PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CEREZYME® 400 powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each reconstituted vial contains 400 units imiglucerase per 10 mL (40 U/mL).

Contains sugar alcohol: each reconstituted vial contains 320 mg mannitol per 10 mL.

An enzyme unit (U) is defined as the amount of enzyme that catalyses the hydrolysis of 1 micromole of the synthetic substrate para-nitrophenyl-ß-D-glucopyranoside (pNP-Glc) per minute at 37 °C.

Imiglucerase is a modified form of human acid β-glucosidase and is produced by recombinant DNA technology using a mammalian Chinese hamster ovary (CHO) cell culture, with mannose modification for targeting macrophages.

Excipient with known effect:

CEREZYME contains sodium (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

CEREZYME is supplied as a sterile, non-pyrogenic, white to off-white lyophilised cake of powder.

The reconstituted powder is a clear, colourless liquid, free from foreign matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CEREZYME is indicated for long-term enzyme replacement therapy for paediatric and adult patients with a confirmed diagnosis of non-neuronopathic (Type I) or chronic neuronopathic (Type 3) Gaucher disease who exhibit clinically significant non-neurological manifestations of the disease.

The non-neurological manifestations of Gaucher disease include one or more of the following conditions:

a. anaemia after exclusion of other causes, such as iron deficiency,

b. thrombocytopenia,

c. bone disease after exclusion of other causes, such as vitamin D deficiency, and

d. hepatomegaly or splenomegaly.

4.2 Posology and method of administration

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

Posology

CEREZYME is administered by intravenous infusion over 1 – 2 hours.

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

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.

Paediatric population:

No dose adjustment is necessary for the paediatric population.

Chronic neuronopathic Gaucher patients:

The efficacy of CEREZYME on neurological symptoms of chronic neuronopathic Gaucher patients has not been established, and no special dosage regimen can be recommended for these manifestations.

Method of administration

After reconstitution and dilution, the preparation is administered by intravenous infusion. At initial infusions, CEREZYME should be administered at a rate not exceeding 0,5 U/kg/min. At subsequent administrations, infusion rate may be increased, but should not exceed 1 U/kg/min. Infusion rate increases should occur under supervision of a health care provider.

Home infusion:

Infusion of CEREZYME at home may be considered for patients who have tolerated their infusions well for several months. The decision to have the patient move to home infusion should be made after evaluation and recommendation by the treating health care provider. Infusion of CEREZYME by the patient or caregiver at home requires training by a health care provider in a clinical setting. The patient or caregiver will be instructed in infusion technique and the keeping of a treatment diary. Patients experiencing adverse events during the infusion, need to immediately stop the infusion process and contact a health care provider. Subsequent infusions may need to occur in a clinical setting. Dose and infusion rate should remain constant while at home, and not be changed

without supervision of a health care provider.

For instructions on reconstitution and dilution of CEREZYME before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active ingredient, imiglucerase, or to any other inactive ingredients listed in section 6.1.

4.4 Special warnings and precautions for use

Approximately 15 % of patients treated and tested to date have developed IgG antibodies to CEREZYME during the first year of therapy. Patients who developed IgG antibodies 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.

Patients with antibodies to CEREZYME have a higher risk of hypersensitivity reaction. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibodies. It is suggested that patients be monitored periodically for IgG antibody formation during the first year of treatment.

Treatment with CEREZYME should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the product.
Anaphylactoid reaction has 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 rate of infusion and pretreatment with antihistamines and/or corticosteroids.

In less than 1 % of the patient population, pulmonary hypertension and pneumonia have also been observed during treatment with CEREZYME. Pulmonary hypertension and pneumonia are known complications of Gaucher disease, and have been observed both in patients receiving and not receiving CEREZYME. No causal relationship with CEREZYME has been established. Patients with respiratory symptoms in the absence of fever 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.

Caution may be advisable in administration of CEREZYME to patients previously treated with placenta-derived glucocerebrosidase and who have exhibited symptoms of hypersensitivity or developed antibody to placenta-derived glucocerebrosidase.

Paediatric use:

The safety and effectiveness of CEREZYME have been established in patients between 2 and 16 years of age. Use of CEREZYME in this age group is supported by evidence from adequate and well-controlled studies of CEREZYME and CEREDASE® (alglucerase injection) in adult and paediatric patients, with additional data obtained from the medical literature and from long-term post-marketing experience. CEREZYME has been administered to patients younger than 2 years of age, however, the safety and effectiveness in patients younger than 2 years have not been established.

Sodium:

CEREZYME contains approximately 34 mg sodium per reconstituted vial (i.e 3,4 mg/mL), equivalent to 1,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult. Additionally, CEREZYME is administered in 0,9 % sodium chloride intravenous solution (see section 6.6). To be taken into consideration by patients on a sodium-controlled diet.

4.5 Interaction with other medicines and other forms of interaction

Data regarding interactions with other medication are not available.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established.

Limited data are available suggesting that the use of CEREZYME is beneficial to control the underlying Gaucher disease in pregnancy.
This data indicate no malformative toxicity for the fetus by CEREZYME, although the statistical evidence is low. Fetal demise has been reported rarely, although it is not clear whether this is related to the use of CEREZYME or to the underlying Gaucher disease.

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

In pregnant Gaucher patients and those intending to become pregnant, a risk-benefit treatment assessment is required for each pregnancy. Patients who have Gaucher disease and become pregnant may experience a period of increased disease activity during pregnancy and the puerperium. This includes an increased risk of skeletal manifestations, exacerbation of cytopenia, haemorrhage, and an increased need for transfusion. Both pregnancy and lactation are known to

stress maternal calcium homeostasis and to accelerate bone turnover. This may contribute to skeletal disease burden in Gaucher disease.

Treatment naïve women should be advised to consider commencing therapy prior to conception, in order to attain optimal health. In women receiving CEREZYME treatment, continuation throughout pregnancy should be considered. Close monitoring of the pregnancy and clinical manifestations of Gaucher disease is necessary for the individualisation of the dose, according to the needs of the patient and therapeutic response.

Caution should be exercised when prescribing to pregnant women.

Lactation

It is not known whether imiglucerase is excreted in human breast milk, however, the enzyme is likely to be digested in the child's gastrointestinal tract. Many substances are excreted in human milk, therefore caution should be exercised when CEREZYME is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

CEREZYME has no or negligible influence on the ability to drive a vehicle and use machines.

4.8 Undesirable effects

Since the approval of CEREZYME in May 1994, a worldwide post-marketing database of spontaneously-reported adverse events and adverse events discussed in the medical literature has been maintained. The percentage of events for each reported adverse reaction term has been calculated, using the number of patients from these sources as the denominator for total patient exposure to CEREZYME since 1994. Actual patient exposure is difficult to obtain due to the voluntary nature of the database and continuous accrual and loss of patients over that span of time. The actual number of patients exposed to CEREZYME since 1994 is likely to be greater than

estimated from these voluntary sources and, therefore, the percentage calculated for the frequencies of adverse reactions are most likely greater than the actual incidences.

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.

Tabulated list of adverse reactions:

Adverse reactions are listed by system organ class and frequency: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data).

System organ class	Common	Uncommon	Not known
Immune system disorders	Hypersensitivity[1] Anaphylactoid reactions[2]		
Nervous system disorders	Fatigue[4] Dizziness[4] Headache[4]		
Cardiac disorders	Cyanosis* Tachycardia[4]		
Vascular disorders	Hypotension* Flushing*		
Respiratory, thoracic and mediastinal disorders	Chest discomfort* Dyspnoea* Coughing*		
Gastrointestinal disorders	Nausea[4] Vomiting[4]		

	Abdominal pain[4] Diarrhoea[4]		
Skin and subcutaneous tissue disorders	Angioedema* Urticaria* Pruritus* Rash[4]		Transient peripheral oedema
General disorders and administration site conditions	Backache[4] Fever[4] Chills[4]	Infusion site discomfort, pruritus, burning, swelling or sterile abscess at the site of venipuncture[3]	

[1] Symptoms suggestive of hypersensitivity (* marked in the table above) have been noted in approximately 6,6 % of patients. Onset of such symptoms has occurred during or shortly after infusions.

[2] Each of these events was found to occur in < 1,5 % of the total patient population. Pretreatment with antihistamines and/or corticosteroids and reduced rate of infusion has allowed continued use of CEREZYME in most patients. Also see section 4.4.

[3] Some of the adverse events were related to the route of administration. Each of these events was found to occur in < 1 % of the total patient population.

[4] Additional adverse reactions have been reported in approximately 6,5 % of patients treated with CEREZYME. Each of these events was found to occur in < 1,5 % of the total patient population therefore the frequency for all is “common”.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of CEREZYME is important. It allows continued monitoring of the benefit/risk balance of CEREZYME. Health care providers are asked to report any suspected adverse reactions to:

- The Pharmacovigilance Unit at Sanofi: za.drugsafety@sanofi.com (email) or 011 256 3700 (tel), or
- SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Experience with doses up to 240 U/kg every 2 weeks have been reported. At that dose there have been no reports of obvious toxicity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 31. Enzymatic preparation.

Pharmacotherapeutic group: Enzymes – Imiglucerase (recombinant macrophage targeted β-glucocerebrosidase).

ATC code: A16AB02.

CEREZYME is an analogue of the human enzyme ß-glucocerebrosidase produced by recombinant DNA technology. ß-Glucocerebrosidase (D-glucosyl-N-acylsphingosine glucohydrolase, E.C. 3.2.1.45) is a lysosomal glycoprotein enzyme, which catalyses the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

Gaucher disease is a rare recessively inherited metabolic disorder that results from a deficiency of the lysosomal enzyme acid β-glucosidase. This enzyme breaks down glucosylceramide, a key component of the lipid structure of cell membranes, into glucose and ceramide. In individuals with Gaucher disease, glucosylceramide degradation is insufficient, leading to accumulation of large

quantities of this substrate within the lysosomes of macrophages (termed “Gaucher cells”), leading to widespread secondary pathology.

Gaucher cells are typically found in liver, spleen and bone marrow and occasionally in lung, kidney and intestine. Clinically, Gaucher disease is a heterogeneous phenotypic spectrum. The most frequent disease manifestations are hepatosplenomegaly, thrombocytopenia, anaemia and skeletal pathology. The skeletal abnormalities are frequently the most debilitating and disabling features of Gaucher disease. These skeletal manifestations include bone marrow infiltration, osteonecrosis, bone pain and bone crises, osteopenia and osteoporosis, pathological fractures and growth impairment. Gaucher disease is associated with increased glucose production and increased resting energy expenditure rate, which may contribute to fatigue and cachexia. Patients with Gaucher disease may also have a low-grade inflammatory profile. In addition, Gaucher disease has been associated with an increased risk of immunoglobulin abnormalities such as hyperimmunoglobulinaemia, polyclonal gammopathy, monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma. The natural history of Gaucher disease usually shows progression, with the risk of irreversible complications arising in various organs over time. The clinical manifestations of Gaucher disease can adversely affect quality of life. Gaucher disease is associated with increased morbidity and early mortality. Signs and symptoms presenting in childhood typically represent more severe Gaucher disease. In children, Gaucher disease can lead to growth retardation and delayed puberty.

Imiglucerase (recombinant macrophage targeted acid ß-glucosidase) replaces the deficient enzyme activity, hydrolysing glucosylceramide, thus correcting initial pathophysiology and preventing secondary pathology. CEREZYME reduces spleen and liver size, improves or normalises thrombocytopenia and anaemia, improves or normalises bone mineral density and bone marrow burden, and reduces or eliminates bone pain and bone crises. CEREZYME reduces resting energy expenditure rate. CEREZYME has been shown to improve both mental and physical aspects in the quality of life of Gaucher disease. CEREZYME decreases chitotriosidase, a

biomarker for glucosylceramide accumulation in macrophages and response to treatment. In children, CEREZYME has been shown to enable normal pubertal development, and to induce catch-up growth, leading to normal height and bone mineral density in adulthood.

It is reported that enzyme replacement therapy has stabilised and/or slowed the progression of neurological involvement in some patients with chronic neuronopathic disease. However, no controlled clinical studies have been conducted.

5.2 Pharmacokinetic properties

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 ± SD: 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 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. The pharmacokinetics of CEREZYME do not appear to be different from placenta-derived glucocerebrosidase.

In patients who develop IgG antibodies 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 antibodies (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trisodium citrate (for pH adjustment)

Disodium hydrogen citrate (for pH adjustment)

Mannitol

Polysorbate 80.

6.2 Incompatibilities

In the absence of compatibility studies CEREZYME should not be mixed with other medicines.

6.3 Shelf life

Unopened vials:

36 months.

Reconstituted solution:

Since CEREZYME does not contain any preservatives, vials should be promptly diluted after reconstitution and not be 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.

Diluted solution:

From a microbiological safety point of view, the diluted solution should be used immediately. If not used immediately, in-use storage and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2 – 8 °C, protected from light.

6.4 Special precautions for storage

Store at 2 – 8 °C.

Discard any unused portion of the solution.

Do not use CEREZYME after the expiration date on the vial.

6.5 Nature and contents of container

The sterile lyophilised powder is packed into 20 mL clear glass vials, each packed into a unit carton.

Pack size: 1 vial.

6.6 Special precautions for disposal and other handling

Each vial of CEREZYME is for single use only.

CEREZYME powder for concentrate for solution for infusion has to be reconstituted with sterile water for injection, diluted with 0,9 % sodium chloride intravenous solution and then administered by intravenous infusion.

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

Relatively low toxicity, combined with the extended time course of response, allows small dosage adjustments to be made to avoid discarding partially used vials. Dosages may be rounded to the nearest full vial, as long as the monthly administered dosage remains substantially unaltered.

Use aseptic techniques:

Reconstitution:

Reconstitute each vial with 10,2 mL sterile water for injection. Avoid forceful impact of water for injections on the powder and, by mixing gently, avoid foaming of the solution. The reconstituted volume is 10,6 mL. The pH of the reconstituted solution is approximately 6,1.

The final concentration and administration volume 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

After reconstitution, the solution is a clear, colourless liquid, free from foreign matter. The reconstituted solution should be further diluted. 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. Since CEREZYME does not contain any preservatives, vials should be promptly diluted after reconstitution and not be stored for subsequent use.

For in-use storage time after reconstitution, see section 6.3.

Dilution:

The reconstituted solution contains 40 units imiglucerase per mL. The reconstituted volume allows accurate withdrawal of 10,0 mL (equal to 400 units) from each vial. Withdraw 10,0 mL reconstituted solution from each vial and combine the withdrawn volumes. The appropriate amount of CEREZYME for each patient is diluted with 0,9 % sodium chloride injection, to a final volume of 100 – 200 mL.

Administration:

Because CEREZYME is a protein solution, slight flocculation (described as thin translucent fibres) occurs occasionally after dilution. The diluted solution may be filtered through an in-line low protein-binding 0,2 µm filter during administration in order to remove any protein particles. This will not lead to any loss of imiglucerase activity. It is recommended that the diluted solution be administered within 3 hours. The product diluted in 0,9 % sodium chloride intravenous solution will retain chemical stability if stored up to 24 hours at 2 °C to 8 °C under protection from light; but microbiological safety will depend on the reconstitution and dilution having been performed aseptically.

For in-use storage time after dilution, refer to section 6.3.

7. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBER

36/31/0179

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

7 March 2003

10. DATE OF REVISION OF THE TEXT

15 August 2022

Namibia

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