PRODUCT INFORMATION

CEREZYME®

NAME OF THE MEDICINE

Non-proprietary Name

imiglucerase - rch powder for solution for infusion.

DESCRIPTION

CEREZYME is provided as a white to off - white sterile lyophilised powder in a clear glass vial and contains a nominal value of 200 Units* or 400 Units of imiglucerase and the excipients mannitol, sodium citrate dihydrate, citric acid monohydrate and polysorbate 80. The reconstituted solution must be diluted further.

*An Enzyme Unit (U) is defined as the amount of enzyme that catalyses the hydrolysis of one micromole of the synthetic substrate para-nitrophenyl β-D-glucopyranoside (pnp-Glc) per minute at 37°C.

It is recommended that the diluted solution be filtered through an in - line low protein - binding 0.2µ filter during administration.

PHARMACOLOGY

Pharmacodynamics

Imiglucerase is a recombinant, macrophage - targeted, variant of human β - glucocerebrosidase, purified from Chinese Hamster Ovary cells. It catalyses the hydrolysis of the glycolipid, glucocerebroside, to glucose and ceramide following the normal degradation pathway for membrane lipids.

Glucocerebroside is primarily derived from haematopoietic cell turnover. Gaucher disease is characterised by a functional deficiency in β - glucocerebrosidase enzymatic activity and the resultant accumulation of lipid glucocerebroside in tissue macrophages, which become engorged and are termed Gaucher cells.

Gaucher cells are typically found in liver, spleen and bone marrow and occasionally, as well, in lung, kidney and intestine. Secondary haematological sequelae include severe anaemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly. The skeletal complications are a common, and frequently the most debilitating and disabling, feature of Gaucher

disease. Possible skeletal complications are osteonecrosis, osteopenia with secondary pathological fractures, remodelling failure, osteosclerosis and bone crises.

Pharmacokinetics

During 1 hour intravenous infusions of 4 doses (7.5, 15, 30 and 60 U/kg) of CEREZYME, steady state enzymatic activity was achieved within 30 minutes. Following infusion, plasma enzymatic activity declined rapidly with a half - life ranging from 3.6 to 10.4 minutes. Plasma clearance ranged from 9.8 to 20.3 mL/min/kg (mean ± S.D., 14.5 ± 4.0 mL/min/kg). The volume of distribution corrected for weight ranged from 0.09 to 0.15 L/kg (mean ± S.D., 0.12 ± 0.02 L/kg). These variables do not appear to be influenced by dose or duration of infusion, however, only 1 or 2 patients were studied at each dose level and infusion rate.

CLINICAL TRIALS

After the completion of the pivotal clinical trial, at 6 months, patients continued to be followed for an extended study period of 26 to 29 months. In addition, a separate dosing schedule comparison study 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 design features and results of these studies.

CLINICAL TRIAL INFORMATION SUMMARY

Protocol #	**RC91-0110 – Pivotal Trial**	**RC92-501 – Extension to Pivotal Trial**	**RC92-301**
Investigators	1. Barton, NW; 2. Grabowski, GA	1. Barton, NW; 2. Pastores, G	Zimran, A
Publications	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		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 Disease. *Lancet* 1995; 345: 1479-80.
Location of Study	Mt. Sinai School of Medicine in New York, NY. Nat'l Inst. of Neurolog. Disorders and Strokes in Bethesda, MD		Shaare-Zedek Medical Centre, Jerusalem, Israel
Dates	Jan. 1992 - Sept. 1992	July 1992 - May 1994	Not reported
Study Design	CONT, DB, RAND, parallel	CONT, DB, RAND, parallel	CONT, RAND, matched pair
Treatment	CDASE or CZYME 60 U/kg IV q other wk	60 U/kg IV q other wk	A: 15 U/kg IV q other wk B: 2.5 U/kg IV 3x/wk
# Entered	30 (15 CDASE; 15 CZYME)	30 (15 CDASE; 15 CZYME)	10 (5 in each group)
# Completed	30	30* (29 CZYME)	10
Age: Mean	32.7 years old	32.7 years old	32.2 years old

Range	12-69	12-69	18-46
Avg. Weight	62.4 kg	62.4 kg	58.4 kg
M/F	17/13	17/13	2/8
Duration	6 months	26-29 months	1.5 to 2 years
Efficacy Results	Stat. Sign Improvement from baseline for all 1" endpoints; Sign ↑ in haematologic parameters; sign ↓ in hepatomegaly/splenomegaly; ↓ cachexia; improvements in skeleton and disease markers		↓ hepatomegaly; improvement in haematology parameters and disease markers; possible minimal improvement in skeletal manifestations
Safety Results	185 non-serious AEs; 0 serious AEs	385 non-serious AEs; 0 serious AEs	35 non-serious AEs; 0 serious AEs. Most frequent events were pain and nausea
	Most frequent events were pain, ecchymosis, epistaxis, pharyngitis, diarrhoea, rash, fever, headache, rhinitis, dizziness, menorrhagia, pruritus		

CONT = controlled; RAND = randomised; DB = double blinded; CDASE = Ceredase; CZYME = CEREZYME®;
AE = adverse event. *All patients were converted to CEREZYME® by the end of the trial.

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%
RC92-501	**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%
RC92-301	**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%

INDICATIONS

CEREZYME is indicated for long - term enzyme replacement therapy for patients with a confirmed diagnosis of Type 1 Gaucher disease that results in one or more of the following conditions:

a) anaemia;

b) thrombocytopenia;

c) bone disease;

d) hepatomegaly or splenomegaly.

CONTRAINDICATIONS

There are no known contraindications to the use of CEREZYME. Treatment with Cerezyme should be carefully re-evaluated if there is significant clinical evidence of hypersensitivity to the product.

PRECAUTIONS

Hypersensitivity reactions to CEREZYME may occur. Treatment should be carefully evaluated if there is significant clinical evidence of hypersensitivity to the product (See CONTRAINDICATIONS).

Current data suggest that, during the first year of therapy, IgG antibodies to CEREZYME are formed in approximately 15% of the treated patients. It appears that patients who will develop IgG antibody are most likely to do so within 6 months of treatment and will rarely develop antibodies to CEREZYME after 12 months of therapy. It is suggested that patients be monitored periodically for IgG antibody formation to imiglucerase during the first year of treatment.

Patients with antibody to CEREZYME have a higher risk of hypersensitivity reaction (see ADVERSE EFFECTS). If a patient experiences a reaction suggestive of hypersensitivity, subsequent testing for imiglucerase antibodies is advised. Anaphlyactoid reactions have been reported in less than 1% of the patient population. Further treatment with imiglucerase should be conducted with caution. Most patients have successfully continued therapy after a reduction in the rate of infusion and pretreatment with antihistamines and/or corticosteroids.

Patients who have developed antibodies or symptoms of hypersensitivity to CEREDASE® (alglucerase) should be treated with caution when administering CEREZYME.

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.

Patients who have undergone a splenectomy have an increased risk of pulmonary hypertension. CEREZYME therapy reduces the requirement for splenectomy in most cases and early treatment with CEREZYME has been associated with a reduced risk of pulmonary hypertension. Routine evaluation to detect the presence of pulmonary hypertension after diagnosis of Gaucher disease and over time is recommended. Patients diagnosed with pulmonary hypertension, in particular, should receive adequate doses of CEREZYME to ensure control of underlying Gaucher disease as well as be evaluated for the need of additional pulmonary hypertension specific treatments.

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

There is insufficient evidence that the use of imiglucerase improves neurologic symptoms in patients with Type 2 or Type 3 Gaucher disease.

There are no data to support the use of imiglucerase in the acute management of bone crises associated with Gaucher disease.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Studies have not been conducted to assess the potential effects of CEREZYME on carcinogenesis or impairment of fertility in animals or human. No evidence of mutagenic activity was seen in the bacterial gene mutation tests, however, assays for chromosomal aberrations have not been carried out.

Use in Pregnancy – Pregnancy (Category B2)

Animal reproduction studies have not been conducted with CEREZYME.

It is not known whether CEREZYME can cause foetal harm when administered to a pregnant woman, or can affect reproductive capacity. CEREZYME should be given to a pregnant woman only if clearly needed and after a careful risk / benefit analysis has been conducted for both the mother and foetus.

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

Animal studies are insufficient with respect to assessing the effects of CEREZYME on human pregnancy, embryonal / foetal development, parturition and postnatal development. It is not known whether CEREZYME passes via the placenta to the developing foetus. No clinical trial data on exposed pregnancies are available for CEREZYME. From extensive post marketing experience, however, safety information on the use of CEREZYME in over 150 pregnancies is available. These data suggest that CEREZYME may be used to better control progression of underlying Gaucher disease in pregnancy.

Among over 150 CEREZYME exposed pregnancies, the nature and prevalence of major congenital malformation and foetal death were not different from the occurrences expected in the general population. The available post marketing data show that CEREZYME treatment in pregnant patients has, in the majority of cases, led to uncomplicated pregnancies and birth of healthy infants.

In pregnant Gaucher patients and those intending to become pregnant, a risk - benefit treatment assessment is required for each pregnancy. Treatment naïve women should be advised to consider commencing therapy prior to conception in order to attain optimal health. In women receiving CEREZYME treatment, continuation throughout pregnancy should be considered. Close monitoring of the pregnancy and clinical manifestations of Gaucher disease is necessary for the individualisation of dose according to the patient's needs and therapeutic response.

Caution should be exercised when prescribing to pregnant women.

Use in Lactation

It is not known whether CEREZYME is excreted in human milk. However, the enzyme is likely to be digested in the child's gastrointestinal tract. Caution should therefore be exercised when CEREZYME is administered to a nursing woman. There are no animal studies on the effects of imiglucerase on lactation or the potential for excretion of imiglucerase in milk.

Effects on Ability to Drive and Use Machines

CEREZYME is presumed to be safe and unlikely to produce an effect on ability to drive or use machines.

INTERACTIONS WITH OTHER MEDICINES

Interactions between CEREZYME and other medicinal products have not been studied. Other forms of interactions such as with food are unlikely.

ADVERSE EFFECTS

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

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 pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnoea, coughing, cyanosis and hypotension (see PRECAUTIONS). Anaphylactoid reaction have also been reported (see PRECAUTIONS). Each of these events were found to occur in < 1.5% of the total patient population. Pre - treatment with antihistamines and / or corticosteroids and reduced rate of infusion has allowed continued use of CEREZYME in most patients.

Additional adverse reactions that have been reported in approximately 6.2% of patients treated with CEREZYME include nausea, abdominal pain, vomiting, diarrhoea, rash, fatigue, headache, fever, dizziness, chills, backache and tachycardia. Each of these events were found to occur in < 1.5% of the total patient population.

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

DOSAGE AND ADMINISTRATION

After reconstitution with water for injection and dilution with 0.9% Sodium Chloride intravenous solution the preparation is administered by intravenous infusion over 1 to 2 hours.

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

Preparation and Administration Instructions: Use Aseptic Techniques

The lyophilised powder has to be reconstituted with water for injection, diluted with 0.9% Sodium Chloride intravenous solution and then administered by intravenous infusion.

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

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

2. Reconstitute each vial with water for injection. The final concentrations and administration volumes are provided in the following table:

	200 Unit Vial	400 Unit Vial
Sterile water for reconstitution	5.1 mL	10.2 mL
Final volume of reconstituted product	5.3 mL	10.6 mL
Concentration after reconstitution	40U/mL	40U/mL
Withdrawal volume	5.0 mL	10.0 mL
Units of enzyme within final volume	200 Units	400 Units

Avoid forceful impact of water for injection on the powder and, by mixing gently, avoid foaming of the solution. The pH of the reconstituted solution is approximately 6.1.

3. Before further dilution, visually inspect the reconstituted solution in each vial for foreign particles and discolouration. Do not use vials exhibiting foreign particles or discolouration. Do not use CEREZYME after the expiration date on the vial.

CEREZYME contains no preservatives or antimicrobial agent. Use once and discard any residue. Any unused reconstituted solution must be discarded appropriately.

4. The reconstituted solution contains 40 units imiglucerase per mL. The reconstituted volume allows accurate withdrawal of a nominal volume of 5.0 mL for the 200 Unit vial (10.0 mL for the 400 Unit vial).

5. Withdraw the reconstituted solution from each of the reconstituted vials and dilute with 0.9% Sodium Chloride intravenous solution to a total volume of 100 to 200 mL. Mix the infusion solution gently. Being a protein solution, slight flocculation (described as thin translucent fibers) occurs occasionally after dilution. The diluted solution may be filtered through an in-line low protein-binding 0.2 μm filter during administration.

It is recommended that the diluted solution be administered within 3 hours. The product diluted in 0.9% Sodium Chloride intravenous solution will retain chemical stability if stored for up to 24 hours

between 2° and 8°C, protected from light, but microbial safety will depend on the reconstitution and dilution having been performed aseptically.

OVERDOSAGE

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

CEREZYME is supplied in clear glass 20 mL vials. The closure consists of a siliconised butyl rubber stopper with a tamper-proof flip-top cap.

Each vial is for single use only.

To provide sufficient volume to allow accurate dispensing, each vial is formulated to contain an overfill of 0.3 mL.

Pack size: 200 Unit vial or 400 Unit vial.

The lyophilised product is stored between 2° - 8°C. If necessary, the product diluted in 0.9% Sodium Chloride intravenous solution can be stored for up to 24 hours between 2° - 8°C, protected from light, but microbiological safety will depend on the reconstitution and dilution having been performed aseptically.

CEREZYME, after reconstitution, has been shown to be stable for up to 12 hours when stored at room temperature (25°C) and at 2° - 8°C. CEREZYME, when diluted, has been shown to be stable for up to 24 hours when stored at 2° - 8°C. After reconstitution, promptly dilute vials and do not store for subsequent use.

NAME AND ADDRESS OF THE SPONSOR

AUSTRALIA

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POISON SCHEDULE OF THE MEDICINE

Schedule 4, Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE ARTG

25 May 1999

DATE OF MOST RECENT AMENDMENT

09 September 2016

200 Unit vial, AUST R 68331

400 Unit vial, AUST R 74277

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