteristics (SmPC) dated April 2023