ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cerezyme 400 Units Powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 400 units* of imiglucerase**.

After reconstitution, the solution contains 40 units (approximately 1.0 mg) of imiglucerase per ml (400 U/10 ml). Each vial must be further diluted before use (see section 6.6).

* 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.
** 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.

Excipients with known effect:

Each vial contains 41 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
Cerezyme is a white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cerezyme (imiglucerase) is indicated for use as 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 clinically significant 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

4.2 Posology and method of administration

Disease management should be directed by physicians knowledgeable in the treatment of Gaucher disease.

Posology

Due to the heterogeneity and the multi-systemic nature of Gaucher disease, dosage should be individualised for each patient based on a comprehensive evaluation of all clinical manifestations of

the disease. Once individual patient response for all relevant clinical manifestations is well-established, dosages and frequency of administration may be adjusted with the goal to either maintain already reached optimal parameters for all clinical manifestations or further improve those clinical parameters which have not yet been normalised.

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.

Paediatric population
No dose adjustment is necessary for the paediatric population.

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 (see section 5.1).

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 unit per kg body weight per minute. At subsequent administrations, infusion rate may be increased but should not exceed 1 unit per kg body weight per minute. Infusion rate increases should occur under supervision of a health care professional.

Infusion of Cerezyme at home may be considered for patients who are tolerating their infusions well for several months. Decision to have patient move to home infusion should be made after evaluation and recommendation by the treating physician. Infusion of Cerezyme by the patient or caregiver at home requires training by a health care professional 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** seek the attention of a healthcare professional. 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 professional.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

Medical or healthcare professionals are encouraged to register Gaucher patients, including those with chronic neuronopathic manifestations of the disease, in the “ICGG Gaucher Registry” (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity

Current data using a screening ELISA followed by a confirmatory radioimmunoprecipitation assay, suggest that, during the first year of therapy, IgG antibodies to imiglucerase 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 suspected of a decreased response to the treatment be monitored periodically for IgG antibody formation to imiglucerase.

Patients with antibody to imiglucerase have a higher risk of hypersensitivity reactions (see section 4.8). If a patient experiences a reaction suggestive of hypersensitivity, subsequent testing for imiglucerase antibodies is advised. As with any intravenous protein product, severe allergic-type hypersensitivity reactions are possible, but occur uncommonly. If these reactions occur, immediate discontinuation of the Cerezyme infusion is recommended and appropriate medical treatment should be initiated. The current medical standards for emergency treatment are to be observed.

Patients who have developed antibodies or symptoms of hypersensitivity to Ceredase (alglucerase) should be treated with caution when administering Cerezyme (imiglucerase).

Infusion-Associated Reactions (IAR)

Infusion-associated reactions (IAR) such as angioedema, pruritus, rash, urticaria, chest discomfort, chills, fatigue, infusion-site burning, infusion-site discomfort, infusion-site swelling, pyrexia and transient hypertension have been observed in patients treated with imiglucerase (see section 4.8).

Careful consideration should be given to the patient's clinical status prior to administration of Cerezyme.

Antihistamines, antipyretics, and/or corticosteroids can be given to prevent or reduce IARs. However, IARs may still occur in patients after receiving pre-treatment. If mild or moderate IARs occur regardless of pre-treatment, decreasing the infusion rate or temporarily stopping the infusion may ameliorate the symptoms. If severe IARs occur, immediate discontinuation of the administration of Cerezyme should be considered and appropriate medical treatment should be initiated. The benefits and risks of re-administering Cerezyme following severe IARs should be considered (see section 4.8).

Sodium

This medicinal product contains 41 mg sodium per vial, equivalent to 2% of the WHO recommended maximum daily intake of 2 g sodium for an adult. It is administered in 0.9% sodium chloride intravenous solution (see section 6.6). To be taken into consideration by patients on a controlled sodium diet.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Limited experience from 150 pregnancy outcomes (primarily based on spontaneous reporting and literature review) is available suggesting that use of Cerezyme is beneficial to control the underlying Gaucher disease in pregnancy. Furthermore, these data indicate no malformative toxicity for the foetus by Cerezyme, although the statistical evidence is low. Foetal demise has been reported rarely, although it is not clear whether this 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/foetal development, parturition and postnatal development. It is not known whether Cerezyme passes via the placenta to the developing foetus.

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 individualization of dose according to the patient's needs and therapeutic response.

Breast-feeding

It is not known whether this active substance is excreted in human milk, however, the enzyme is likely to be digested in the child's gastrointestinal tract

4.7 Effects on ability to drive and use machines

Cerezyme has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

Adverse 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 reactions are presented in order of decreasing seriousness.

MedDRA System Organ Class	Common	Uncommon	Rare	Not known
Nervous system disorders		Dizziness, headache, paraesthesia		
Cardiac disorders		Tachycardia, cyanosis		
Vascular disorders		Flushing, hypotension		Transient hypertension
Respiratory, thoracic and mediastinal disorders	Dyspnoea, coughing			
Gastrointestinal disorders		Vomiting, nausea, abdominal cramping, diarrhoea		
Immune system disorders	Hypersensitivity reactions		Anaphylactoid reactions	
Skin and subcutaneous tissue disorders	Urticaria, angioedema, pruritus, rash			
Musculoskeletal and connective tissue disorders		Arthralgia, backache		
General disorders and administration site conditions		Infusion site discomfort, infusion site burning, infusion site swelling, injection site sterile abscess, chest discomfort, fever, rigors, fatigue		

Description of selected adverse reactions

Hypersensitivity (including anaphylaxis)

Symptoms suggestive of hypersensitivity have been noted, overall, in approximately 3% of the patients. Onset of such symptoms like paraesthesia, tachycardia, cyanosis, flushing, hypotension, dyspnoea, coughing, Urticaria/angioedema, pruritus, rash, backache and chest discomfort has occurred during or shortly after infusions (see section 4.4).

Infusion-Associated Reactions

Infusion-associated reactions (IAR) such as angioedema, pruritus, rash, urticaria, chest discomfort, chills, fatigue, infusion-site burning, infusion-site discomfort, infusion-site swelling, pyrexia and transient hypertension have been observed in patients treated with imiglucerase (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported. In patients dosages up to 240 U/kg body weight once every two weeks have been used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Enzymes-Imiglucerase (recombinant macrophage targeted β-glucocerebrosidase), ATC code: A16AB02.

Mechanism of action

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 hyperimmunoglobulinemia, 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.

Pulmonary hypertension is a known complication of Gaucher disease. 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.

Pharmacodynamic effects

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.

Clinical efficacy and safety

The rate and extent of response to Cerezyme treatment is dose dependent. Generally, improvements in organ systems with a faster turnover rate, such as the haematological, can be noted far more rapidly than in those with a slower turnover, such as the bone.
In an ICGG Gaucher Registry analysis of a large cohort of patients (n=528) with Gaucher disease type 1, a time- and dose-dependent effect for Cerezyme was observed for haematological and visceral parameters (platelet count, haemoglobin concentration, spleen and liver volume) within the dose range of 15, 30 and 60 U/kg body weight once every 2 weeks. Patients treated with 60 U/kg body weight every 2 weeks showed a faster improvement and a greater maximum treatment effect as compared to patients receiving the lower doses.

Similarly, in an ICGG Gaucher Registry analysis of bone mineral density using dual-energy X-ray absorptiometry (DXA) in 342 patients, after 8 years of treatment normal bone mineral density was achieved with a Cerezyme dose of 60 U/kg body weight once every 2 weeks, but not with lower doses of 15 and 30 U/kg body weight once every 2 weeks (Wenstrup et al, 2007).

In a study investigating 2 cohorts of patients treated with a median dose of 80 U/kg body weight every 4 weeks and a median dose of 30 U/kg body weight every 4 weeks, among the patients with bone marrow burden score ≥ 6, more patients in the higher dose cohort (33%; n=22) achieved a decrease in the score of 2 points after 24 months of Cerezyme treatment compared with patients in the lower dose cohort (10%; n=13) (de Fost et al, 2006).

Treatment with Cerezyme at a dose of 60 U/kg body weight once every 2 weeks, showed improvement in bone pain as early as 3 months, decrease in bone crises within 12 months, and improvement in bone mineral density after 24 months of treatment (Sims et al, 2008).

The usual frequency of infusion is once every 2 weeks (see section 4.2). 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. Changes from baseline in haemoglobin, platelets, liver and spleen volumes, bone crisis, and bone disease comprised a predefined composite endpoint; achievement or maintenance of established Gaucher disease therapeutic goals for the hematologic and visceral parameters comprised an additional endpoint. Sixty-three percent of Q4- and 81% of Q2-treated patients met the composite endpoint at Month 24; the difference was not statistically significant based on the 95% CI (-0.357, 0.058). Eighty-nine percent of Q4- and 100% of Q2-treated patients met the therapeutic goals-based endpoint; the difference was not statistically significant based on the 95% CI (-0.231, 0.060). A Q4 infusion regimen may be a therapeutic option for some adult patients with stable residual Gaucher disease type 1, but clinical data are limited.

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.

Medical or healthcare professionals are encouraged to register Gaucher patients, including those with chronic neuronopathic manifestations of the disease, in the "ICGG Gaucher Registry". Patient data will be anonymously collected in this Registry. The objectives of the "ICGG Gaucher Registry" are to enhance the understanding of Gaucher disease and to evaluate the effectiveness of enzyme replacement therapy, ultimately leading to improvement in the safe and efficacious use of Cerezyme.

5.2 Pharmacokinetic properties

During 1 hour intravenous infusions of 4 doses (7.5, 15, 30, 60 U/kg) of imiglucerase, 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 (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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol,
sodium citrate (to adjust pH),
citric acid monohydrate (to adjust pH),
polysorbate 80.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vials:
3 years

Diluted solution:
From a microbiological safety point of view, the product 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°C - 8°C under protection from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Cerezyme is supplied in type I borosilicate (clear) glass 20 ml vials. The closure consists of a siliconized butyl stopper with a tamper proof flip-off cap.

To provide sufficient volume to allow accurate dispensing, each vial is formulated to contain an overfill of 0.6 ml.

Pack sizes: 1, 5 or 25 vials per carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each vial of Cerezyme is for single use only.

The powder for concentrate for solution for infusion has to be reconstituted with water for injections, 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 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.

Use Aseptic Technique

Reconstitution
Reconstitute each vial with 10.2 ml water for injections; 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 6.2.

After reconstitution it is a clear, colourless liquid, free from foreign matter. The reconstituted solution must be further diluted. Before further dilution, visually inspect the reconstituted solution in each vial for foreign particles and discoloration. Do not use vials exhibiting foreign particles or discoloration. After reconstitution, promptly dilute vials and do not store for subsequent use.

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. Then dilute the combined volumes with 0.9% sodium chloride intravenous solution to a total volume of 100 to 200 ml. Mix the infusion solution gently.

Administration
It is recommended to administer the diluted solution through an in-line low protein-binding 0.2 µm filter 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 and 8°C under protection from light; but microbiological safety will depend on the reconstitution and dilution having been performed aseptically.

Cerezyme contains no preservatives. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi B.V., Paasheuvelweg 25, 1105 BP, Amsterdam, the Netherlands

8. MARKETING AUTHORISATION NUMBERS

EU/1/97/053/003
EU/1/97/053/004
EU/1/97/053/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 November 1997
Date of latest renewal: 17 September 2007

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Resilience US, Inc., 500 Soldiers Field Road, Allston, MA 02134, United States
Lonza Biologics Inc., 101 International Drive, Portsmouth, NH 03801, United States
Genzyme Corporation, 8, 45, 68, 74, 80 New York Avenue, Framingham, MA 01701, United States

Name and address of the manufacturers responsible for batch release

Genzyme Ireland Limited., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Educational materials for the use of Cerezyme in home infusion, consisting of:
- Manual for patients with Gaucher disease who receive home infusion;
- Guide for Healthcare Professionals Treating Patients with Gaucher Disease.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (1 VIAL, 5 VIALS, 25 VIALS)

1. NAME OF THE MEDICINAL PRODUCT

Cerezyme 400 Units Powder for concentrate for solution for infusion
imiglucerase

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 400 units of imiglucerase.

3. LIST OF EXCIPIENTS

Excipients: mannitol, sodium citrate, citric acid monohydrate and polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for concentrate for solution for infusion.
5 vials of powder for concentrate for solution for infusion.
25 vials of powder for concentrate for solution for infusion.

5. METHOD AND ROUTE OF ADMINISTRATION

Intravenous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

For single use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution should be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi B.V.
Paasheuvelweg 25–1105 BP Amsterdam
The Netherlands

12. MARKETING AUTHORIZATION NUMBERS

EU/1/97/053/003 1 vial of powder for concentrate for solution for infusion
EU/1/97/053/004 5 vials of powder for concentrate for solution for infusion
EU/1/97/053/005 25 vial of powder for concentrate for solution for infusion

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cerezyme 400 U

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL / VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Cerezyme 400 Units Powder for concentrate for solution for infusion
imiglucerase

2. METHOD OF ADMINISTRATION

Intravenous use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains 400 units of imiglucerase.

6. OTHER

Sanofi B.V. - NL

Store in a refrigerator.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Cerezyme 400 Units powder for concentrate for solution for infusion
Imiglucerase

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cerezyme is and what it is used for

Cerezyme contains the active substance imiglucerase and is used to treat patients who have a confirmed diagnosis of Type I or Type 3 Gaucher disease, who show signs of the disease such as: anaemia (low number of red blood cells), a tendency to bleed easily (due to low numbers of platelets – a type of blood cell), spleen or liver enlargement or bone disease.

People with Gaucher disease have low levels of an enzyme called acid β-glucosidase. This enzyme helps the body control levels of glucosylceramide. Glucosylceramide is a natural substance in the body, made of sugar and fat. In Gaucher disease glucosylceramide levels can get too high.

Cerezyme is an artificial enzyme called imiglucerase - this can replace the natural enzyme acid β-glucosidase which is lacking or not active enough in patients with Gaucher disease.

The information in this leaflet applies to all patient groups including children, adolescents, adults and the elderly.

2. What you need to know before you are given Cerezyme

Do not use Cerezyme
- if you are allergic to imiglucerase or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before using Cerezyme:
- if you are treated with Cerezyme, you may experience infusion associated reactions (IARs) or an allergic reaction while you are being given the medicine or shortly after. The IARs or allergic reaction is any side effect occurring during the infusion or until the end of the infusion day (see section 4). If you experience a reaction like this, you should **tell your doctor immediately**. You may need to be given additional medicines to prevent such reactions from occurring. Your doctor may test if you have an allergic reaction to imiglucerase.

- some patients with Gaucher disease have high blood pressure in the lungs (pulmonary hypertension). The cause can be unknown, or it can be due to heart, lung or liver problems. It can occur whether the patient is treated with Cerezyme or not. But, if you suffer with any **shortness of breath** you should tell your doctor.

Other medicines and Cerezyme
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Cerezyme should not be given as a mixture with other medicinal products in the same infusion (drip).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Cautious use of Cerezyme during pregnancy and breastfeeding is recommended.

Cerezyme contains sodium
This medicine contains 41 mg sodium (main component of cooking/table salt) per vial. This is equivalent to 2% of the recommended maximum daily dietary intake of sodium for an adult. It is administered in 0.9% sodium chloride intravenous solution. This should be taken into consideration by patients on a controlled sodium diet.

3. How Cerezyme is given

Instructions for proper use
Cerezyme is given through a drip into a vein (by intravenous infusion).

It is supplied as a powder which will be mixed with sterile water before it is given.

Cerezyme is only used under the supervision of a doctor who is knowledgeable in the treatment of Gaucher disease. Your doctor may advise that you can be treated at home provided you meet certain criteria. Please contact your doctor if you would like to be treated at home.

Your dose will be specific to you. Your doctor will work out your dose based on how severe your symptoms are, and other factors. The recommended dose is 60 units/kg body weight given once every 2 weeks.

Your doctor will keep a close check on your response to your treatment, and may change your dose (up or down) until he/she finds the best dose to control your symptoms.

Once this dose is found your doctor will still keep a check on your responses to make sure you are using the right dose. This might be every 6 to 12 months.

There is no information on the effect of Cerezyme on brain-based symptoms of patients with chronic neuronopathic Gaucher disease. Therefore no special dosage regimen can be recommended.

The ICGG Gaucher Registry
You can ask your doctor to register your patient information into the “ICGG Gaucher Registry”. The aims of this Registry are to increase the understanding of Gaucher disease and to check how well enzyme replacement therapy, like Cerezyme, works. This should lead to improvement in the safe and effective use of Cerezyme. Your patient data will be registered anonymously– nobody will know it is information about you.

If you use more Cerezyme than you should
There are no cases of overdose of Cerezyme reported.

If you forget to use Cerezyme
If you have missed an infusion, please contact your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

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

Uncommon (may affect up to 1 in 100 people):
- dizziness
- headache
- a sensation of tingling, pricking, burning or numbness of the skin
- increased heart rate
- bluish skin
- flushing
- fall in blood pressure
- vomiting
- nausea
- abdominal cramping
- diarrhoea
- pain in the joints
- infusion site discomfort
- infusion site burning
- infusion site swelling
- injection site sterile abscess
- chest discomfort
- fever
- rigors
- fatigue
- backache

Rare (may affect up to 1 in 1,000 people):
- anaphylactoid reactions

Not Known (frequency cannot be estimated from the available data):
- temporary high blood pressure

Some side effects were seen primarily while patients were being given the medicine or shortly after. These have included itching, flushing, hives/localised swelling of the skin or lining of the mouth or throat, chest discomfort, chills, fatigue, increased heart rate, bluish skin, breathlessness, a sensation of tingling, pricking, burning or numbness of the skin, fall in blood pressure and backache. If you experience any of these symptoms, please **tell your doctor immediately**. You may need to be given additional medicines to prevent an allergic reaction (e.g. antihistamines and/or corticosteroids).

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How Cerezyme is stored

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date printed on the labelling after the letters "EXP". The expiry date refers to the last day of that month.

Unopened vials:
Store in a refrigerator (2°C – 8°C)

Diluted solution:
It is recommended that Cerezyme is used immediately after it has been mixed with sterile water. The mixed solution in the vial cannot be stored and should be promptly diluted in an infusion bag; only the diluted solution can be held for up to 24 hours if it is kept cool (2°C – 8°C) and in the dark.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6 Contents of the pack and other information

What Cerezyme contains
- The active substance is imiglucerase. Imiglucerase is a modified form of the human enzyme acid β-glucosidase produced by recombinant DNA technology. One vial contains 400 units of imiglucerase. After reconstitution, the solution contains 40 units of imiglucerase per ml.
- The other ingredients are: mannitol, sodium citrate, citric acid monohydrate and polysorbate 80.

What Cerezyme looks like and contents of the pack
Cerezyme, 400 Units, is presented as a powder for concentrate for solution for infusion (in a vial, pack size of 1, 5 or 25). Not all pack sizes may be marketed.

Cerezyme is supplied as a white to off-white powder. After reconstitution it is a clear, colourless liquid, free from foreign matter. The reconstituted solution must be further diluted.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Sanofi B.V., Paasheuvelweg 25, 1105 BP, Amsterdam, the Netherlands

Manufacturer
Genzyme Ireland Limited., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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This leaflet was last revised in:

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/. There are also links to other websites about rare diseases and treatments.

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The following information is intended for healthcare professionals only:

Instructions for use – reconstitution, dilution and administration
Each vial of Cerezyme is for single use only. After reconstitution, each vial of Cerezyme contains 400 units of imiglucerase in 10.0 ml (40 units per ml).

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

Use Aseptic Technique

Reconstitution
Reconstitute each vial with 10.2 ml water for injections; 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 6.2.

After reconstitution it is a clear, colourless liquid, free from foreign matter. The reconstituted solution must be further diluted. Before further dilution, visually inspect the reconstituted solution in each vial for foreign particles and discoloration. Do not use vials exhibiting foreign particles or discoloration. After reconstitution, promptly dilute vials and do not store for subsequent use.

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. Then dilute the combined volumes with 0.9% sodium chloride intravenous solution to a total volume of 100 to 200 ml. Mix the infusion solution gently.

Administration
It is recommended to administer the diluted solution through an in-line low protein-binding 0.2 µm filter 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 and 8°C under protection from light; but microbiological safety will depend on the reconstitution and dilution having been performed aseptically.

Cerezyme contains no preservatives. Any unused product or waste material should be disposed of in accordance with local requirements.