FULL PRESCRIBING INFORMATION

Cerezyme 400 units

Imiglucerase 400 units/vial

Powder for concentrate for solution for infusion

1 INDICATIONS AND USAGE

Cerezyme 400 units is indicated for the 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:

- anemia
- thrombocytopenia
- bone disease
- hepatomegaly or splenomegaly

2 DOSAGE AND ADMINISTRATION

Cerezyme® is administered by intravenous infusion over 1-2 hours. Dosage should be individualized to each patient. Initial dosages range from 2.5 U/kg of body weight 3 times a week to 60 U/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for which the most data are available. Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration. Dosage adjustments should be made on an individual basis, and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations.
Cerezyme should be stored at 2-8°C. After reconstitution, **Cerezyme** should be inspected visually before use. Because this is a protein solution, slight flocculation (described as thin translucent fibers) occurs occasionally after dilution. The diluted solution may be filtered through an in-line low protein-binding 0.2 μm filter during administration. Any vials exhibiting opaque particles or discoloration should not be used. DO NOT USE **Cerezyme** after the expiration date on the vial.
On the day of use, after the correct amount of **Cerezyme** to be administered to the patient has been determined, the appropriate number of vials are each reconstituted with Sterile Water for Injection, USP. The final concentrations and administration volumes are provided in the following table:

	400 Unit Vial
Sterile water for reconstitution	10.2 mL
Final volume of reconstituted product	10.6 mL
Concentration after reconstitution	40 U/mL

Withdrawal volume	10.0 mL
Units of enzyme within final volume	400 units

A nominal 10.0 mL for the 400 unit vial is withdrawn from each vial. The appropriate amount of **Cerezyme** for each patient is diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 100-200 mL. **Cerezyme** is administered by intravenous infusion over 1-2 hours. Aseptic techniques should be used when diluting the dose. Since **Cerezyme** does not contain any preservative, after reconstitution, vials should be promptly diluted and not stored for subsequent use. **Cerezyme**, after reconstitution, has been shown to be stable for up to 12 hours when stored at room temperature (25°C) and at 2-8°C. **Cerezyme**, when diluted, has been shown to be stable for up to 24 hours when stored at 2-8°C.
Relatively low toxicity, combined with the extended time course of response, allows small dosage adjustments to be made occasionally to avoid discarding partially used bottles. Thus, the dosage administered in individual infusions may be slightly increased or decreased to utilize fully each vial as long as the monthly administered dosage remains substantially unaltered.

3 DOSAGE FORMS AND STRENGTHS

For injection: 400 units of imiglucerase as a white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity and Infusion-Associated Reactions

Hypersensitivity reactions, some of which are serious and include anaphylaxis, have been reported. In addition, hypersensitivity and other infusion-associated reactions have been reported during or shortly after infusion and include pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, cough, cyanosis, tachycardia, and hypotension *[see Adverse Reactions (6.1)]*. Patients with antibody to imiglucerase have a higher risk of hypersensitivity reactions. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody. Consider periodic monitoring of patients during the first year of treatment for IgG antibody formation *[see Adverse Reactions (6.2)]*.

If a severe hypersensitivity reaction occurs, discontinue Cerezyme treatment and initiate appropriate medical treatment.

6 ADVERSE REACTIONS

6.1 Clinical Trials and Postmarketing Experience

The following adverse reactions associated with the use of imiglucerase were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

System Organ Class	Adverse Reactions
Nervous system disorders	dizziness, headache
Cardiac disorders	tachycardia
Vascular disorders	cyanosis,* flushing,* hypotension*
Respiratory, thoracic and mediastinal disorders	cough,* dyspnea,* pneumonia, pulmonary hypertension
Gastrointestinal disorders	abdominal pain, diarrhea, nausea, vomiting
Immune system disorders	anaphylaxis,* hypersensitivity
Skin and subcutaneous tissue disorders	angioedema,* pruritus,* rash, urticaria*
Musculoskeletal and connective tissue disorders	back pain
General disorders and administration site conditions	chest discomfort,* chills, fatigue, infusion-site burning, infusion-site discomfort, infusion-site swelling, pyrexia

* Signs and symptoms suggestive of hypersensitivity and other infusion-associated reactions *[see Warnings and Precautions (5.1)]*.

Adverse reactions reported in pediatric patients 2 years of age and older were similar to adults.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other imiglucerase products may be misleading.

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 did so largely within 6 months of treatment and rarely developed antibodies to Cerezyme after 12 months of therapy. Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity. Patients with antibody to Cerezyme have higher risk of hypersensitivity reaction *[see Warnings and Precautions (5.1)]*. Patients who developed IgG antibody to Cerezyme had increased elimination half-life compared to patients without antibody *[see Clinical Pharmacology (12.3)]*.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Cerezyme during pregnancy. Pregnant women exposed to Cerezyme and health care providers

are encouraged to contact the Gaucher patient registry at 1-800-745-4447, extension 15500 or visit www.registrynxt.com.

Risk Summary

Available data on more than 500 pregnancies from the international Gaucher Disease registry, postmarketing reports, published observational studies and case reports with Cerezyme or non–US-licensed imiglucerase use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks associated with symptomatic Type I Gaucher disease in pregnancy *(see Clinical Considerations)*. No animal reproduction studies have been conducted with imiglucerase.

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnancy may exacerbate existing Type 1 Gaucher disease symptoms or result in new disease manifestations. Untreated symptomatic Type 1 Gaucher may lead to complications during pregnancy, including hepatosplenomegaly, which can interfere with the normal growth of a pregnancy and thrombocytopenia, which can lead to excessive bleeding.

8.2 Lactation

Risk Summary

Available published literature suggests a small amount of imiglucerase is present in breast milk immediately following an infusion of imiglucerase. Published case reports and postmarketing reports of breastfed infants have not reported adverse effects due to Cerezyme exposure. There are no data available on the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Cerezyme and any potential adverse effects on the breastfed infant from imiglucerase or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of Cerezyme for treatment of Type 1 Gaucher disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly have been established in pediatric patients 2 years of age and older. Use of Cerezyme for this indication is supported by evidence from adequate and well-controlled studies of Cerezyme and alglucerase in adults and pediatric patients 12 years of age and older, with additional data obtained from the medical literature and from postmarketing experience in pediatric patients as young as 2 years of age *[see Adverse Reactions (6.1), Clinical Studies (14)]*.

The safety and effectiveness of Cerezyme have not been established in pediatric patients younger than 2 years of age.

11 DESCRIPTION

Imiglucerase is a hydrolytic lysosomal glucocerebrosidase-specific enzyme. It is an analogue of

the human enzyme b-glucocerebrosidase (b-D-glucosyl-N-acylsphingosine glucohydrolase, E.C. 3.2.1.45), produced by recombinant DNA technology using mammalian cell culture (Chinese hamster ovary). Purified imiglucerase is a monomeric glycoprotein of 497 amino acids, containing 4 N-linked glycosylation sites (Mr=60,430). Imiglucerase differs from placental glucocerebrosidase by one amino acid at position 495, where histidine is substituted for arginine. The oligosaccharide chains at the glycosylation sites have been modified to terminate in mannose sugars. The modified carbohydrate structures on imiglucerase are somewhat different from those on placental glucocerebrosidase.

Cerezyme (imiglucerase) for injection is intended for intravenous use. It is supplied as a sterile, nonpyrogenic, white to off-white lyophilized powder for reconstitution with Sterile Water for Injection, USP. Each single-dose vial contains 424 units imiglucerase, mannitol, sodium citrate, citric acid monohydrate and polysorbate 80,.

An enzyme unit (U) is defined as the amount of enzyme that catalyzes the hydrolysis of 1 micromole of the synthetic substrate para-nitrophenyl-b-D-glucopyranoside (pNP-Glc) per minute at 37°C. Reconstituted solutions have a pH of approximately 6.1.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gaucher disease is characterized by a deficiency of β-glucocerebrosidase activity, which results in accumulation of glucocerebroside in various tissues including liver, spleen, and bone marrow. The mannose sugars on imiglucerase mediate binding to and internalization by cells including macrophages. Cerezyme catalyzes the hydrolysis of glucocerebroside to glucose and ceramide.

12.2 Pharmacodynamics

No formal pharmacodynamic studies have been conducted with Cerezyme.

12.3 Pharmacokinetics

During one-hour intravenous infusions of four doses (7.5, 15, 30, 60 units/kg) of Cerezyme, steady-state enzymatic activity was achieved by 30 minutes. Following infusion, the half-life of plasma enzymatic activity ranged from 3.6 to 10.4 minutes. Plasma clearance ranged from 9.8 to 20.3 mL/min/kg (mean ± SD, 14.5 ± 4.0 mL/min/kg). The volume of distribution corrected for weight ranged from 0.09 to 0.15 L/kg (mean ± SD, 0.12 ± 0.02 L/kg). These variables do not appear to be influenced by dose or duration of infusion. However, only one or two patients were studied at each dose level and infusion rate.

Antidrug Antibody Effects on Pharmacokinetics

In patients who developed IgG antibody to Cerezyme, an apparent effect on serum enzyme levels resulted in diminished volume of distribution and clearance and increased elimination half-life compared to patients without antibody *[see Adverse Reactions (6.2)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential have not been performed with

imiglucerase.

Mutagenesis

Imiglucerase was negative in the Ames test.

Impairment of Fertility

An animal fertility study was not performed. No histopathological findings on reproductive organs were observed in 13-week toxicity studies conducted in rats and monkeys.

14 CLINICAL STUDIES

Study RC 91-0110 was a randomized, double-blind, active-controlled study of 30 patients (17 male and 13 female), aged 12 to 69 years (mean age of 38 years in the Cerezyme group and mean age of 28 years in the alglucerase group at baseline), with Gaucher disease type 1 and a hemoglobin of at least 1 g/dL below the lower age limit for age and sex. Patients were randomized 1:1 to receive either Cerezyme 60 units/kg every other week or alglucerase for 6 months. Primary efficacy parameters were an increase in hemoglobin concentration of at least 1 g/dL, increase in platelet count and decrease in spleen and liver volume at 6 months. Efficacy results are shown in Table 1.

Table 1: Change from Baseline to Month 6 in Clinical Efficacy Parameters in a Randomized, Double-Blind Active-Controlled Trial of Cerezyme Compared to Alglucerase in Patients 12 Years of Age and Older with Gaucher Disease Type 1

Clinical Parameter		Cerezyme (N=15)	Alglucerase (N=15)	Difference (Cerezyme – Alglucerase) [95% CI]*
Hemoglobin concentration (g/dL)	Baseline	10.7	10.9	–
	Absolute Change from Baseline	1.9	1.6	0.3 [-0.6, 1.3]
Platelet count ($\times 10^3/mL^3$)	Baseline	68.5	74.2	–
	Absolute Change from Baseline	22.7	15.8	6.9 [-10.4, 24.1]
Liver volume (mL)	Baseline	2521	2788	–
	Absolute Change from Baseline	-310	-307	-3 [-246, 240]
	Percent Change from Baseline (%)	-11	-10	-1 [-9, 7]
Spleen volume (mL)	Baseline	2369	2603	–
	Absolute Change from Baseline	-902	-874	-28 [-652, 596]
	Percent Change from Baseline (%)	-35	-30	-5 [-14, 4]

* Confidence intervals were calculated using the t distribution (appropriate for small sample sizes) and the standard error of the difference in sample means (i.e. the pooled estimate of the common standard deviation, computed as the weighted average of the standard deviations in the two treatment groups); there was no evidence that the assumption of equal variances between the groups was violated.

Bone x-rays showed improvements in cortical thickness and lucencies in 7 of 11 Cerezyme treated patients.

In study RC 92-0501, twenty-nine patients continued treatment for total duration of 24 months. Patients were unblinded at 9 months and allowed to cross-over to Cerezyme treatment. At 24 months, mean increase in hemoglobin was 2.4 g/dL, mean increase in platelet count was 40

$\times 10^3/mL^3$, mean change in liver volume was -20%, and mean change in spleen volume was -57%.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cerezyme (imiglucerase) for injection, 400 units as a white to off-white lyophilized powder in a single-dose vial.

Store refrigerated at 2°C to 8°C.

For storage of reconstituted and diluted solution see *[Dosage and Administration (2)]*.

The expiry date of the product is indicated on the packaging materials.

17 MARKETING AUTHORISATION HOLDER AND IMPORTER AND ITS ADDRESS

Sanofi-aventis Israel ltd. 10 Beni Gaaon St., POB 8090, Netanya 4250499

18 REGISTRATION NUMBER

119-65-29980

Revised in March 2023 according to MoH guidelines.