PRODUCT MONOGRAPH

Pr Cerezyme®

Imiglucerase for injection
(Recombinant human ß-glucocerebrosidase analogue)

Lyophilized Powder
400 Units/vial

Enzyme Replacement Therapy

Sanofi Genzyme, a division of Sanofi-Aventis Canada Inc.
800-2700 Matheson Blvd. East, West Tower
Mississauga, ON
L4W 4V9
www.genzyme.ca

Date of Approval:
November 30, 2016

Submission Control No: 194013

Table of Contents

CEREZYME®

Imiglucerase for Injection
(Recombinant human ß-glucocerebrosidase analogue)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Lyophilized powder for reconstitution and intravenous infusion 400 Units	There are no clinically relevant nonmedicinal ingredients. For a complete listing of non-medicinal ingredients, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

DESCRIPTION

CEREZYME® (imiglucerase for injection) is an analogue of ß-glucocerebrosidase produced by recombinant DNA technology. The lysosomal enzyme catalyses the hydrolysis of glucocerebroside to glucose and ceramide.

INDICATIONS AND CLINICAL USE

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:
- anaemia 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

Pediatrics (2 - 16 years of age):

The safety and effectiveness of CEREZYME® have been established in children and adolescents (from 2 up to 16 years of age). Use of CEREZYME® in these age groups is supported by evidence from well-controlled studies of CEREZYME® and CEREDASE® (alglucerase injection) in adults and pediatric patients, with additional data obtained from the literature and from long term follow-up information.

CONTRAINDICATIONS

- Patients who are severely hypersensitive to this drug or to any ingredient in the formulation or component of the container (see **WARNINGS AND PRECAUTIONS**). For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Disease management with CEREZYME® (imiglucerase for injection) should be directed by physicians knowledgeable in the treatment of patients with Gaucher disease.

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

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

Carcinogenesis and Mutagenesis

Studies have not been conducted in either animals or humans to assess the potential effects of CEREZYME® on carcinogenesis or mutagenesis.

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 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.

Current data, using a screening 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 Ceredase (alglucerase) should be treated with caution when CEREZYME® (imiglucerase) is administered.

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.

Special Populations

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. The Registry may be contacted at 1-800-745-4447. 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 enzyme replacement therapy 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 haemoglobin, 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: 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
- MRI: magnetic resonance imaging
- PT: prothrombin time
- PTT: partial thromboplastin time
- WBC: white blood cells

Table: Ongoing Monitoring [1]

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	
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 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]		X		X	X	X
DXA		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.

Pregnant Women: There are no data from studies in pregnant women. It is not known whether CEREZYME® can cause fetal harm when administered to pregnant women or if it can affect reproductive capacity.

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

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 Genzyme 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.

Nursing Women: No well-controlled clinical trials were conducted in nursing women. It is not known 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.

Pediatrics (< 2 years of age):

There is limited data for pediatric patients under the age of two. The safety & effectiveness of CEREZYME® have been established in children and adolescents (from 2 to 16 years of age).

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.

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Clinical studies are conducted under very specific conditions and the adverse event rates observed in clinical studies may not reflect the rates observed in general practice.

The following safety information is based on the 3 pre-marketing clinical studies completed prior to registration of CEREZYME® (imiglucerase for injection): 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 Ceredase 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: 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)
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.

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 adverse event 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 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 haemoglobin, arthralgia, and bone pain. Treatment emergent AEs were reported in the Q4 (83.9%) and Q2 (63.6%) groups. The AEs ($\geq$ 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 haemoglobin (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, haemoglobin decreased and splenomegaly. The most commonly reported infusion-associated reactions (IARs) 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.

Abnormal Hematologic and Clinical Chemistry 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 haemoglobin 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.

Post-Market Adverse Drug Reactions

Additional adverse events 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 **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.

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, diarrhoea

Immune system disorders	Common:	Hypersensitivity reactions
	Rare :	Anaphylactoid reactions
Skin and subcutaneous tissue disorders	Common:	Urticaria/angioedema, pruritus, rash
Musculoskeletal and connective tissue disorders	Uncommon:	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.

Antibody Formation

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. Genzyme 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.

DRUG INTERACTIONS

Drug-Drug Interactions: Interactions with other drugs have not been established.

Drug-Food Interactions: Interactions with food have not been established.

Drug-Herb Interactions: Interactions with herbal products have not been established.

Drug-Laboratory Interactions: Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

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® (imiglucerase for injection) on neurological symptoms of chronic neuronopathic Gaucher patients has not been established and no special dosage regimen can be recommended for these manifestations.
- 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.

Recommended Dose and Dosage Adjustment

CEREZYME® is administered by intravenous infusion over 1-2 hours. The maximum recommended infusion rate is 1 unit/kg/minute.

Dosage should be individualized to each patient. Treatment 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. Initial dosage may vary, however, 60 units/kg every 2 weeks is the dosage for which most data are available.

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

The vials are single use only. All unused portions must be discarded. To avoid discarding partially used vials, the dose administered at each infusion may be slightly adjusted. Relatively low toxicity, combined with the extended time course of the response, permits small dosage adjustments, but the total dose administered each month should remain substantially unchanged.

Administration

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.

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. The diluted solution may be filtered through an in-line low protein binding 0.2 µm filter during administration.

4. 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.

Since CEREZYME® does not contain any antibacterial preservatives, it must be reconstituted and diluted immediately prior to administration.

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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

CEREZYME® (imiglucerase for injection) 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 anaemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly, skeletal complications, including osteonecrosis and osteopenia with secondary pathological fractures.

In clinical trials, CEREZYME® improved the symptoms associated with Gaucher disease. CEREZYME® improved anaemia and thrombocytopenia, reduced spleen and liver size, decreased cachexia and improved Gaucher disease related skeletal involvement and quality of life. Patients reported beneficial results in their general health, energy levels, mobility and reduction of bone pain while on therapy.

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, CEREZYME® reduces spleen and liver size, improves thrombocytopenia and anaemia, 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 enzyme replacement therapy more quickly than adults. The skeletal response in both pediatric and adult patients to enzyme replacement therapy is generally slower than the hematologic and organ response. The initial primary uptake sites of CEREZYME® 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 CEREZYME® every 2 weeks for the first 24 months. If therapeutic goals

had been met, the patient could maintain the current CEREZYME® 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 CEREZYME® 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.

Pharmacokinetics

During one hour intravenous infusions of four doses (7.5, 15, 30, 60 U/Kg) of CEREZYME® 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 appear to be independent of dose or duration of infusion.

Within the dose range of 7.5 to 60 U/kg, elimination half-life, plasma clearance, and volume of distribution values appear to be independent of the infused dose, suggesting that macrophage uptake was not saturated.

The pharmacokinetics of CEREZYME® do not appear to be different from placental-derived β-glucocerebrosidase (CEREDASE®, alglucerase injection).

STORAGE AND STABILITY

Lyophilized vial

CEREZYME® (imiglucerase for injection)	**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:

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. Although not recommended, CEREZYME®, after reconstitution with Sterile Water for Injection has been shown to be stable for up to 12 hours when stored at room temperature (25EC) and at 2-8EC. Additionally, CEREZYME® when diluted with saline, has been shown to be stable for up to 24 hours when stored at room temperature and at 2-8EC.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CEREZYME® (imiglucerase for injection), lyophilized powder for intravenous infusion, is supplied as a sterile, non-pyrogenic, white to off-white lyophilized product.

The quantitative composition of the lyophilized drug is provided as follows:

- 400 Unit vial is composed of imiglucerase (424 units, which allows for a withdrawal dose of 400 units), mannitol (340 mg), sodium citrates (140 mg), polysorbate 80, NF (1.06 mg)

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.

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

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.

PART II: SCIENTIFIC INFORMATION

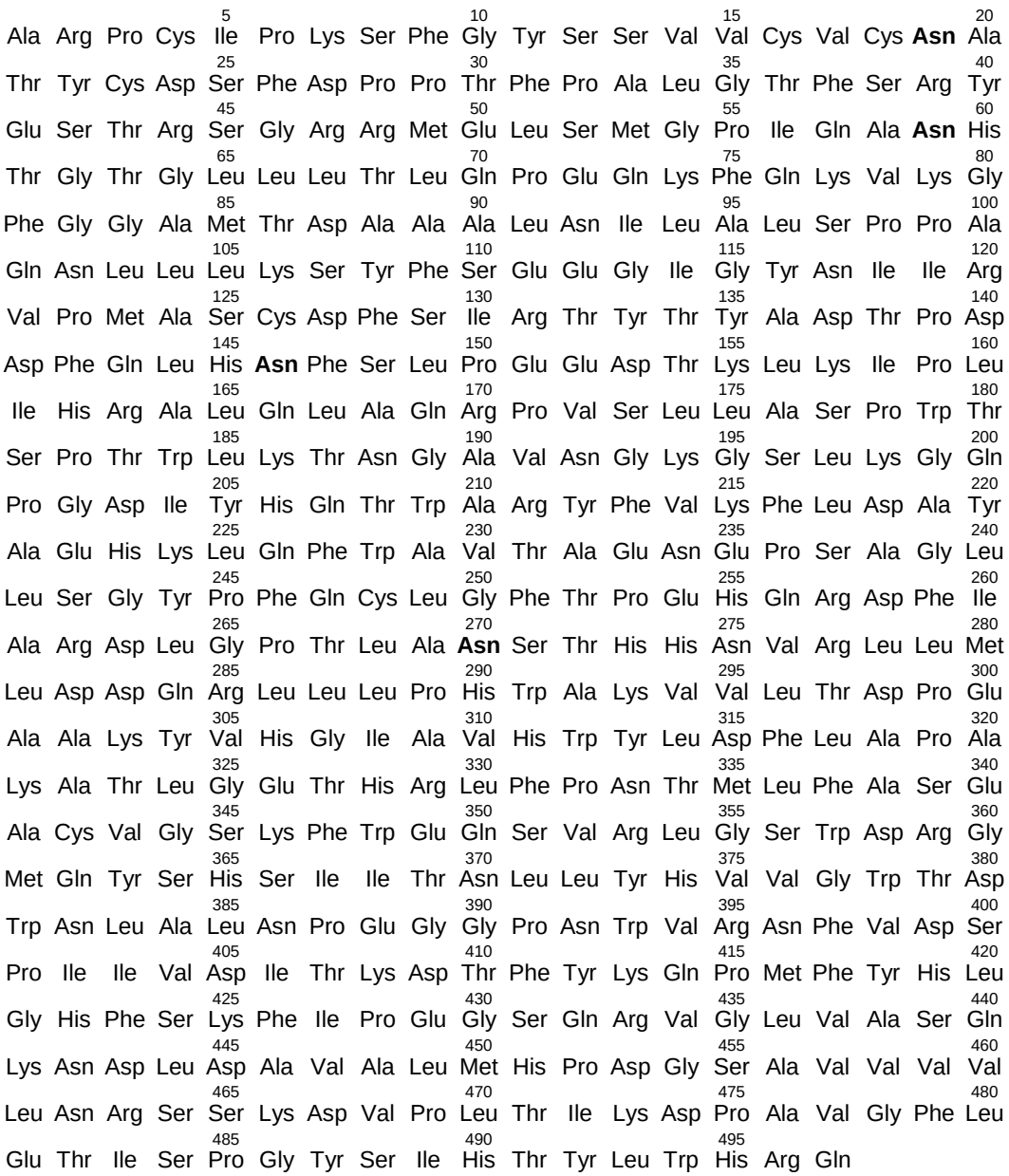
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Imiglucerase
Chemical Name: Recombinant human carbohydrate-modified ß-glucocerebrosidase

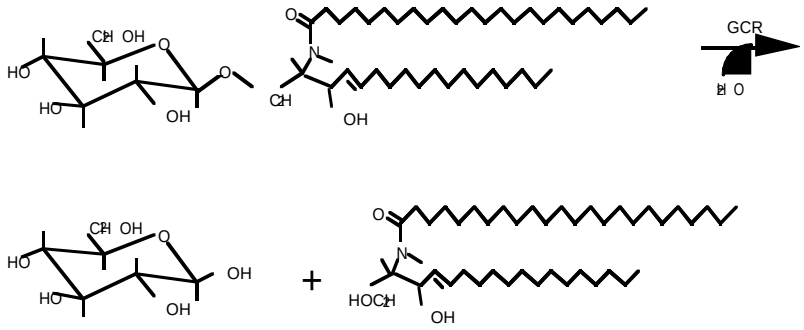
Molecular formula and molecular mass: $C_{2532}H_{3845}N_{671}O_{711}S_{16}$
Molecular Weight: Mr = 60,430 (as determined by Mass Spectroscopy)

Structural formula:



Physicochemical properties:

Provided below is the structural formula of glucocerebroside and the site of action of glucocerebrosidase (GCR). CEREZYME® (imiglucerase for injection), 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. CEREZYME® differs from CEREDASE® (placental glucocerebrosidase) by one amino acid at position 495 where histidine is substituted for arginine. Additionally, 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.



Solubility: Soluble in water

Product Characteristics

CEREZYME®, lyophilized powder for intravenous infusion, is supplied as a sterile, non-pyrogenic, white to off-white lyophilized product. The lyophilized cake is reconstituted with Sterile Water for Injection, USP and diluted with 0.9% Sodium Chloride Injection, USP for intravenous administration.

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.

CLINICAL TRIALS

Study demographics and trial design

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 (imiglucerase for injection) 60 U/kg or Ceredase 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 haematological 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 haematologic 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.

Study results

Clinical Effects on Haematology and Organ Weights (% change compared to baseline):

Report #	Parameter	Haemoglobin	Platelet	Liver	Spleen
RC91-110	**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	**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	**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.

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 **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 haemoglobin, 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. (see **WARNINGS AND PRECAUTIONS: Special Populations**).

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 Haemoglobin, 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 III 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 haematological (haemoglobin, 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 haemoglobin, the majority of patients in both patient populations start treatment with moderate to severe anaemia, 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 anaemia resulting in reclassification of anaemia severity from "severe" to "moderate" / "normal", compared to 69% of the severely anaemic 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.

DETAILED PHARMACOLOGY

Pharmacokinetics

Summary of Pharmacokinetic Data							
Report #	**Description**	**Type of analysis**	**C_{max}**	**AUC**	**t½ [min]**	**Vd [L/kg]**	**Cl [mL/(min.kg)]**
HWI 6354-107	Monkey, IV infusion 60 U/kg	ELISA*	1955 ng/mL	118 µ.min/mL	7.99	0.135	11.8
		Enzymatic Activity**	65.8 mU/mL	3954 mU.min/mL	6	0.157	15.8
RC92-0502	Gaucher patients		Not evaluated	Not evaluated	5.9	0.159	18.9

* Imiglucerase specific

** 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.

Animal Pharmacodynamics

Various studies have been undertaken to assess the organ distribution of imiglucerase. In mice, approximately 50% of the administered imiglucerase activity could be traced to various body organs 20 minutes (about 7 half-lives) post injection. The liver accounts for almost 95% of that activity. Fourteen percent of the activity is found in the Kupffer cells while 51% is found in the hepatocytes. In the 13 week rat study, no imiglucerase was detected in the hepatocytes suggesting no accumulation of imiglucerase in the liver.

TOXICOLOGY

Report #	Study Characteristics	Parameters Evaluated	Results
HWI 6354-102	Rat Single dose 0, 60, 300, 600 U/kg IV 5M, 5F per grp	clinical, food consumption, body weight, haematology, clinical chemistry, organ weight, necropsy, histology	Stat. Sig. 8 platelet & Hgb. 8 neutrophil count in 600 u/kg males.
BDL 12807	Rat 13 weeks 0, 3, 30, 300 U/kg IV 5M, 5F per grp	clinical, food consumption, body weight, haematology, 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 grp	clinical, body weight, haematology, clinical chemistry, urinalysis, organ weight, necropsy, histology	Stat. Sig. 8 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

Mutagenesis

CEREZYME® (imiglucerase for injection) was tested using the Ames mutagenicity test and all concentrations, both with and without activation were negative

REFERENCES

1. Altarescu G, Hill S, Wiggs E, Jeffries N, Kreps C, Parker C, et al. The efficacy of enzyme replacement therapy in patients with chronic neuronopathic Gaucher's disease. J Pediatr 2001;138(4):539-47.

2. Barton NW, Brady RO, Dambrosia JM, DiBisceglie AM, Doppelt SH, Hill SC et al. Replacement therapy for inherited enzyme deficiency - macrophage-targeted glucocerebrosidase for Gaucher's disease. New Engl J Med 1991;324(21):1464-1470.

3. Barton NW, Furbish FS, Murray GJ, Garfield M, Brady RO. Therapeutic response to intravenous infusions of glucocerebrosidase in a patient with Gaucher disease. Proc. Natl. Acad. Science USA 1990;87(5):1913-1916.

4. Barton NW, Rosenthal DI, Mankin HJ et al: Skeletal responses to enzyme replacement therapy in patients with Gaucher disease: what are the goals and expectations of treatment? Gaucher Clinical Perspectives 1996;4(1):2-7.

5. Fallet S, Grace ME, Sibille A, Mendelson DS, Shapiro RS, Hermann G et al. Enzyme augmentation in moderate to life-threatening Gaucher disease. Pediatr Res 1992;31(5):496-502.

6. Grabowski GA, Barton NW, Pastores G, Dambrosia JM, Banerjee TK, McKee M, et al. Enzyme therapy in Type 1 Gaucher Disease: Comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. Ann Intern Med 1995;122:33-9.

7. Ida H, Rennert OM, Kobayashi M, Eto Y. Effects of enzyme replacement therapy in thirteen Japanese paediatric patients with Gaucher disease. Eur J Pediatr 2001;160(1):21-5.

8. Pastores GM, Sibille AR, Grabowski GA. Enzyme therapy in Gaucher Disease Type 1: Dosage efficacy and adverse effects in 33 patients treated for 6 to 24 months. Blood 1003;82(2):408-16.

9. Pastores GM, Weinreb NJ, et al. Therapeutic Goals in the Treatment of Gaucher Disease. Seminars in Hematology 2004; 41(4)S5:4-14.

10. Rice EO, Mifflin TE, Sakallah S, Lee RE, Sansieri CA, Barranger JA. Gaucher disease: studies of phenotype, molecular diagnosis and treatment. Clin Genet 1996;49(3):111-8.

11. Richards SM, Olson TA, McPherson JM. Antibody response in patients with Gaucher disease after repeated infusion with macrophage-targeted glucocerebrosidase. Blood 1993;82(5):1402-9.

12. Rosenthal DI, Doppelt SH, Mankin HJ, Dambrosia JM, Xavier RJ, McKusick KA et al. Enzyme replacement therapy for Gaucher disease: Skeletal responses to macrophage-targeted Glucocerebrosidase. Pediatrics 1995;96(4):629-37.

13. Schiffmann R, Heyes MP, Aerts JM Dambrosia JM, Patterson MC, DeGraba T, et al Prospective study of neurological responses to treatment with macrophage-targeted glucocerebrosidase in patients with Type 3 Gaucher's disease. Ann Neurol 1997; 42:613-21.

14. Tylki-Szymanska A, Czartoryska B. Enzyme replacement therapy in type III Gaucher disease. J Inherit Metab Dis 1999;22(2):203-4.

15. Vellodi A, Bembi B, de Villemeur T, Collin-Histed T, Erikson A, Mengel E, et al. Management of neuronopathic Gaucher disease: A European consensus. Journal of Inherited Metabolic Disease 2001;24(3):319-27.

16. Weinreb NJ, et al. Gaucher Disease Type 1: Revised Recommendations on Evaluations and Monitoring for Adult Patients. Seminars in Hematology 2004; 41(4)S5:15-22.

17. Wenstrup RJ, Kacena KA, Kaplan P, Pastores GM, Prakash-Cheng A, Zimran A, et al. Effect of enzyme replacement therapy with imiglucerase on BMD in type 1 Gaucher disease. J Bone Miner Res 2007;22:119-26.

18. Zimran A, Elstein D, Levy-Lahad E, Zevin S, Hadas-Halpern I, Bar-Ziv Y, et al. Replacement therapy with imiglucerase for type 1 Gaucher's Disease. Lancet 1995;345:1479-80.

PART III: CONSUMER INFORMATION

Cerezyme®
Imiglucerase for injection

This leaflet is part III of a three-part "Product Monograph" published when CEREZYME® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CEREZYME®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
CEREZYME® is used to treat patients with a confirmed diagnosis of non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease resulting in one or more of the following conditions:

- anaemia 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

What it does:
Gaucher disease is a genetic disorder resulting in deficient ß-glucocerebrosidase activity. Therefore, glucocerebroside accumulates in the lysosomes of tissue macrophages in the liver, spleen, bone marrow and occasionally in lung and kidney. 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 deficient enzyme.

When it should not be used:
Do not use CEREZYME® if you are hypersensitive to imiglucerase or to any ingredient in the formulation or component of the container.

What the medicinal ingredient is:
Imiglucerase

What the important nonmedicinal ingredients are:
Mannitol, Polysorbate 80, Sodium citrates
For a full listing of nonmedicinal ingredients see Part 1 of the product monograph.

What dosage forms it comes in:
CEREZYME® is supplied as a sterile lyophilized powder for intravenous infusion.
CEREZYME® is supplied in a 20 mL vial containing either (red label) of imiglucerase.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Do not use CEREZYME® if you are severely hypersensitive to imiglucerase or to any ingredient in the formulation or if you have experienced severe hypersensitivity to imiglucerase.

Anaphylactoid reaction has been reported in less than 1% of the patient population. Further treatment with CEREZYME® should be conducted with caution.

In rare cases, 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. But, if you suffer with any shortness of breath you should tell your doctor.

BEFORE you use CEREZYME® talk to your doctor or pharmacist if:

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

INTERACTIONS WITH THIS MEDICATION

No formal interaction studies have been conducted. Please inform your doctor if you are using any other medicinal products, due to the potential risk of interference with the uptake of imiglucerase.

PROPER USE OF THIS MEDICATION

Usual dose:
Dosage should be individualized to each patient.

Treatment 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.

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).

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects related to CEREZYME® administration have been reported in less than 15% of patients. Each of the following events occurred in less than 2% of the total patient population. Reported side effects include nausea, vomiting, abdominal pain, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, and rapid heart rate. Because CEREZYME® therapy is administered by intravenous infusion, reactions at the site of injection may occur: discomfort, itching, burning, swelling or uninfected abscess. Symptoms suggestive of allergic reaction include anaphylactoid reaction (a serious allergic reaction), itching, flushing, hives, an accumulation of fluid under the skin, chest discomfort, shortness of breath, coughing, cyanosis (a bluish discoloration of the skin due to diminished oxygen), and low blood pressure. Approximately 15% of patients have developed immune reactions (antibodies); periodic monitoring by your physician is suggested.

If you exhibit such a reaction following the administration of CEREZYME®, you should immediately contact your doctor.

Pre-treatment with antihistamines and/or corticosteroids and reduced rate of infusion has allowed continued use of CEREZYME® in most patients.

This is not a complete list of side effects. For any unexpected effects while taking CEREZYME®, contact your doctor or pharmacist.

HOW TO STORE IT

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 4,936 patients (as of March 7, 2008), 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 Genzyme Canada.

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

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  Fax toll-free to 1-866-678-6789, or
  Mail to:
  Canada Vigilance Program
  Health Canada
  Postal Locator 0701D
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.genzyme.ca or by contacting the sponsor, Genzyme Canada, at: 1-877-220-8918

This leaflet was prepared by Genzyme Canada a division of Sanofi-Aventis Canada Inc.
Date of Approval: November 30, 2016