ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Cerezyme 200 U Powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 units* of imiglucerase**.

After reconstitution, the solution contains 40 units (approximately 1.0 mg) of imiglucerase per ml (200 U/5 ml).

* 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:
For a full list of excipients, see section 6.1.
This medicinal product contains sodium and is administered in 0.9% sodium chloride intravenous solution (see section 6.6). After reconstitution, the solution contains 0.62 mmol sodium (200 U/5 mL). To be taken into consideration by patients on a controlled sodium diet.

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 (see section 4.4).

### 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 (alg glucerase) should be treated with caution when administering Cerezyme (imiglucerase).

Excipients
This medicinal product contains sodium and 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

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.

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

Adverse drug reactions are listed by system organ class and frequency (common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000)) in the table below. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Drug Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Uncommon:</td>
<td>Dizziness, headache, paraesthesia*</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Uncommon:</td>
<td>Tachycardia*, cyanosis*</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Uncommon:</td>
<td>Flushing*, hypotension*</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Common:</td>
<td>Dyspnoea*, coughing*</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Uncommon:</td>
<td>Vomiting, nausea, abdominal cramping, diarrhoea</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Common:</td>
<td>Hypersensitivity reactions</td>
</tr>
<tr>
<td></td>
<td>Rare :</td>
<td>Anaphylactoid reactions</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Common:</td>
<td>Urticaria/angioedema*, pruritus*, rash*</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Uncommon:</td>
<td>Arthralgia, backache*</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Uncommon:</td>
<td>Infusion site discomfort, infusion site burning, infusion site swelling, injection site sterile abscess, chest discomfort*, fever, rigors, fatigue</td>
</tr>
</tbody>
</table>

Symptoms suggestive of hypersensitivity (* marked in the table above) have been noted, overall in approximately 3% of the patients. Onset of such symptoms has occurred during or shortly after infusions. These symptoms generally respond to treatment with antihistamines and/or corticosteroids. Patients should be advised to discontinue infusion of the product and contact their physician if these symptoms occur.

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.

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 (term ‘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 gammapathy, monoclonal gammapathy 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.

Imiglucerase (recombinant macrophage targeted acid β-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.

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 hemoglobin, 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:
2 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 of the diluted 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 siliconised 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 0.3 ml.

Package sizes: 1 or 25 vials per carton.
Not all package 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 5.1 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 5.3 ml. The pH of the reconstituted solution is approximately 6.1.

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 5.0 ml (equal to 200 units) from each vial. Withdraw 5.0 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.

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
Genzyme Europe B.V., Gooimeer 10, 1411 DD Naarden, The Netherlands

8. MARKETING AUTHORISATION NUMBERS
EU/1/97/053/001
EU/1/97/053/002

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 product is available on the website of the European Medicines Agency http://www.ema.europa.eu
1. **NAME OF THE MEDICINAL PRODUCT**
Cerezyme 400 U 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).

* 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:
For a full list of excipients, see section 6.1.
This medicinal product contains sodium and is administered in 0.9% sodium chloride intravenous solution (see section 6.6). After reconstitution, the solution contains 1.24 mmol sodium (400 U/10 mL). To be taken into consideration by patients on a controlled sodium diet.

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 (see section 4.4).

### 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).

**Excipients**

This medicinal product contains sodium and 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.

### 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

### 4.6 Fertility, pregnancy and lactation

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.

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

Adverse drug reactions are listed by system organ class and frequency (common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000)) in the table below. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

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Symptoms suggestive of hypersensitivity (* marked in the table above) have been noted, overall in approximately 3% of the patients. Onset of such symptoms has occurred during or shortly after infusions. These symptoms generally respond to treatment with antihistamines and/or corticosteroids. Patients should be advised to discontinue infusion of the product and contact their physician if these symptoms occur.

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.

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.

Imiglucerase (recombinant macrophage targeted acid β-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.

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, 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 hemoglobin, 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:
2 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 of the diluted 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 siliconised 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.

Package sizes: 1, 5 or 25 vials per carton.
Not all package 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 6.1.

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.

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**

Genzyme Europe B.V., Gooimeer 10, 1411 DD Naarden, 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 product is available on the website of the European Medicines Agency http://www.ema.europa.eu
ANNEX II

A.  MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORITY RESPONSIBLE FOR BATCH RELEASE

B.  CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C.  OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

D.  CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Genzyme Corporation
500 Soldiers Field Road – Allston, MA 02134 – USA

Name and address of the manufacturer responsible for batch release

Genzyme Ltd. 37 Hollands Road – Haverhill, Suffolk CB9 8PU - UK
Genzyme Ireland Ltd., 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

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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

The 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- 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 AND THE IMMEDIATE PACKAGING

OUTER CARTON/VIAL

1. NAME OF THE MEDICINAL PRODUCT

Cerezyme 200 U Powder for concentrate for solution for infusion imiglucerase

2. STATEMENT OF ACTIVE SUBSTANCE

Each vial contains 200 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.
25 vials of powder for concentrate for solution for infusion.

5. METHOD AND ROUTE OF ADMINISTRATION

For intravenous infusion.
Read the package leaflet before use.

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

Keep out of the reach and sight 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

Marketing Authorisation Holder:
Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden-NL

12. MARKETING AUTHORIZATION NUMBERS

EU/1/97/053/001
EU/1/97/053/002

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Cerezyme 200 U
### MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

**LABEL/VIAL**

<table>
<thead>
<tr>
<th>1.</th>
<th>NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION</th>
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<td><strong>Cerezyme 200 U</strong> Powder for concentrate for solution for infusion imiglucerase</td>
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<th>2.</th>
<th>METHOD OF ADMINISTRATION</th>
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<td>For intravenous infusion.</td>
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<th>3.</th>
<th>EXPIRY DATE</th>
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<th>BATCH NUMBER</th>
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<td>Batch:</td>
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<th>5.</th>
<th>CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
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<tbody>
<tr>
<td></td>
<td>Each vial contains 200 units of imiglucerase.</td>
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</tbody>
</table>

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<tr>
<th>6.</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Genzyme Europe B.V.-NL</td>
</tr>
<tr>
<td></td>
<td>Store in a refrigerator</td>
</tr>
</tbody>
</table>
PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON/VIAL

1. NAME OF THE MEDICINAL PRODUCT

_Cerezyme 400 U_ 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

For intravenous infusion.
Read the package leaflet before use.

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

Keep out of the reach and sight 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**

Marketing Authorisation Holder:
Genzyme Europe B.V.
Gooimeer 10
1411 DD Naarden-NL

12. **MARKETING AUTHORIZATION NUMBERS**

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

13. **BATCH NUMBER**

Batch:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

Medicinal product subject to medical prescription.

15. **INSTRUCTIONS ON USE**

16. **INFORMATION IN BRAILLE**

Cerezyme 400 U
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL/VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Cerezyme 400 U Powder for concentrate for solution for infusion
imiglucerase

2. METHOD OF ADMINISTRATION

For intravenous infusion.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each vial contains 400 units of imiglucerase

6. OTHER

Genzyme Europe B.V.-NL

Store in a refrigerator
B. PACKAGE LEAFLET
PACKAGE LEAFLET: INFORMATION FOR THE USER

Cerezyme 200 U powder for concentrate for solution for infusion
Imiglucerase

Read all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Cerezyme is and what it is used for.
2. Before you use Cerezyme.
3. How to use Cerezyme.
4. Possible side effects.
5. How to store Cerezyme.
6. Further Information

1. WHAT CEREZYME IS AND WHAT IT IS USED FOR

Cerezyme 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. BEFORE YOU USE CEREZYME

Do not use Cerezyme
- If you are allergic (hypersensitive) to imiglucerase, or
- if you are allergic to any of the other ingredients of Cerezyme.

Take special care with Cerezyme
- If you are treated with Cerezyme, you may experience an allergic reaction while you are being given the medicine or shortly after. If you experience a reaction like this, you should **tell your doctor immediately**. 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.
Using other medicines
Please 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
Ask your doctor or pharmacist for advice before using this medicine if you are pregnant or think you may be pregnant. Cautious use of Cerezyme during pregnancy and breastfeeding is recommended.

Important information about some of the ingredients of Cerezyme
This medicinal product contains sodium and is administered in 0.9% sodium chloride intravenous solution. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE CEREZYME

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 of Cerezyme 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 an 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, Cerezyme can cause side effects, although not everybody gets them.

If you experience any serious side effects or side effects not listed below, please tell your doctor immediately.

Common side effects (occurring in more than 1 in 100 patients) are:
- breathlessness
- coughing
- hives/localised swelling of the skin or lining of the mouth or throat
- itching
- rash

Uncommon side effects (occurring in more than 1 in 1000 patients) are:
- 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

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, 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).

If any of these side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CEREZYME

Keep out of the reach and sight of children.

Do not use Cerezyme after the expiry date printed on the labelling after the letters “EXP”. The expiry date refers to the last date 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER 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 200 units of imiglucerase. After reconstitution, the solution contains 40 units of imiglucerase per ml.
- Other ingredients are:
  - Mannitol, Sodium citrate, Citric acid monohydrate, Polysorbate 80

What Cerezyme looks like and contents of the pack
Cerezyme, 200 U, is presented as a powder for concentrate for solution for infusion (in a vial- pack size of 1 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
Genzyme Europe B.V., Gooimeer 10, 1411 DD, Naarden, The Netherlands

Manufacturer
Genzyme Ltd., 37 Hollands Road, Haverhill, Suffolk CB9 8PU, United Kingdom
Genzyme Ireland Ltd., 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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United Kingdom/Ireland
Genzyme Therapeutics Ltd. (United Kingdom)
Tel: +44 (0) 1865 405200
The following information is intended for medical or 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 200 units of imiglucerase in 5.0 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 5.1 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 5.3 ml. The pH of the reconstituted solution is approximately 6.1.

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 5.0 ml (equal to 200 units) from each vial. Withdraw 5.0 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.
Cerezyme 400 U powder for concentrate for solution for infusion
Imiglucerase

Read all of this leaflet carefully before you start using this medicine.
- 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. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet. please tell your doctor or pharmacist.

In this leaflet:
1. What Cerezyme is and what it is used for.
2. Before you use Cerezyme.
3. How to use Cerezyme.
4. Possible side effects.
5. How to store Cerezyme.
6. Further Information

1. WHAT CEREZYME IS AND WHAT IT IS USED FOR

Cerezyme 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 bleeding 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. BEFORE YOU USE CEREZYME

Do not use Cerezyme
- If you are allergic (hypersensitive) to imiglucerase, or
- if you are allergic to any of the other ingredients of Cerezyme.

Take special care with Cerezyme
- If you are treated with Cerezyme, you may experience an allergic reaction while you are being given the medicine or shortly after. If you experience a reaction like this, you should tell your doctor immediately. 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.
Using other medicines
Please 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
Ask your doctor or pharmacist for advice before using this medicine if you are pregnant or think you may be pregnant. Cautious use of Cerezyme during pregnancy and breastfeeding is recommended.

Important information about some of the ingredients of Cerezyme
This medicinal product contains sodium and is administered in 0.9% sodium chloride intravenous solution. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE CEREZYME

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 of Cerezyme 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, Cerezyme can cause side effects, although not everybody gets them.

If you experience any serious side effects or side effects not listed below, please tell your doctor immediately.

**Common side effects** (occurring in more than 1 in 100 patients) are:
- breathlessness
- coughing
- hives/localised swelling of the skin or lining of the mouth or throat
- itching
- rash

**Uncommon side effects** (occurring in more than 1 in 1000 patients) are:
- 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

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, 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).

If any of these side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE CEREZYME

Keep out of the reach and sight of children.

Do not use Cerezyme after the expiry date printed on the labelling after the letters “EXP”. The expiry date refers to the last date 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER 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.
- Other ingredients are:
  - Mannitol, Sodium citrate, Citric acid monohydrate, Polysorbate 80

What Cerezyme looks like and contents of the pack
Cerezyme, 400 U, 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

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Genzyme Europe B.V., Gooimeer 10, 1411 DD, Naarden, The Netherlands

Manufacturer
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Genzyme Ireland Ltd., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland
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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 6.1.

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.