PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr CEREZYME®

Imiglucerase for injection

Lyophilized Powder, 400 Units/vial, for solution for intravenous infusion

Produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells

Enzyme Replacement Therapy

ATC code: A16AB02

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

CEREZYME® (imiglucerase for injection) is indicated for:

- 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 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

1.1 Pediatrics

Pediatrics (2 - 16 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Cerezyme in pediatric patients aged 2 to 16 years have been established. Therefore, Health Canda has authorized an indication for pediatric use in patients aged 2 to 16 years. Use of Cerezyme in these age groups is supported by evidence from well-controlled studies of Cerezyme in adult and pediatric patients, with additional data obtained from the literature and from long term follow-up information.

Pediatrics (<2 years of age): No data are available to Health Canada for pediatric patients less than 2 years of age; therefore, Health Canada has not authorized an indication for pediatric use in patients less than 2 years of age.

1.2 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

Imiglucerase is contraindicated in patients who are severely hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container (see 7 WARNINGS AND PRECAUTIONS). For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- 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 non-neurological manifestations.
- The efficacy of Cerezyme on neurological symptoms of chronic neuronopathic Gaucher patients has not been established.
- In situations where Cerezyme will be administered in a home care environment, it is suggested that the health care professional be trained and prepared for the possibility of an allergic-type reaction.

4.2 Recommended Dose and Dosage Adjustment

Dosage should be individualized to each patient. Treatment in pediatric and adult patients may be initiated from 2.5 units/kg of body weight 3 times a week up to 60 U/kg administered as frequently as once every two weeks. Titrate the dosage based on clinical manifestations of disease and therapeutic goals for the patient.

Higher doses (up to 120 U/kg every 2 weeks) have been given safely to Type 3 patients.

4.3 Reconstitution

Parenteral Products:

Preparation of Solution for Intravenous Infusion:

1. Using aseptic technique, reconstitute 400 U vial of Cerezyme with 10.2 mL of Sterile Water for Injection, USP, without preservatives. (Reconstitution yields a total volume 10.6 mL for the 400U vial). This results in a final concentration of 40 U/mL for each 400 U vial.

Table 1: Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal concentration per mL
400 units	10.2 mL Sterile Water for Injection, USP	10.0 mL	40 U/mL

2. Gently swirl each vial to mix the solution. *Important: Avoid excessive agitation during the reconstitution.*
3. Bubbles may be present in the solution following reconstitution. Let the solution sit for several minutes to allow any bubbles to dissipate and the lyophilized product to be thoroughly dissolved.
4. The reconstituted preparation results in a clear solution. Inspect vials visually for particulate matter or discolouration before further dilution. Vials exhibiting opaque particles or discolouration

should not be used. Because this is a protein solution, slight flocculation (described as thin translucent fibers) occurs occasionally after dilution.

Dilution

1. The total volume following dilution may vary from 100-200mL. The amount of Normal Saline within the range used for dilution does not affect the amount of Cerezyme administered to the patient.
2. Using aseptic technique, withdraw the contents of each vial and dilute it with 0.9% Sodium Chloride Injection, USP (Normal Saline) to a total volume of 100-200mL.
3. When more than 10 vials of Cerezyme are required, the drug itself prior to dilution yields a volume of 100 mL. The upper range (200mL) for total volume offers the flexibility for ensuring dilution of the drug in these instances.
4. Discard any unused portion remaining in the vials.

Since Cerezyme does not contain any antibacterial preservatives, it must be reconstituted and diluted immediately prior to administration (see 11 STORAGE, STABILITY AND DISPOSAL).

4.4 Administration

Cerezyme is administered by intravenous infusion over 1-2 hours. The maximum recommended infusion rate is 1 unit/kg/minute. The diluted solution may be filtered through an in-line low protein binding 0.2 µm filter during administration.

The vials are single use only. All unused portions must be discarded.

4.5 Missed Dose

It is important to have the infusion on a regular basis to avoid the accumulation of glucocerebroside. The total dose administered each month should remain substantially unchanged. If you have missed a dose, please contact your doctor.

5 OVERDOSAGE

Experience with doses up to 240 U/kg body weight every two weeks has been reported. At that dose, there have been no reports of obvious toxicity.

In the event of an overdose, stop the infusion immediately and monitor the patient closely in a hospital setting for the development of infusion-associated reactions. For the management of adverse reactions, see 7 WARNINGS AND PRECAUTIONS and 8 ADVERSE REACTIONS.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number

(DIN) and the batch/lot number of the product supplied.

Table 2: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Lyophilized powder for reconstitution 400 Units	mannitol, nitrogen, polysorbate 80, sodium citrates (disodium hydrogen citrate and trisodium citrate)

Cerezyme is intended for intravenous infusion. It is supplied as a sterile, non-pyrogenic, white to off-white lyophilized powder.

The total sodium citrate composition is made up of trisodium citrate and disodium hydrogen citrate in a ratio of 26:9.

Citric acid and/or sodium hydroxide may be present to adjust the pH to approximately 6.3.

Cerezyme is preservative-free.

Cerezyme is supplied in Type I glass vials capped with a 20 mm plastic cap and a flip-off aluminum crimp seal. Cerezyme is supplied in a 20 mL vial containing 400U (red label) of imiglucerase.

Individual cartons are available in shrink-wrapped bundles of 100, 108 and 120 vials.

7 WARNINGS AND PRECAUTIONS

General
Treatment with Cerezyme should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the product (see **Immune** heading below and 8 ADVERSE REACTIONS).

Caution is advisable in administration of Cerezyme to patients previously treated with placental-derived ß-glucocerebrosidase (alglucerase injection) and who have developed antibody or who have exhibited symptoms of hypersensitivity to placental-derived ß-glucocerebrosidase (alglucerase injection).

Immune
Cerezyme is contraindicated for patients who are severely hypersensitive (e.g., anaphylactic reactions) to this drug or to any ingredient in the formulation or component of the container (see 2 CONTRAINDICATIONS).

Patients should be closely monitored during the Cerezyme infusion. If significant/severe/life-threatening hypersensitivity reaction (e.g., anaphylactic reactions) occurs during or after infusions, Cerezyme infusion should be discontinued immediately and appropriate medical treatment should be initiated.

Treatment with Cerezyme should be approached with caution and be closely monitored during the infusion in patients who have the history of mild or moderate hypersensitivity reaction (e.g., eczema, pruritis, flushing, rash, etc) to the active ingredient or excipients in the drug product. Pre-treatment with antihistamines and/or corticosteroids and reduction in the rate of infusion has allowed continued use of Cerezyme in most patients.

Anaphylactoid reaction has been reported in less than 1% of the patient population. Further treatment with Cerezyme should be conducted with caution. Most patients have successfully continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and/or corticosteroids.

Data from clinical trials, using a screening enzyme-linked immunosorbent assay (ELISA) followed by a confirmatory radioimmunoprecipitation assay, suggest that approximately 15% of patients treated and tested to date have developed IgG antibody to Cerezyme during the first year of therapy. Patients who developed IgG antibody largely did so 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. It is recommended that patients suspected of a decreased response to treatment be monitored periodically for the formation of IgG antibody to imiglucerase. Patients with antibody to imiglucerase have a higher risk of hypersensitivity reactions. Patients who have developed antibodies or symptoms of hypersensitivity to placental-derived ß-glucocerebrosidase (alglucerase) should be treated with caution when Cerezyme (imiglucerase) is administered.

Monitoring and Laboratory Tests

Patients with antibodies to Cerezyme have a higher risk of hypersensitivity reactions, although not all patients with symptoms of hypersensitivity have detectable IgG antibodies. It is suggested that patients be monitored periodically during the first year of therapy (approximately every 3 months) and at approximately 18 months for IgG antibody formation.

A comprehensive set of response parameters and treatment guidelines have been established and should be followed for the evaluation of Gaucher patients' response to therapy. An ongoing database, known as the International Collaborative Gaucher Group (ICGG) Registry, has been established for the world-wide collection of uniform data to improve the understanding of the disease and the clinical response to enzyme replacement therapy (ERT). The Registry may be contacted at 1-800-745-4447 or information can be found at www.gaucherregistry.com. The Gaucher Registry should be used by Canadian physicians as a monitoring vehicle for all Gaucher patients in Canada. Enrollment of patients is the responsibility of the treating physician. The Registry will be used to monitor the long term effectiveness of ERT when used in the community. All references to specific patients should be made by initials or Registry identification (ID) number, not by name.

The parameters monitored by the Registry include hemoglobin, platelet count, spleen and liver volume, and location and degree of skeletal involvement. Recommended primary assessments and assessment schedules for various evaluations for untreated patients and those on ERT are presented in the tables below.

Table 3: Initial Assessment

A complete history of patient and family, preferably including a pedigree
A comprehensive physical examination (annual)

Quality of life (annual): Patient-reported functional health and well-being (SF-36 Health Survey)
Blood tests Primary tests • Hemoglobin • Platelet count Biochemical markers (one or more of these biochemical markers should be consistently monitored in conjunction with other clinical assessments of disease activity; chitotriosidase, when available as a validated procedure, may be the most sensitive indicator of changing disease activity, and is therefore preferred, although approximately 5% of the general population do not express any chitotriosidase activity due to genetic variability in enzyme expression) • Chitotriosidase • ACE • TRAP Additional blood tests (to be evaluated selectively based on each patient's age and clinical status) • WBC, PT, and PTT • Iron, iron binding capacity, ferritin, vitamin B_{12} • AST and/or ALT; alkaline phosphatase; calcium, phosphorous, albumin, total protein, total and direct bilirubin • Serum immunoelectrophoresis • Hepatitis profile
β-glucosidase and mutation analysis
Antibody sample*
Visceral (contiguous transaxial 10-mm thick sections for sum of region of interest) Spleen volume (volumetric MRI or CT) Liver volume (volumetric MRI or CT)
Skeletal MRI (coronal; T1- and T2-weighted) of the entire femora X-ray (AP view of the entire femora)** and lateral view of the spine DXA lumbar spine and femoral neck
Pulmonary (recommended every 12-24 months for patients with borderline or above normal pulmonary pressures at baseline) ECG, chest x-ray, and Doppler echocardiogram (right ventricular systolic pressure) for patients > 18 years old

* A baseline sample to be stored at Genzyme Corporation; an optional subsequent sample at 6 months after

starting enzyme replacement therapy (ERT). The samples will be tested only if clinically indicated such as for a suspected immune-mediated adverse event, or for suspected loss of ERT effectiveness.

** Optimally from hips to below knees

Abbreviations:

- ACE: angiotension-converting enzyme
- TRAP: tartrate-resistant acid phosphatase
- AP: anterior-posterior
- ALT: alanine transaminase
- AST: aspartate transaminase
- CT: computed tomography
- DXA: dual energy x-ray absorptiometry
- ECG: electrocardiogram
- MRI: magnetic resonance imaging
- PT: prothrombin time
- PTT: partial thromboplastin time
- WBC: white blood cells

Table 4: Ongoing Monitoring 1

Parameters			**Patients on Enzyme Therapy**			
	Patients Not on Enzyme Therapy		**Not Achieved Therapeutic Goals**		**Achieved Therapeutic Goals**	**At Time of Dose Change or Significant Clinical Complication**
	Every 12 months	**Every 12-24 months**	**Every 3 months**	**Every 12 months**	**Every 12-24 months**	
A comprehensive physical examination	X			X	X (annual)	
SF-36 (QOL) survey	X			X	X (annual)	X
Blood tests						
Hemoglobin	X		X		X	X
Platelet Count	X		X		X	X
Biochemical markers [2]	X		X		X	X
Chitotriosidase						
ACE						
TRAP						
Additional blood tests	To be followed appropriately if abnormal based on each patient's age and clinical status					
Visceral (contiguous transaxial 10mm thick sections for						

Parameters	Patients Not on Enzyme Therapy		Patients on Enzyme Therapy			
			Not Achieved Therapeutic Goals		Achieved Therapeutic Goals	At Time of Dose Change or Significant Clinical Complication
	Every 12 months	Every 12-24 months	Every 3 months	Every 12 months	Every 12-24 months	
sum of region of interest)						
Spleen volume (volumetric MRI or CT)		X		X	X	X
Liver volume (volumetric MRI or CT)		X		X	X	X
Skeletal [3]						
MRI of entire femora (coronal; T1- & T2- weighted) [4]		X		X	X	X
X-ray [4,5]						
DXA		X		X	X	X
		X		X	X	X
Pulmonary	Recommended every 12-24 months for patients with borderline or above normal pulmonary pressures at baseline					

[1] A comprehensive physical examination should be performed at least annually.
[2] One or more of these biochemical markers should be consistently monitored every 12 months and in conjunction with other clinical assessments of disease activity and response to treatment; chitotriosidase, when available as a validated procedure, may be the most sensitive indicator of changing disease activity, and is therefore preferred.
[3] Anatomical sites not included here should be evaluated if symptoms develop in such locations.
[4] AP view of the entire femora (optimally from hips to below knees), and lateral view of the spine
[5] Optional in absence of new symptoms or evidence of disease progression

Medical or health care professionals are encouraged to register Gaucher patients, including those with chronic neuronopathic manifestations of the disease, in the "ICGG Gaucher Registry".

For more information please consult the Registry website: www.gaucherregistry.com.

Respiratory
In less than 1% of the patient population, pulmonary hypertension has also been observed during treatment with Cerezyme. Pulmonary hypertension is a known complication of Gaucher disease and

has been observed both in patients receiving and not receiving Cerezyme. No causal relationship with Cerezyme has been established. Patients with respiratory symptoms should be evaluated for the presence of pulmonary hypertension.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from studies in pregnant women. It is unknown whether Cerezyme can cause fetal harm when administered to pregnant women or if it can affect reproductive capacity. It is unknown whether Cerezyme passes via the placenta to the developing fetus.

No animal studies have been carried out with respect to assessing the effects of Cerezyme on pregnancy, embryonal/fetal development, parturition and postnatal development.

The use of Cerezyme in pregnant women with Gaucher disease may be considered only after individual patient risk-benefit assessment has been made. In pregnant Gaucher patients and in those intending to become pregnant, a risk-benefit treatment assessment is required for each pregnancy. Irrespective of the decision about treatment, specific monitoring should be available throughout the pregnancy to ascertain or pre-empt complications related to the disease.

Limited experience on 158 pregnancy outcomes is available from the Sponsor pharmacovigilance database. Gaucher disease in pregnant women may be complicated by increase visceromegaly, worsening anemia, thrombocytopenia, bleeding, bone crises and osteonecrosis. Spontaneous abortions and fetal demises at any time in pregnant women receiving Cerezyme have been reported. The causal association with Cerezyme has not been established.

7.1.2 Breast-feeding

No well-controlled clinical trials were conducted in nursing women. It is unknown whether Cerezyme is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Cerezyme is administered to nursing women.

7.1.3 Pediatrics

Pediatrics (< 2 years of age): No data are available to Health Canada for pediatric patients less than 2 years of age; therefore, Health Canada has not authorized an indication for pediatric use in patients less than 2 years of age.

Pediatrics (2 - 16 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Cerezyme in pediatric patients aged 2 to 16 years have been established. Therefore, Health Canda has authorized an indication for pediatric use in patients aged 2 to 16 years.

7.1.4 Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials therefore may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following safety information is based on the 3 pre-marketing clinical studies completed prior to registration of Cerezyme: the Pivotal study (RC91-0110), the Extension study (RC92-0501) and the Israeli study (RC92-0301). All patients were Type 1 Gaucher patients. Cerezyme naïve patients refer to those patients who were randomized to receive Cerezyme for 6 months at a dose of 60 U/kg every 2 weeks during the Pivotal study and continued on Cerezyme during the Extension study. Cerezyme cross-over patients refer to those patients who were randomized to receive alglucerase injection during the Pivotal study then were switched to Cerezyme during the Extension study. Some dose reductions based on maintenance of efficacy occurred during the Extension study. The 10 patients in the Israeli study received Cerezyme for 18 to 24 months at doses of either 15 U/kg every other week or 2.5 U/kg three times weekly.

Table 5: All related adverse events (≥1%) in Cerezyme treated patients during the Pivotal, Extension and Israeli studies (by COSTART body system)

	Cerezyme naïve (N=15) **No. (%)**	**Cerezyme cross-over (N=15)** **No. (%)**	**Cerezyme Israeli Study (N=10)** **No. (%)**
BODY AS A WHOLE			
Headache	4 (27)	0 (0)	0 (0)
Abdominal pain	0 (0)	0 (0)	1 (10)
Fever	0 (0)	1 (6.7)	0 (0)
Chest pain	0 (0)	1 (6.7)	0 (0)
CARDIOVASCULAR SYSTEM			
Hypotension	1 (6.7)	0 (0)	0 (0)
Vasodilation	0 (0)	1 (6.7)	1 (10)
DIGESTIVE SYSTEM			
Nausea	1 (6.7)	0 (0)	1 (10)
Diarrhea	0 (0)	1 (6.7)	0 (0)
NERVOUS SYSTEM			
Dizziness	1 (6.7)	0 (0)	0 (0)
Emotional lability	0 (0)	1 (6.7)	0 (0)

	Cerezyme naïve (N=15) No. (%)	Cerezyme cross-over (N=15) No. (%)	Cerezyme Israeli Study (N=10) No. (%)
Paresthesia	0 (0)	1 (6.7)	0 (0)
Hyperesthesia	0 (0)	0 (0)	1 (10)
Nervousness	0 (0)	0 (0)	1 (10)
SKIN AND APPENDAGES			
Pruritus	1 (6.7)	1 (6.7)	0 (0)
Rash	1 (6.7)	0 (0)	0 (0)
Rash macular-papular	0 (0)	1 (6.7)	0 (0)
UROGENITAL SYSTEM			
Oliguria	1 (6.7)	0 (0)	0 (0)

During the 3 pre-marketing clinical studies, no additional adverse events were reported as potentially related to Cerezyme treatment. No serious adverse events were reported in any of the 3 studies.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial Findings

In the Phase IV study (CZ-011-01), 5.6% (Q4 group) and 3.8% (Q2 group) of patients had shifts from normal at baseline to low hemoglobin levels at month 24. Patients who had shifts from normal at baseline to low platelet levels were 14.8% (Q4) and 3.8% (Q2) at month 3, 7.8% (Q4) and 0% (Q2) at month 12, and 16.7% (Q4) and 3.8% (Q2) at month 24.

In a Phase IV open-label study (RC96-1101, treated patients n = 33), 1 patient (3%) had an ALT value ≥ 5 x ULN and 5 (15%) others had an ALT value ≥ 1.5 x ULN; 2 patients (6%) had an AST value ≥ 3 x ULN and 2 (6%) others had an AST value ≥ 1.5 x ULN. Five patients (15%) had a bilirubin (total) value ≥ 1.5 x ULN.

8.5 Post-Market Adverse Reactions

Additional adverse events (AEs) have been identified during post-marketing use of Cerezyme. Due to the voluntary nature of post-marketing reporting and the continuous accrual and loss of patients over time, actual patient exposure and event frequencies are difficult to obtain and are therefore estimates. Post-marketing reports in patients treated with Cerezyme revealed that approximately 13.8% of patients experienced adverse drug reactions.

Symptoms suggestive of hypersensitivity have been noted in approximately 6.6% of patients. Onset of such symptoms has occurred during or shortly after infusions; these symptoms include pruritis, flushing, rash, urticaria/angioedema, chest discomfort, tachycardia, dyspnea, coughing, cyanosis, paresthesia and backache. Hypotension associated with hypersensitivity has also been reported rarely (see 7 WARNINGS AND PRECAUTIONS, Immune).

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.

Table 6: Adverse drug reactions are listed by system organ class and frequency

Nervous system disorders		
	Uncommon:	Dizziness, headache
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, diarrhea
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:	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
	Rare:	Transient peripheral edema

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.

A completed post-marketing clinical study conducted in Japan (protocol 8-98) investigated the use of Cerezyme in patients with neuronopathic Gaucher disease. During this study, one Type 3 Gaucher

patient experienced an AE of nail disorder which was considered potentially related to Cerezyme therapy. No additional adverse events were reported that were related to Cerezyme.

A Phase IV study (RC96-1101) was conducted to evaluate and quantify skeletal responses compared to baseline in patients receiving Cerezyme therapy over a period of 48 months. This was a multicenter, open-label, prospective study in treatment naïve patients (n = 33). The most common AEs were chills (7 events), flushing (6 events), and arthralgia (6 events), each reported in 4 patients (12%). The most common severe AEs were aseptic necrosis of bone and bone pain, both reported in 2 patients (6%). The most common AEs considered, at least possibly related to study drug were chills, reported in 4 patients (12%). Only 5 other AEs considered related to study treatment were reported in more than 1 patient: chest discomfort, flushing, nausea, pruritus and alanine aminotransferase (ALT) increased. Eleven patients experienced a total of 31 serious adverse events (SAEs). Two patients experienced SAEs considered at least possibly related to study drug consistent with infusion-associated reactions at approximately month 6; both of these patients were antibody-positive at Month 3. General disorders and administration site conditions were reported in 6 patients (18%). One AE in this SOC (one incidence of chills) was considered severe. One patient withdrew from the study due to an SAE consistent with an infusion reaction. Another patient withdrew due to a diagnosis of lung cancer.

A Phase IV, multicenter, randomized study (CZ-011-01) was conducted to assess the safety and efficacy of Cerezyme infusions every four weeks (Q4) versus every two weeks (Q2), at the same cumulative dose, in the maintenance therapy of patients with Type 1 Gaucher Disease (n = 37 Q2; n = 65 Q4). Five (8.4%) patients from the Q4 and 1 (3.0%) patient from the Q2 groups withdrew from the study due to adverse events. All 5 of the Q4-treated patients withdrew due to symptoms consistent with Gaucher disease. These symptoms include splenomegaly, decreased hemoglobin, arthralgia, and bone pain. Treatment emergent AEs were reported in the Q4 (83.9%) and Q2 (63.6%) groups. The AEs (≥ 5% and occurring more often in Q4 group than in the Q2 group) are: back pain (16.1% vs. 0%), arthralgia (16.1% vs. 9.1%), fatigue (9.7% vs. 0%), headache (9.7% vs. 6.1%), decreased hemoglobin (8.1% vs. 0%), platelet count decreased (8.1% vs. 0%), bone pain (8.1% vs. 6.1%), pain in extremity (8.1% vs. 6.1%), sinusitis (8.1% vs. 6.1%), gastroenteritis viral (6.5% vs. 0%), influenza (6.5% vs. 0%) and, cough (6.5% vs. 3.0%). The AEs considered as related to study medication were approximately twice the rate in the Q4 group compared to the Q2 group (11.3% vs. 6.1%). They are fatigue, pain in extremity, infusion site erythema, infusion site pain, dizziness, tremor, hemoglobin decreased and splenomegaly. The most commonly reported infusion-associated reactions include: pruritus, urticaria, muscle spasms, fatigue, infusion site erythema, and infusion site pain. There were 2 (3.2%) patients in the Q4 group, none in the Q2 group, who experienced infusion site erythema or infusion site pain. Two patients (3.2%) in the Q4 group reported hypersensitivity and multiple allergies. No immune system disorders were reported in Q2-treated patients.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity (see 7 WARNINGS AND PRECAUTIONS, Immune). The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

A voluntary immunosurveillance program was initiated in 1991 to better determine the extent of antibody formation in patients receiving alglucerase, which was then extended to patients receiving imiglucerase treatment. The Sponsor offers this service to the Gaucher-treating physicians world-wide. As part of the immunosurveillance program, patients are monitored for the development of IgG

antibodies to the enzyme using an ELISA test. The resultant absorbance values are compared to a cut-off established from a normal human serum distribution study. Confirmation by the radioimmunoprecipitation (RIP) test of the "above normal range" ELISA indicates that the patient developed antibodies to glucocerebrosidase.

During post-marketing safety surveillance of imiglucerase, the seroconversion rate in patients treated with imiglucerase only has remained at approximately 15%. This overall seroconversion rate is consistent with the rate of antibody formation in patients treated with imiglucerase only reported in the US Pivotal/Extended (3/15, 20%) and Israeli (1/10, 10%) Studies. Patients who develop IgG antibody largely do so within 6 months of treatment and rarely develop antibodies to imiglucerase after 12 months of therapy. Infusion-associated reactions have been reported in approximately half of patients with detectable IgG antibodies to imiglucerase. The most commonly reported symptoms, which are mostly mild to moderate in nature, include pruritus, rash, urticaria, headache, dyspnea and chills. Reactions in most cases are managed by a slower infusion rate and/or pretreatment with anti-pyretics or antihistamines. Patients with antibodies to imiglucerase have a higher risk of infusion-associated reactions; however, not all patients experiencing infusion-associated reactions have detectable IgG antibodies. It is suggested that patients be monitored periodically for IgG antibody formation.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Imiglucerase is an analogue of ß-glucocerebrosidase produced by recombinant DNA technology. The lysosomal enzyme catalyses the hydrolysis of glucocerebroside to glucose and ceramide. Gaucher disease is an autosomal genetic disorder characterized by a deficiency of ß-glucocerebrosidase activity, resulting in accumulation of glucocerebroside in the lysosomes of tissue macrophages in the liver, spleen, bone marrow and occasionally in lung and kidney. Secondary hematologic sequelae include severe anemia and thrombocytopenia in addition to the characteristic progressive

hepatosplenomegaly, skeletal complications, including osteonecrosis and osteopenia with secondary pathological fractures.

10.2 Pharmacodynamics

Imiglucerase (recombinant macrophage targeted acid ß-glucosidase) replaces the deficient enzyme activity, hydrolysing glucosylceramide, thus correcting initial pathophysiology and preventing secondary pathology. In clinical trials, imiglucerase reduces spleen and liver size, improves thrombocytopenia and anemia, improves bone marrow burden, and reduces bone pain and bone crises. Patients have been shown to consistently respond to therapy regardless of the heterogeneity or severity of Gaucher disease. Pediatric patients generally respond to ERT more quickly than adults. The skeletal response in both pediatric and adult patients to ERT is generally slower than the hematologic and organ response. The initial primary uptake sites of imiglucerase are the spleen and liver.

In a Phase IV open-label study (RC96-1101) in patients with Type 1 Gaucher disease, 33 patients received 60 U/kg of imiglucerase every 2 weeks for the first 24 months. If therapeutic goals had been met, the patient could maintain the current imiglucerase dose or the dose could be reduced to 45 U/kg or 30 U/kg every 2 weeks. Reduction in bone pain was observed with imiglucerase treatment by Month 3. Among the 32 patients with follow-up data, 12 patients (38%) who had moderate, severe, or extreme pain at baseline, had dropped to 6 (19%) by Month 3. The number of patients with no pain had risen from 9 (28%) at baseline to 16 (52%), 65% and 60% on months 6, 21 and 48. While 13 patients were reported to have a history of bone crises and 5 patients reported at least one bone crisis within the 2 months prior to baseline, bone crises were reported in only 3 patients in the 48 months of the study.

10.3 Pharmacokinetics

Table 7: Summary of Pharmacokinetic Data

Report #	Descrip-tion	Type of analysis	Cmax	AUC	t½ [min][1]	Vd [L/kg][1]	Cl [mL/(min.kg)][1]
RC92-0502	Gaucher patients	Enzymatic activity*	Not evaluated	Not evaluated	5.9	0.159	18.9

*p-nitrophenyl-ß-D-glucopyranoside (pNP-ß-D-glucopyranoside) as a substrate. An enzyme unit (U) is defined as the amount of enzyme that catalyses the hydrolysis of one micromole of the synthetic substrate p-nitrophenyl ß-D-glucopyranoside (pNP-Glc) per minute at 37 ºC.

[1]Mean values reported.

Absorption: Imiglucerase is administered IV. 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.

Distribution: The volume of distribution corrected for weight ranged from 0.09 to 0.15 L/Kg (0.12 ± 0.02 L/kg). These variables appear to be independent of dose or duration of infusion. Within the dose range of 7.5 to 60 U/kg, volume of distribution values appear to be independent of the infused dose.

Metabolism: Imiglucerase is not a substrate for drug metabolizing enzymes.

Elimination: Similar to other enzymes, imiglucerase is broken down by endogenous protease and peptidase. 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). Within the dose range of 7.5 to 60 U/kg, elimination half-life and plasma clearance appear to be independent of the infused dose.

11 STORAGE, STABILITY AND DISPOSAL

Lyophilized vial

Table 8: Storage for Lyophilized vial

Cerezyme	Temperature	Recommended maximum storage time
lyophilized vial	2-8 ºC	Do not use past expiry date on label
lyophilized vial	23-27 ºC	do not exceed 48 hours

Reconstituted Solutions

Stability of reconstituted and diluted solutions are noted below:

Table 9: Storage for Reconstituted Solutions

Cerezyme Condition	Temperature	Recommended maximum storage time
Reconstituted vial (WFI)	2-8 ºC	up to 12 hours
Reconstituted vial (WFI)	28-32 ºC	up to 12 hours
Diluted with 0.9% NaCl	2 – 8 ºC	up to 24 hours
Diluted with 0.9% NaCl	20 – 25 ºC	up to 24 hours

Note: Reconstituted vials of Cerezyme are single use only. Use the vials immediately upon reconstitution. Additionally, Cerezyme when diluted with saline, has been shown to be stable for up to 24 hours when stored at room temperature and at 2-8ºC.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance:

Proper name: Imiglucerase

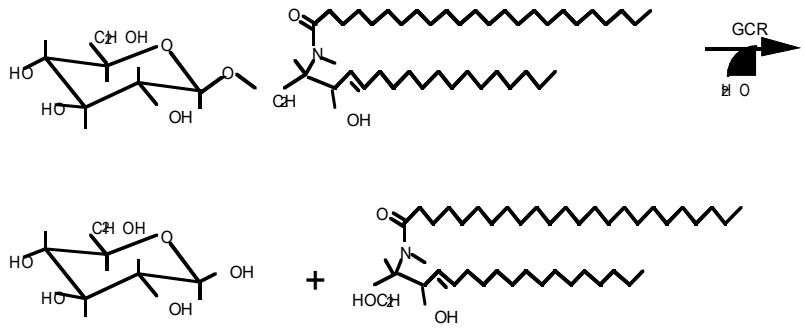
Chemical name: Recombinant human carbohydrate-modified ß-glucocerebrosidase

Molecular formula and molecular mass: $C_{2532}H_{3845}N_{671}O_{711}S_{16}$ / Mr = 60,430 (as determined by Mass Spectroscopy)

Structural formula:

Ala	Arg	Pro	Cys	Ile	Pro	Lys	Ser	Phe	Gly	Tyr	Ser	Ser	Val	Val	Cys	Val	Cys	**Asn**	Ala
				5					10					15					20
Thr	Tyr	Cys	Asp	Ser	Phe	Asp	Pro	Pro	Thr	Phe	Pro	Ala	Leu	Gly	Thr	Phe	Ser	Arg	Tyr
				25					30					35					40
Glu	Ser	Thr	Arg	Ser	Gly	Arg	Arg	Met	Glu	Leu	Ser	Met	Gly	Pro	Ile	Gln	Ala	**Asn**	His
				45					50					55					60
Thr	Gly	Thr	Gly	Leu	Leu	Leu	Thr	Leu	Gln	Pro	Glu	Gln	Lys	Phe	Gln	Lys	Val	Lys	Gly
				65					70					75					80
Phe	Gly	Gly	Ala	Met	Thr	Asp	Ala	Ala	Ala	Leu	Asn	Ile	Leu	Ala	Leu	Ser	Pro	Pro	Ala
				85					90					95					100
Gln	Asn	Leu	Leu	Leu	Lys	Ser	Tyr	Phe	Ser	Glu	Glu	Gly	Ile	Gly	Tyr	Asn	Ile	Ile	Arg
				105					110					115					120
Val	Pro	Met	Ala	Ser	Cys	Asp	Phe	Ser	Ile	Arg	Thr	Tyr	Thr	Tyr	Ala	Asp	Thr	Pro	Asp
				125					130					135					140
Asp	Phe	Gln	Leu	His	**Asn**	Phe	Ser	Leu	Pro	Glu	Glu	Asp	Thr	Lys	Leu	Lys	Ile	Pro	Leu
				145					150					155					160
Ile	His	Arg	Ala	Leu	Gln	Leu	Ala	Gln	Arg	Pro	Val	Ser	Leu	Leu	Ala	Ser	Pro	Trp	Thr
				165					170					175					180
Ser	Pro	Thr	Trp	Leu	Lys	Thr	Asn	Gly	Ala	Val	Asn	Gly	Lys	Gly	Ser	Leu	Lys	Gly	Gln
				185					190					195					200
Pro	Gly	Asp	Ile	Tyr	His	Gln	Thr	Trp	Ala	Arg	Tyr	Phe	Val	Lys	Phe	Leu	Asp	Ala	Tyr
				205					210					215					220
Ala	Glu	His	Lys	Leu	Gln	Phe	Trp	Ala	Val	Thr	Ala	Glu	Asn	Glu	Pro	Ser	Ala	Gly	Leu
				225					230					235					240
Leu	Ser	Gly	Tyr	Pro	Phe	Gln	Cys	Leu	Gly	Phe	Thr	Pro	Glu	His	Gln	Arg	Asp	Phe	Ile
				245					250					255					260
Ala	Arg	Asp	Leu	Gly	Pro	Thr	Leu	Ala	**Asn**	Ser	Thr	His	His	Asn	Val	Arg	Leu	Leu	Met
				265					270					275					280
Leu	Asp	Asp	Gln	Arg	Leu	Leu	Leu	Pro	His	Trp	Ala	Lys	Val	Val	Leu	Thr	Asp	Pro	Glu
				285					290					295					300
Ala	Ala	Lys	Tyr	Val	His	Gly	Ile	Ala	Val	His	Trp	Tyr	Leu	Asp	Phe	Leu	Ala	Pro	Ala
				305					310					315					320
Lys	Ala	Thr	Leu	Gly	Glu	Thr	His	Arg	Leu	Phe	Pro	Asn	Thr	Met	Leu	Phe	Ala	Ser	Glu
				325					330					335					340
Ala	Cys	Val	Gly	Ser	Lys	Phe	Trp	Glu	Gln	Ser	Val	Arg	Leu	Gly	Ser	Trp	Asp	Arg	Gly
				345					350					355					360
Met	Gln	Tyr	Ser	His	Ser	Ile	Ile	Thr	Asn	Leu	Leu	Tyr	His	Val	Val	Gly	Trp	Thr	Asp
				365					370					375					380
Trp	Asn	Leu	Ala	Leu	Asn	Pro	Glu	Gly	Gly	Pro	Asn	Trp	Val	Arg	Asn	Phe	Val	Asp	Ser
				385					390					395					400
Pro	Ile	Ile	Val	Asp	Ile	Thr	Lys	Asp	Thr	Phe	Tyr	Lys	Gln	Pro	Met	Phe	Tyr	His	Leu
				405					410					415					420
Gly	His	Phe	Ser	Lys	Phe	Ile	Pro	Glu	Gly	Ser	Gln	Arg	Val	Gly	Leu	Val	Ala	Ser	Gln
				425					430					435					440
Lys	Asn	Asp	Leu	Asp	Ala	Val	Ala	Leu	Met	His	Pro	Asp	Gly	Ser	Ala	Val	Val	Val	Val
				445					450					455					460
Leu	Asn	Arg	Ser	Ser	Lys	Asp	Val	Pro	Leu	Thr	Ile	Lys	Asp	Pro	Ala	Val	Gly	Phe	Leu
				465					470					475					480
Glu	Thr	Ile	Ser	Pro	Gly	Tyr	Ser	Ile	His	Thr	Tyr	Leu	Trp	His	Arg	Gln			
				485					490					495					

Provided below is the structural formula of glucocerebroside and the site of action of glucocerebrosidase (GCR).



Physicochemical Properties:

Imiglucerase, an analogue of the human enzyme β-glucocerebrosidase, is a lysosomal glycoprotein enzyme which catalyses the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide. Imiglucerase has oligosaccharide chains, which have been modified to terminate in mannose sugars. These mannose-terminated oligosaccharide chains of imiglucerase are specifically recognized by endocytic carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease.

Product Characteristics:

Cerezyme (imiglucerase for injection) is a sterile, non-pyrogenic, white to off-white lyophilized powder. Imiglucerase is manufactured in Chinese Hamster Ovary (CHO) cells using a cell culture and expansion process, and purified using a series of chromatographic and membrane filtration. The imiglucerase Drug Substance is formulated with formulation buffer, processed through a nanofilter, and adjusted to achieve the final protein concentration. The Formulated Drug Substance is then pooled, sterile filtered, filled aseptically into glass vials, and lyophilized to produce the Drug Product. The lyophilized vials are then capped, labelled and packaged.

Viral Inactivation:

The viral safety of Cerezyme is confirmed by a combination of selection and qualification of vendors, raw material testing, cell bank characterization studies, validation of the viral removal and inactivation capacity of the purification process, and routine in-process testing.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Gaucher Disease

Table 10: Summary of patient demography for clinical trials in 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 non-neurological manifestations of the disease

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
RC91-0110 **Pivotal Trial**	Randomized, controlled, double blind, parallel	Cerezyme 60 U/kg or alglucerase injection 60 U/kg every 2 weeks, intravenous infusion, 6 months	Gaucher patients (n = 30)	32.7 years (12 to 69 years)	17 M / 13 F
RC92-0501 **Extension to Pivotal Trial (RC91-0110)**	Randomized, controlled, double blind, parallel	Cerezyme 60 U/kg every 2 weeks, intravenous infusion, 26 to 29 months*	Gaucher patients (n = 30)**	32.7 years (12 to 69 years)	17 M / 13 F
RC92-0301	Randomized, controlled, matched pair	Cerezyme 15 U/kg every 2 weeks or Cerezyme 2.5 U/kg 3 times a week, intravenous infusion, 1.5 to 2 years	Gaucher patients (n=10)	32.2 years (18 to 46 years)	2 M / 8 F
CZ-011-01	Open-label, randomized	Cerezyme 40-120 U/kg in a 4-week period. Total 4-week dose in 2 infusions (1 infusion/2 weeks), Q2; or total 4-week dose in 1 infusion, Q4, intravenous infusion, 24 months	Gaucher patients (n=95)***	46.8 years (18 to 82 years)	48 M / 47 F

*Patients in extension study RC92-0501 initially received doses of Cerezyme at 60 U/kg which was reduced at the 9 month evaluation period. Doses were adjusted based upon achievement of specified hematological responses, but not skeletal responses.
**Twenty-nine patients completed treatment on Cerezyme.
*** One hundred two patients were randomized to treatment but 95 patients received one ore more doses of study treatment.

After the completion of the pivotal trial (RC91-0110), at 6 months, patients continued to be followed for an extended study period (RC92-0501) of 26 to 29 months. In addition, a separate dosing schedule comparison study (RC92-0301) was conducted. In the pivotal trial, some initial positive effects on bone were observed but according to protocol design, doses were reduced once hematologic improvements were achieved. Reports in the literature indicate that effects on bone may require longer treatment with higher doses. The tables below describe the results of these studies.

Table 71: Clinical Effects on Hematology and Organ Weights (% change compared to baseline):

Report #	Parameter	Hemoglobin	Platelet	Liver	Spleen
RC91-110 Pivotal Trial Cz arm N15 (6 months results change compared to baseline):	**Mean**	20%	33%	- 11%	- 35%
	p value	p < 0.001	p = 0.001	p <0.001	p <0.001
	Response	↑ ≥ 1.0 g/dL	↑ ≥ 30%	↓ ≥ 10%	↓ ≥ 10%
	Response rate	13/15 87%	9/15 60%	8/15 53%	15/15 100%
RC92-0501 Extension (28 months results compared to baseline)	**Mean**	28%	80%	- 21%	- 54.7%
	Response	↑ ≥ 1.0 g/dL	↑ ≥ 30%	↓ ≥ 10%	↓ ≥ 10%
	Response rate	12/15 80%	11/15 73%	14/15 93%	14/15 93%
RC92-0301 (2-year period)	**Mean**	12.5%	97%	- 19%	- 42.5%
	Response	↑ ≥ 1.0 g/dL	↑ ≥ 30%	↓ ≥ 10%	↓ ≥ 10%
	Response rate	7/10 70%	5/10 50%	7/10 70%	9/10 90%

Effects on Bone:

Long term changes in cortical bone thickness and radiographic assessment were evaluated in a group of 11 patients who participated in the Pivotal/Extended study. Cortical thickness was evaluated as the difference between the periosteal and endosteal diameters at the midshaft of the bone.

Table 82: Long term changes in cortical bone thickness and radiographic assessment

Measurement	**% improvement from baseline**	**N**
Cortical thickness of the Humeri	43%	3 out of 7 evaluated
Cortical thickness of the Femora	60%	6 out of 10 evaluated
Radiographic Assessment	63%	7 out of 11 evaluated

Effects on Clinical Stability for Varied Dosing Regimens:

The usual frequency of infusion is once every 2 weeks (see 4 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. A total of 102 patients (37 Q2, 65 Q4) were randomized to treatment and 95 patients (33 Q2, 62 Q4) received one or more doses of study treatment. A total of 80 patients were included in the analysis at month 12 (27 Q2, 53 Q4) and a total of 83 patients were included in the analysis at month 24 (26 Q2, 57 Q4). The mean age at randomization in the Q2 group was 44.8 (19-82) and in the Q4 group was 47.8 (18-78).

Changes from baseline in hemoglobin, platelets, liver and spleen volumes, bone crises, and bone disease comprised a predefined composite endpoint; The primary efficacy endpoint was the proportion of patients with a clinical success (success rate). Patients were considered to be a clinical success if ALL of the following were met:

- The patient's hemoglobin did not fall more than 1.25g/dL for women or 1.5 g/dL for men below the patient's baseline value.
- The patient's platelet count did not fall more than 25% below the patient's baseline value and did not fall below 80,000 mm^3.
- The patient's liver and spleen volumes were not greater than 20% above the patient's baseline value.
- The patient had no new on-study finding or progression of bone disease, including no new incidence of pathologic fractures, medullary infarctions, lytic lesions or avascular necrosis.
- The patient had no bone crises during the study.

In the Q2 group, the mean infusion dose received by patients was 66.7 U/Kg/4wk (range 37-118) and the mean infusion duration was 182.3 minutes/4wk (range 119-316). In the Q4 group, the mean infusion dose received by patients was 69 U/Kg/4wk (range 29-120) and the mean infusion duration was 135.9 minutes/4wk (range 60-306). Fifty-three percent (n=33) of Q4-treated patients received the high dose Cerezyme (>60 U/kg Cerezyme every 4 weeks) compared with 36% (n=12) of Q2-treated patients.

Of ITT patients with a known clinical outcome, a total of 63% of Q4-treated patients met the criteria for clinical success at Month 24/discontinuation compared with 81% of Q2-treated patients. The success

rates at Month 12 for Q4 was 60% and for Q2 was 96%. Two Q2 (6%) and 13 Q4 patients (21%) withdrew due to clinical failure.

Of ITT patients, 0 of the Q2 treated patients had a liver size increase from baseline ≥20% at 12 months of treatment and 1 (3%) had an increase from baseline ≥20% at 24 months of treatment. Five (8%) of the Q4 treated patients had liver size increases from baseline ≥20% at 12 months of treatment and 2 (3%) had increases from baseline ≥20% at 24 months of treatment. Of ITT patients, 0 of the Q2 treated patients had a spleen size increase from baseline ≥20% at 12 months of treatment and 2 (6%) had an increase from baseline ≥20% at 24 months of treatment. Seven (11%) of the Q4 treated patients had spleen size increases from baseline ≥20% at 12 months of treatment and 4 (6%) had increases from baseline ≥20% at 24 months of treatment.

Effects on Neurological Manifestations:

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.

Effects on Gaucher Patients (Type 3):

Evaluation of treatment efficacy data captured from the International Collaborative Gaucher Group Registry (ICGG/Gaucher Registry) and from a Japanese post-marketing study show evidence of improvement in non-neurological manifestations (anemia, thrombocytopenia, bone disease, hepatomegaly, and splenomegaly) for Type 3 patients, similar to that observed in Type 1 patients.

The post-marketing clinical study performed in Japan was designed as an open study for patients with Type 2 and Type 3 Gaucher disease. It was designed to address conditions for approval of Cerezyme in Japan. The aim of the study was to assess the efficacy and safety of the drug in the commercial setting over 3 years.

Separate analyses of the safety and efficacy for the Type 3 patients in the Japanese study were performed. Results showed that laboratory parameters such as Hemoglobin, Platelet count, ACE activity and ACP activity were dramatically improved within 24-48 weeks and maintained until the end of the study (144 weeks). Size and volume of liver or spleen were decreased within 24 weeks and maintained until the end of the study (144 weeks). General symptoms could have improved in some patients, but efficacy for bone or neurological symptoms were very limited. However, physicians judged overall improvement was found at rate of 50% and clinical efficacy of ERT was confirmed to all of Type 3 patient. Safety profile was acceptable. Only one patient experienced an adverse event of nail disorder which was considered potentially related to Cerezyme therapy. Unrelated but serious adverse events reported included: pneumonia, complications of bone marrow transplant, acute cholecystitis, cholelithiasis, convulsions, aspiration pneumonia, bronchitis, intestinal obstruction, inguinal hernia, pyrexia, urticaria, increased bronchial secretions, respiratory failure, femur fracture and tonsillar hypertrophy. The majority of unrelated, serious events recorded in the patients with Type 3 disease are related to the nature of the severe underlying Gaucher disease.

In addition to the Japanese data, multiple analyses comparing the hematological (hemoglobin, platelets) and visceral (liver, spleen) responses to ERT in chronic neuronopathic (Type 3) versus non-neuronopathic (Type 1) Gaucher patients were performed using data from the Gaucher Registry from a

total of 2637 patients. This data set consisted of 130 neuronopathic Gaucher patients, of whom 117 have received ERT. In respect to platelet responses, the presented data suggest that the responses to ERT are at least similar in both patient populations.

In regards to platelet count, the responses to therapy from patients in the Registry seem to be most prominent in the first 2 years of treatment and the patients' ability to have an increase of platelet counts in response to ERT does not seem to be influenced by the presence or absence of the spleen.

In the first 6 months of treatment, the majority (83%) of neuronopathic patients showed amelioration of thrombocytopenia resulting in reclassification of thrombocytopenia severity from "severe" to "moderate" / "normal", compared to one third (35%) of the "severe" non-neuronopathic population.

For hemoglobin, the majority of patients in both patient populations start treatment with moderate to severe anemia, and reach normal or near normal hemoglobin values within the first 12 or 18 months of treatment.

In the first 6 months of treatment, 64% of neuronopathic patients showed improvement of their anemia resulting in reclassification of anemia severity from "severe" to "moderate" / "normal", compared to 69% of the severely anemic non-neuronopathic population.

In both populations, the liver volumes decrease, as indicated by the mean and median reduction in liver volume MN at 12 and 24 months and a reduction in severity of hepatomegaly category distribution during the first 6 months of treatment.

Both patient groups had moderate to severe splenomegaly at baseline, and demonstrated improvement over time. Despite the substantial reduction in spleen size, the majority of neuronopathic patients still fall within the severe splenomegaly category (> 15 x MN) after 6 months of enzyme replacement therapy, indicating relatively severe underlying disease.

In the short term (6 month) analyses of change from baseline for all the parameters tested, the experience of neuronopathic patients is always numerically superior to that of non-neuronopathic patients. The 12 to 24 month analyses tend to confirm the initial response results. Virtually all measurements of change from baseline are larger among neuronopathic patients than among non-neuronopathic patients. The more severe systemic manifestations at baseline in the neuronopathic population and the higher ERT doses used in neuronopathic Gaucher disease may have influenced these observations.

In conclusion, the analyses of the Registry data show a comparable response to ERT between non-neuronopathic and neuronopathic Gaucher patients with regard to the systemic manifestations of Gaucher disease, as measured by the parameters analysed.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Table 93: Overview of toxicology studies

Report #	Study Characteristics	Parameters Evaluated	Results
HWI 6354-102	Rat Single dose 0, 60, 300, 600 U/kg IV 5M, 5F per group	clinical, food consumption, body weight, hematology, clinical chemistry, organ weight, necropsy, histology	Statistically significant increased platelet and hemoglobin. Increased neutrophil count in 600 u/kg males.
BDL 12807	Rat 13 weeks 0, 3, 30, 300 U/kg IV 5M, 5F per group	clinical, food consumption, body weight, hematology, clinical chemistry, urinalysis, organ weight, necropsy, histology	Dose-dependant antibody response in >50% of animals.
CHV 6354-109	Monkey 13 weeks 0, 30, 100, 300 U/kg IV 3M, 3F per group	clinical, body weight, hematology, clinical chemistry, urinalysis, organ weight, necropsy, histology	Statistically significant increase in mean spleen weight, spleen-to-body weight ratio, spleen-to-brain ratio in 300 u/kg females. Dose-dependant antibody response in >50% of animals.

Carcinogenicity: No long-term animal studies have been performed to evaluate the carcinogenic potential of imiglucerase.

Genotoxicity: Imiglucerase was tested using the Ames mutagenicity test and all concentrations, both with and without activation, were negative.

Reproductive and Developmental Toxicology: No animal studies have been performed to evaluate the effects of imiglucerase on fertility/reproduction, embryo-fetal development, or post-natal development.

Juvenile Toxicity: No animal studies have been performed to evaluate the potential toxicity of imiglucerase in juvenile animals.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

CEREZYME ®

Imiglucerase for injection
Read this carefully before you start taking **Cerezyme** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Cerezyme**.

What is Cerezyme used for?
Cerezyme is used to treat patients with a confirmed diagnosis of non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease. The non-neurological Gaucher disease may result in one or more of the following conditions:

- anemia, after exclusion of other causes, such as iron deficiency
- thrombocytopenia (reduced blood platelets count)
- bone disease (such as weakened bones and increased risk of fracture), after exclusion of other causes, such as Vitamin D deficiency
- hepatomegaly (liver enlargement) or splenomegaly (spleen enlargement)

How does Cerezyme work?
Gaucher disease is a rare genetic disorder in which the body is deficient in an enzyme called ß-glucocerebrosidase. This enzyme breaks down a fatty substance called glucocerebroside. In Gaucher disease, glucocerebroside becomes high in the tissue macrophages in the liver, spleen, bone marrow and occasionally in lung and kidney, because this enzyme is missing. Cerezyme is a form of β-glucocerebrosidase produced by recombinant DNA technology. Cerezyme can help to treat some of the symptoms of Gaucher disease by replacing the natural enzyme that is missing in Gaucher disease.

What are the ingredients in Cerezyme?
Medicinal ingredients: Imiglucerase

Non-medicinal ingredients: mannitol, nitrogen, polysorbate 80, sodium citrates (disodium hydrogen citrate and trisodium citrate)

Cerezyme comes in the following dosage forms:
Cerezyme is supplied as a sterile lyophilized powder for intravenous infusion.
Cerezyme is supplied in a 20 mL vial containing 400U (red label) of imiglucerase.

Do not use Cerezyme if:

- You are hypersensitive to imiglucerase or to any ingredient in the formulation or component of the container.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Cerezyme. Talk about any health conditions or problems you may have, including if:

- You have been treated with placental-derived ß-glucocerebrosidase (alglucerase injection) and have developed antibody or exhibited symptoms of hypersensitivity to placental-derived ß-glucocerebrosidase (alglucerase injection)

- You have had a severe hypersensitivity or anaphylactic reaction to administration of Cerezyme
- You have any allergies to this drug or its ingredients or components of the container
- You are pregnant or plan to become pregnant or are breast-feeding.
- You experience any shortness of breath, before or after starting Cerezyme. Your doctor will evaluate if this is a sign of a condition called pulmonary hypertension, a condition that occurs rarely with Gaucher disease, whether or not patients are on Cerezyme.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Cerezyme:
Studies to test how Cerezyme interacts with other drugs have not been done. Please inform your doctor if you are using any other medicinal products, due to the potential risk of interference with the uptake of imiglucerase.

How to take Cerezyme:

Usual dose:
Dosage should be individualized to each patient.

Your health care professional will prescribe you the dose that is suitable for you.

Treatment may be initiated at a dose of 2.5 units/kg of body weight 3 times a week up to 60 U/kg of body weight administered as frequently as once every two weeks.

If Cerezyme is to be administered in a home care environment, it is suggested that the health care professional be trained and prepared for the possibility of an allergic-type reaction.

Overdose:

There have been no reports of obvious toxicity for doses up to 240 U/kg (every two weeks).
In the event of an overdose, stop the infusion immediately and monitor the patient closely in a hospital setting for the development of infusion-associated reactions.

If you think you, or a person you are caring for, have taken too much Cerezyme, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have missed a Cerezyme infusion, please contact your doctor. It is important to have your infusion on a regular basis to avoid the accumulation of glucocerebroside. The total dose administered each month should remain substantially unchanged.

What are possible side effects from using Cerezyme?

These are not all the possible side effects you may have when taking Cerezyme. If you experience any side effects not listed here, tell your healthcare professional.

Common (may affect up to 1 in 10 people):
- shortness of breath
- coughing
- hives/localised swelling of the skin or lining of the mouth or throat
- itching
- rash

Uncommon (may affect up to 1 in 100 people):
- dizziness
- headache
- a sensation of tingling, pricking, burning or numbness of the skin
- flushing
- vomiting
- nausea
- abdominal cramping/pain
- diarrhea
- pain in the joints
- infusion site discomfort
- infusion site burning
- infusion site swelling
- injection site uninfected abscess
- fever
- rigors
- fatigue
- backache

Frequency Unknown:
- chills
- infusion site itching
- rapid heartbeat

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
RARE			
Allergic reactions including anaphylactoid reaction (a serious allergic reaction) with the following symptoms: itching, flushing, hives, swelling, chest discomfort, shortness of breath,			**X**

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
coughing, bluish skin, low blood pressure, increased heart rate			

Approximately 15% of patients have developed immune reactions (antibodies); periodic monitoring by your physician is suggested.

If you have such a reaction following the administration of Cerezyme, you should immediately contact your doctor.

Your healthcare professional will monitor you closely during the infusion, especially if you have a history of mild or moderate hypersensitivity reaction (e.g., eczema, itching, flushing, rash, etc.). If needed, pre-treatment with antihistamines and/or corticosteroids and reduced rate of infusion can help reduce the possibility of infusion related reactions.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Keep out of reach and sight of children.

Store under refrigeration at 2 ºC to 8 ºC. Do not use after the expiration date on the vial.

Since Cerezyme does not contain any preservative, after reconstitution, vials should be promptly diluted and not stored for subsequent use.

International Collaborative Gaucher Group (ICGG) Registry

The ICGG Registry is a longitudinal prospective study that includes over ~6900 patients (as of October 4, 2023), with Gaucher disease from around the world. The Registry was established to assist physicians in the treatment and management of patients with Gaucher disease.

Treatment centres involved with Registry enrolled patients are required to collect data on a regular basis.

In Canada, the ICGG Annual Report is made available at the beginning of each year. This report details the data collected in the seven provinces with Gaucher patients. The Canadian Annual Report is available upon request through sanofi-aventis Canada.

Information regarding the registry program may be found by calling (800) 745-4447. If you are interested in participating, please contact your doctor.

If you want more information about Cerezyme:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.sanofi.ca, or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

Last Revised: