ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fabrazyme 35 mg powder for concentrate for solution for infusion
Fabrazyme 5 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fabrazyme 35 mg powder for concentrate for solution for infusion
Each vial of Fabrazyme contains a nominal value of 35 mg of agalsidase beta. After reconstitution with 7.2 ml water for injections, each vial of Fabrazyme contains 5 mg/ml (35 mg/7 ml) of agalsidase beta. The reconstituted solution must be diluted further (see section 6.6).

Fabrazyme 5 mg powder for concentrate for solution for infusion
Each vial of Fabrazyme contains a nominal value of 5 mg of agalsidase beta. After reconstitution with 1.1 ml water for injections, each vial of Fabrazyme contains 5 mg/ml of agalsidase beta. The reconstituted solution must be diluted further (see section 6.6).

Agalsidase beta is a recombinant form of human α-galactosidase A and is produced by recombinant DNA technology using a mammalian Chinese Hamster Ovary (CHO) cell culture. The amino acid sequence of the recombinant form, as well as the nucleotide sequence which encoded it, are identical to the natural form of α-galactosidase A.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
White to off-white lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fabrazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency).

Fabrazyme is indicated in adults, children and adolescents aged 8 years and older.

4.2 Posology and method of administration

Fabrazyme treatment should be supervised by a physician experienced in the management of patients with Fabry disease or other inherited metabolic diseases.

Posology
The recommended dose of Fabrazyme is 1 mg/kg body weight administered once every 2 weeks as an intravenous infusion.

Lower dosing regimens have been used in clinical studies. In one of these studies, performed in adult male patients, after an initial dose of 1.0 mg/kg every 2 weeks for 6 months, 0.3 mg/kg every 2 weeks may maintain clearance of GL-3 in certain cell types in some patients; however, the long term clinical relevance of these findings has not been established (see section 5.1).

The initial infusion rate should be no more than 0.25 mg/min (15 mg/hour) to minimise the potential occurrence of infusion-associated reactions. After patient tolerance is established, the infusion rate may be increased gradually with subsequent infusions.

Infusion of Fabrazyme at home may be considered for patients who are tolerating their infusions well. The decision to have a patient move to home infusion should be made after evaluation and recommendation by the treating physician. Patients experiencing adverse events during the home 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 healthcare professional.

Special populations
Renal impairment
No dose adjustment is necessary for patients with renal insufficiency.

Hepatic impairment
Studies in patients with hepatic insufficiency have not been performed.

Elderly
The safety and efficacy of Fabrazyme in patients older than 65 years have not been established and no dosage regimen can presently be recommended in these patients.

Paediatric population
The safety and efficacy of Fabrazyme in children aged 0 to7 years have not yet been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on posology can be made in children aged 5 to 7 years. No data are available in children 0 to 4 years
No dose adjustment is necessary for children 8-16 years

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

4.3 Contraindications

Life threatening hypersensitivity (anaphylactic reaction) to the active substance or any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Immunogenicity
Since agalsidase beta (r-hαGAL) is a recombinant protein, the development of IgG antibodies is expected in patients with little or no residual enzyme activity. The majority of patients developed IgG antibodies to r-hαGAL, typically within 3 months of the first infusion with Fabrazyme. Over time, the majority of seropositive patients in clinical trials demonstrated either a downward trend in titers (based on a ≥ 4-fold reduction in titer from the peak measurement to the last measurement) (40% of the patients), tolerised (no detectable antibodies confirmed by 2 consecutive radioimmuno-precipitation (RIP) assays) (14% of the patients) or demonstrated a plateau (35% of the patients).

Infusion associated reactions
Patients with antibodies to r-hαGAL have a greater potential to experience infusion-associated reactions (IARs), which are defined as any related adverse event occurring on the infusion day. These patients should be treated with caution when re-administering agalsidase beta (see section 4.8). Antibody status should be regularly monitored.

In clinical trials, sixty seven percent (67 %) of the patients experienced at least one infusion-associated reaction (see section 4.8). The frequency of IARs decreased over time. Patients experiencing mild or moderate infusion-associated reactions when treated with agalsidase beta during clinical trials have continued therapy after a reduction in the infusion rate (~0.15 mg/min; 10 mg/hr) and/or pre-treatment with antihistamines, paracetamol, ibuprofen and/or corticosteroids.

Hypersensitivity
As with any intravenous protein medicinal product, allergic-type hypersensitivity reactions are possible.

A small number of patients have experienced reactions suggestive of immediate (Type I) hypersensitivity. If severe allergic or anaphylactic-type reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered and appropriate treatment initiated. The current medical standards for emergency treatment are to be observed. With careful rechallenge Fabrazyme has been re-administered to all 6 patients who tested positive for IgE antibodies or had a positive skin test to Fabrazyme in a clinical trial. In this trial, the initial rechallenge administration was at a low dose and a lower infusion rate ($^1/_2$ the therapeutic dose at $^1/_{25}$ the initial standard recommended rate). Once a patient tolerates the infusion, the dose may be increased to reach the therapeutic dose of 1 mg/kg and the infusion rate may be increased by slowly titrating upwards, as tolerated.

Patients with advanced renal disease
The effect of Fabrazyme treatment on the kidneys may be limited in patients with advanced renal disease.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies and no *in vitro* metabolism studies have been performed. Based on its metabolism, agalsidase beta is an unlikely candidate for cytochrome P450 mediated drug-drug interactions.

Fabrazyme should not be administered with chloroquine, amiodarone, benoquin or gentamycin due to a theoretical risk of inhibition of intra-cellular α-galactosidase A activity.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of agalsidase beta in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal development (see section 5.3).

Fabrazyme should not be used during pregnancy unless clearly necessary.

Breast-feeding
Agalsidase beta may be excreted in milk. Because there are no data available on effects in neonates exposed to agalsidase beta via breast milk, it is recommended to stop breast-feeding when Fabrazyme is used.

Fertility
Studies have not been conducted to assess the potential effects of Fabrazyme on impairment of fertility.

4.7 Effects on ability to drive and use machines

Fabrazyme may have a minor influence on the ability to drive or use machines on the day of Fabrazyme administration because dizziness, somnolence, vertigo and syncope may occur (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Since agalsidase beta (r-hαGAL) is a recombinant protein, the development of IgG antibodies is expected in patients with little or no residual enzyme activity. Patients with antibodies to r-hαGAL have a greater potential to experience infusion-associated reactions (IARs). Reactions suggestive of

immediate (Type I) hypersensitivity have been reported in a small number of patients (see section 4.4).

Very common adverse reactions included chills, pyrexia, feeling cold, nausea, vomiting, headache and paraesthesia. Sixty seven percent (67%) of the patients experienced at least one infusion-associated reaction. Anaphylactoid reactions have been reported in the postmarketing setting.

Tabulated list of adverse reactions

Adverse reactions reported from clinical trials with a total of 168 patients (154 males and 14 females) treated with Fabrazyme administered at a dose of 1 mg/kg every 2 weeks for a minimum of one infusion up to a maximum of 5 years are listed by System Organ Class and frequency (very common ≥ 1/10; common ≥ 1/100 to < 1/10 and uncommon ≥ 1/1000 to < 1/100) in the table below. The occurrence of an adverse reaction in a single patient is defined as uncommon in light of the relatively small number of patients treated. Adverse reactions only reported during the Post Marketing period are also included in the table below at a frequency category of “not known” (cannot be estimated from the available data). Adverse reactions were mostly mild to moderate in severity:

Incidence of adverse reactions with Fabrazyme treatment

System organ class	Very common	Common	Uncommon	Not known
Infections and infestations	---	nasopharyngitis	rhinitis	
Immune system disorders	---	---	---	anaphylactoid reaction
Nervous system disorders	headache, paraesthesia	dizziness, somnolence, hypoaesthesia, burning sensation, lethargy, syncope	hyperaesthesia, tremor	---
Eye disorders	---	lacrimation increased	eye pruritus, ocular hyperaemia	---
Ear and labyrinth disorders	---	tinnitus, vertigo	auricular swelling, ear pain	---
Cardiac Disorders	---	tachycardia, palpitations, bradycardia	sinus bradycardia	---
Vascular disorders	---	flushing, hypertension, pallor, hypotension, hot flush	peripheral coldness	---
Respiratory, thoracic and mediastinal disorders	---	dyspnoea, nasal congestion, throat tightness, wheezing, cough, dyspnoea exacerbated	bronchospasm, pharyngolaryngeal pain, rhinnorhoea, tachypnoea, upper respiratory tract congestion	hypoxia
Gastrointestinal Disorders	nausea, vomiting	abdominal pain, abdominal pain upper, abdominal discomfort, stomach discomfort, hypoaesthesia oral, diarrhoea	dyspepsia, dysphagia	---
Skin and subcutaneous tissue disorders	---	pruritus, urticaria, rash, erythema, pruritus generalized, angioneurotic oedema, swelling face, rash maculo-papular	livedo reticularis, rash erythematous, rash pruritic, skin discolouration, skin discomfort	leukocytoclastic vasculitis
Musculoskeletal and connective tissue disorders	---	pain in extremity, myalgia, back pain, muscle spasms, arthralgia, muscle tightness, musculoskeletal stiffness	musculoskeletal pain	---
General disorders and administration site conditions	chills, pyrexia, feeling cold	fatigue, chest discomfort, feeling hot, oedema peripheral, pain, asthenia, chest pain, face oedema, hyperthermia	feeling hot and cold, influenza-like illness, infusion site pain, infusion site reaction, injection site thrombosis, malaise, oedema	---
Investigations				oxygen saturation decreased

For the purpose of this table, ≥1% is defined as reactions occurring in 2 or more patients.
Adverse reaction terminology is based upon the Medical Dictionary for Regulatory Activities (MedDRA)

Description of selected adverse reactions

Infusion associated reactions

Infusion associated reactions consisted most often of fever and chills. Additional symptoms included mild or moderate dyspnoea, hypoxia (oxygen saturation decreased), throat tightness, chest discomfort, flushing, pruritus, urticaria, face oedema, angioneurotic oedema, rhinitis, bronchospasm, tachypnoea, wheezing, hypertension, hypotension, tachycardia, palpitations, abdominal pain, nausea, vomiting, infusion-related pain including pain at the extremities, myalgia, and headache.

The infusion-associated reactions were managed by a reduction in the infusion rate together with the administration of non-steroidal anti-inflammatory medicinal products, antihistamines and/or corticosteroids. Sixty seven percent (67%) of the patients experienced at least one infusion-associated reaction. The frequency of these reactions decreased over time. The majority of these reactions can be attributed to the formation of IgG antibodies and/or complement activation. In a limited number of patients IgE antibodies were demonstrated (see section 4.4).

Paediatric population

Limited information from clinical trials suggests that the safety profile of Fabrazyme treatment in paediatric patients ages 5-7, treated with either 0.5 mg/kg every 2 weeks or 1.0 mg/kg every 4 weeks is similar to that of patients (above the age of 7) treated at 1.0 mg/kg every 2 weeks.

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

In clinical trials doses up to 3 mg/kg body weight were used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, enzymes. ATC code: A16AB04.

Fabry disease

Fabry disease is an inherited heterogeneous and multisystemic progressive disease, that affects both males and females. It is characterised by the deficiency of α-galactosidase. Reduced or absent α-galactosidase activity results in the accumulation of GL-3 in the lysosomes of many cell types including the endothelial and parenchymal cells, ultimately leading to life-threatening clinical deteriorations as a result of renal, cardiac and cerebrovascular complications.

Mechanism of action

The rationale for enzyme replacement therapy is to restore a level of enzymatic activity sufficient to clear the accumulating substrate in the organ tissues; thereby, preventing, stabilizing or reversing the progressive decline in function of these organs before irreversible damage has occurred.

After intravenous infusion, agalsidase beta is rapidly removed from the circulation and taken up by vascular endothelial and parenchymal cells into lysosomes, likely through the mannose-6 phosphate, mannose and asialoglycoprotein receptors.

Clinical efficacy and safety

Efficacy and safety of Fabrazyme was evaluated in two studies with children, one dose-finding study, two double-blind placebo-controlled studies, and one open-label extension study in both male and female patients.

In the dose finding study, the effects of 0.3, 1.0 and 3.0 mg/kg once every 2 weeks and 1.0 and 3.0 mg/kg once every 2 days were evaluated. A reduction in GL-3 was observed in kidney, heart, skin and plasma at all doses. Plasma GL-3 was cleared in a dose dependent manner, but was less consistent at the dose of 0.3 mg/kg. In addition, infusion-associated reactions were dose dependent.

In the first placebo-controlled clinical trial, Fabrazyme was effective in clearing GL-3 from the vascular endothelium of the kidney after 20 weeks of treatment. This clearance was achieved in 69% (20/29) of the Fabrazyme treated patients, but in none of the placebo patients ($p<0.001$). This finding was further supported by a statistically significant decrease in GL-3 inclusions in kidney, heart and skin combined and in the individual organs in patients treated with agalsidase beta compared to placebo patients ($p<0.001$). Sustained clearance of GL-3 from kidney vascular endothelium upon agalsidase beta treatment was demonstrated further in the open label extension of this trial. This was achieved in 47 of the 49 patients (96%) with available information at month 6, and in 8 of the 8 patients (100%) with available information at the end of the study (up to a total of 5 years of treatment). Clearance of GL-3 was also achieved in several other cell types from the kidney. Plasma GL-3 levels rapidly normalised with treatment and remained normal through 5 years.

Renal function, as measured by glomerular filtration rate and serum creatinine, as well as proteinuria, remained stable in the majority of the patients. However, the effect of Fabrazyme treatment on the kidney function was limited in some patients with advanced renal disease.

Although no specific study has been conducted to assess the effect on the neurological signs and symptoms, the results also indicate that patients may achieve reduced pain and enhanced quality of life upon enzyme replacement therapy.

Another double-blind, placebo-controlled study of 82 patients was performed to determine whether Fabrazyme would reduce the rate of occurrence of renal, cardiac, or cerebrovascular disease or death. The rate of clinical events was substantially lower among Fabrazyme-treated patients compared to placebo-treated patients (risk reduction = 53% intent-to-treat population ($p=0.0577$); risk reduction = 61 % per-protocol population ($p=0.0341$)). This result was consistent across renal, cardiac and cerebrovascular events.

The results of these studies indicate that Fabrazyme treatment at 1 mg/kg every other week provides clinical benefit on key clinical outcomes in patients with early and advanced Fabry disease. Because this condition is slowly progressive, early detection and treatment is critical to achieve the best outcomes.

In an additional study, 21 male patients were enrolled to follow GL3 clearance in kidney and skin tissues at an alternative dosing regimen. Following treatment with 1 mg/kg every other week for 24 weeks, a dose regimen of 0.3 mg/kg every 2 weeks for 18 months was able to maintain the clearance of cellular GL-3 in the capillary endothelium of the kidney, other kidney cell types and skin (superficial skin capillary endothelium) in the majority of patients. However, at the lower dose, IgG antibodies may play a role with respect to GL-3 clearance in some patients. Due to the limitations of the study design (small number of patients), no definitive conclusion regarding the dose maintenance regimen can be drawn, but these findings suggest that, after an initial debulking dose of 1.0 mg/kg every 2 weeks, 0.3 mg/kg every 2 weeks may be sufficient in some patients to maintain clearance of GL-3.

In the postmarketing setting, experience was gained in patients who initiated treatment at a dose of 1 mg/kg every 2 weeks and subsequently received a reduced dose for an extended period. In some of these patients, an increase of some of the following symptoms was spontaneously reported: pain, paraesthesia and diarrhoea, as well as cardiac, central nervous system and renal manifestations. These reported symptoms resemble the natural course of Fabry disease.

Paediatric population
In one open-label paediatric study, sixteen patients with Fabry disease (8-16 years old; 14 males, 2 females) had been treated for one year at 1.0 mg/kg every 2 weeks. Clearance of GL-3 in the superficial skin vascular endothelium was achieved in all patients who had accumulated GL-3 at baseline. The 2 female patients had little or no GL-3 accumulation in the superficial skin vascular endothelium at baseline, making this conclusion applicable in male patients only.

In an additional 5-year open-label paediatric study, 31 male patients aged 5 to 18 years were randomized prior to the onset of clinical symptoms involving major organs and treated with two lower dose regimens of agalsidase beta, 0.5 mg/kg every 2 weeks or 1.0 mg/kg every 4 weeks. Results were similar between the two treatment groups. Superficial skin capillary endothelium GL-3 scores were reduced to zero or maintained at zero at all time points post-baseline upon treatment in 19/27 patients completing the study without a dose increase. Both baseline and 5-year kidney biopsies were obtained in a subset of 6 patients: in all, kidney capillary endothelium GL-3 scores were reduced to zero but highly variable effects were observed in podocyte GL-3, with a reduction in 3 patients. Ten (10) patients met per protocol dose increase criteria, two (2) had a dose increase to the recommended dose of 1.0 mg/kg every 2 weeks.

5.2 Pharmacokinetic properties

Following an intravenous administration of agalsidase beta to adults at doses of 0.3 mg, 1 mg and 3 mg/kg body weight, the AUC values increased more than dose proportional, due to a decrease in clearance, indicating a saturated clearance. The elimination half-life was dose independent and ranged from 45 to 100 minutes.

After intravenous administration of agalsidase beta to adults with an infusion time of approximately 300 minutes and at a dose of 1 mg/kg body weight, biweekly, mean C_{max} plasma concentrations ranged from 2000-3500 ng/ml, while the AUC_{inf} ranged from 370-780 µg min/ml. Vss ranged from 8.3-40.8 l, plasma clearance from 119-345 ml/min and the mean elimination half-life from 80-120 minutes.

Agalsidase beta is a protein and is expected to be metabolically degraded through peptide hydrolysis. Consequently, impaired liver function is not expected to affect the pharmacokinetics of agalsidase beta in a clinically significant way. Renal elimination of agalsidase beta is considered to be a minor pathway for clearance.

Paediatric population
Fabrazyme pharmacokinetics was also evaluated in two paediatric studies. In one of these studies, 15 paediatric patients with available pharmacokinetics data, aged 8.5 to 16 years weighing 27.1 to 64.9 kg were treated with 1.0 mg/kg every 2 weeks. Agalsidase beta clearance was not influenced by weight in this population. Baseline CL was 77 ml/min with a Vss of 2.6 l; half-life was 55 min. After IgG seroconversion, CL decreased to 35 ml/min, Vss increased to 5.4 l, and half-life increased to 240 min. The net effect of these changes after seroconversion was an increase in exposure of 2- to 3-fold based on AUC and C_{max}. No unexpected safety issues were encountered in patients with an increase in exposure after seroconversion.
In another study with 30 paediatric patients with available pharmacokinetics data, aged 5 to 18 years, treated with two lower dose regimens of 0.5 mg/kg every 2 weeks and 1.0 mg/kg every 4 weeks, mean CL was 4.6 and 2.3 ml/min/kg, respectively, mean Vss was 0.27 and 0.22 l/kg, respectively, and mean elimination half-life was 88 and 107 minutes, respectively. After IgG seroconversion, there was no apparent change in CL (+24% and +6%, resp.), while Vss was 1.8 and 2.2 fold higher, with the net effect being a small decrease in C_{max} (up to -34% and -11%, resp.) and no change in AUC (-19% and -6%, resp.).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, single dose toxicity, repeated dose toxicity and embryonal/foetal toxicity. Studies with regard to other stages of the development have not been carried out. Genotoxic and carcinogenic potential are not expected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium phosphate monobasic, monohydrate
Sodium phosphate dibasic, heptahydrate

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

Reconstituted and diluted solutions
From a microbiological 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. The reconstituted solution cannot be stored and should be promptly diluted; only the diluted solution can be held for up to 24 hours at 2°C-8°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

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

6.5 Nature and contents of container

Fabrazyme 35 mg powder for concentrate for solution for infusion
Fabrazyme 35 mg is supplied in clear Type I glass 20 ml vials. The closure consists of a siliconised butyl stopper and an aluminium seal with a plastic flip-off cap.

Package sizes: 1, 5 and 10 vials per carton.
Not all pack sizes may be marketed.

Fabrazyme 5 mg powder for concentrate for solution for infusion
Fabrazyme 5 mg is supplied in clear Type I glass 5 ml vials. The closure consists of a siliconised butyl stopper and an aluminium seal with a plastic flip-off cap.

Package sizes: 1, 5 and 10 vials per carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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. Use Aseptic Technique

Determine the number of vials to be reconstituted based on the individual patient's weight and remove the required vials from the refrigerator in order to allow them to reach room temperature (in approximately 30 minutes). Each vial of Fabrazyme is intended for single use only.

Reconstitution

Fabrazyme 35 mg powder for concentrate for solution for infusion
Reconstitute each vial of Fabrazyme 35 mg with 7.2 ml water for injections. Avoid forceful impact of the water for injections on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilized cake. Roll and tilt each vial gently. Do not invert, swirl or shake the vial.

Fabrazyme 5 mg powder for concentrate for solution for infusion
Reconstitute each vial of Fabrazyme 5 mg with 1.1 ml water for injections. Avoid forceful impact of the water for injections on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilized cake. Roll and tilt each vial gently. Do not invert, swirl or shake the vial.

The reconstituted solution contains 5 mg agalsidase beta per ml, and appears as a clear colourless solution. The pH of the reconstituted solution is approximately 7.0. Before further dilution, visually inspect the reconstituted solution in each vial for particulate matter and discoloration. Do not use the solution if foreign particles are observed or if the solution is discoloured.

After reconstitution it is recommended to promptly dilute the vials, to minimise protein particle formation over time.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Dilution

Fabrazyme 35 mg powder for concentrate for solution for infusion
Prior to adding the reconstituted volume of Fabrazyme required for the patient dose, it is recommended to remove an equal volume of 0.9% sodium chloride intravenous solution, from the infusion bag.

Remove the airspace within the infusion bag to minimize the air/liquid interface.

Slowly, withdraw 7.0 ml (equal to 35 mg) of the reconstituted solution from each vial up to the total volume required for the patient dose. Do not use filter needles and avoid foaming.

Then slowly inject the reconstituted solution directly into the 0.9% sodium chloride intravenous solution (not in any remaining airspace) to a final concentration between 0.05 mg/ml and 0.7 mg/ml. Determine the total volume of sodium chloride 0.9% solution for infusion (between 50 and 500 ml) based on the individual dose. For doses lower than 35 mg use a minimum of 50 ml, for doses 35 to 70 mg use a minimum of 100 ml, for doses 70 to 100 mg use a minimum of 250 ml and for doses greater than 100 mg use only 500 ml. Gently invert or lightly massage the infusion bag to mix the diluted solution. Do not shake or excessively agitate the infusion bag.

Fabrazyme 5 mg powder for concentrate for solution for infusion
Prior to adding the reconstituted volume of Fabrazyme required for the patient dose, it is recommended to remove an equal volume of 0.9% sodium chloride intravenous solution, from the infusion bag.

Remove the airspace within the infusion bag to minimize the air/liquid interface.

Slowly, withdraw 1.0 ml (equal to 5 mg) of the reconstituted solution from each vial up to the total volume required for the patient dose. Do not use filter needles and avoid foaming.

Then slowly inject the reconstituted solution directly into the 0.9% sodium chloride intravenous solution (not in any remaining airspace) to a final concentration between 0.05 mg/ml and 0.7 mg/ml. Determine the total volume of sodium chloride 0.9% solution for infusion (between 50 and 500 ml) based on the individual dose. For doses lower than 35 mg use a minimum of 50 ml, for doses 35 to 70 mg use a minimum of 100 ml, for doses 70 to 100 mg use a minimum of 250 ml and for doses greater than 100 mg use only 500 ml. Gently invert or lightly massage the infusion bag to mix the diluted solution. Do not shake or excessively agitate the infusion bag.

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 which will not lead to any loss of agalsidase beta activity. The initial infusion rate should be no more than 0.25 mg/min (15 mg/hour) to minimise the potential occurrence of infusion-associated reactions. After patient tolerance is established, the infusion rate may be increased gradually with subsequent infusions.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/188/001 Fabrazyme 35 mg 1 vial of powder for concentrate for solution for infusion
EU/1/01/188/002 Fabrazyme 35 mg 5 vials of powder for concentrate for solution for infusion
EU/1/01/188/003 Fabrazyme 35 mg 10 vials of powder for concentrate for solution for infusion
EU/1/01/188/004 Fabrazyme 5 mg 1 vial of powder for concentrate for solution for infusion
EU/1/01/188/005 Fabrazyme 5 mg 5 vials of powder for concentrate for solution for infusion
EU/1/01/188/006 Fabrazyme 5 mg 10 vials of powder for concentrate for solution for infusion

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 August 2001
Date of last renewal: 03 August 2006

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. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) 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. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Genzyme Corp.
45, 51, 68, 74, 76 and 80 New York Avenue
Framingham
MA 01701-9322
USA

Name and address of the manufacturer responsible for batch release

Genzyme Ltd.
37 Hollands Road
Haverhill
Suffolk CB9 8PU
United Kingdom

Genzyme Ireland Ltd.
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 requirements for submission of periodic safety update reports 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 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**

The Marketing Authorisation Holder (MAH) shall agree the details of the educational programme for Fabrazyme home infusion with the National Competent Authorities prior to implementing the programme nationally.

The MAH shall ensure that all Healthcare Professional who are expected to prescribe/use Fabrazyme are provided with an educational pack aiming to facilitate the training of the patients/caregivers and also to guide prescribers regarding patient evaluation and selection and organisational requirements for home infusion.

The educational pack should contain the following:
- Home infusion manual for healthcare professionals
- Home infusion manuals for patients
- Summary of Product Characteristics and Package Leaflet

The educational material for healthcare professionals should include information on the following key elements:
- Guidance regarding patient evaluation and selection and organisational requirements for home infusion.
- That it is the responsibility of the prescribing physician to determine which patients may be suitable for home or self-administration of Fabrazyme.
- That it is the responsibility of the prescribing physician to provide appropriate training to the non-healthcare professional, such as the patient for self-administration or a caregiver who will administer the treatment at home, if the treating physician decides that this is appropriate.
- Regular review of the administration by the patient and/or caregiver needs to be performed to ensure maintenance of optimal practice.
- The training to be provided to the patient and /or caregiver should address the following elements:
  - That it is essential to follow strictly the prescribed dose and infusion rate
  - Method of preparation and administration of Fabrazyme
  - Instructions in handling possible adverse events
  - Instruction to seek emergency treatment by healthcare professionals in the event of any adverse reactions during an infusion
  - The need to seek urgent treatment in the event of failure to gain venous access or if there is a lack of efficacy
  - The need to keep a diary to document each treatment received at home and to bring it at each visit
- It is the responsibility of the prescribing physician to verify that all necessary skills have been acquired by the non-healthcare professional and that Fabrazyme may be safely and effectively administered at home.

The educational material for patients should include information on the following key elements:
- The prescribing physician may decide that Fabrazyme may be administered at home. The level of support required for home infusion will be discussed and agreed by the patient and/or caregiver with the prescribing physician.
- The treating physician will be responsible for determining which patients may be suitable for home or self-administration of Fabrazyme and for arranging for treatment at home and training the patient and/or caregiver in the appropriate skills necessary for this.
- Necessary skills have to be acquired by non-healthcare professionals before Fabrazyme may be safely and effectively administered at home.

- Their prescribing physician will provide training on the following elements:
  - That it is essential to follow strictly the prescribed dose and infusion rate
  - Method of preparation and administration of Fabrazyme
  - Instructions in handling possible adverse events
  - Instruction to seek emergency treatment by healthcare professionals in the event of any adverse reactions during an infusion
  - The need to seek urgent treatment in the event of failure to gain venous access or if there is a lack of efficacy
  - The need to keep a diary to document each treatment received at home and to bring it at each visit

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (1 VIAL, 5 VIALS, 10 VIALS)

1. NAME OF THE MEDICINAL PRODUCT

Fabrazyme 35 mg powder for concentrate for solution for infusion
agalsidase beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 35 mg of agalsidase beta.

3. LIST OF EXCIPIENTS

Excipients:
mannitol
sodium phosphate monobasic, monohydrate
sodium phosphate dibasic, heptahydrate
See the leaflet for further information.

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.
10 vials of powder for concentrate for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous 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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).

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

Genzyme Europe B.V.
Gooimeer 10
1411DD Naarden - NL

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/188/001 1 vial of powder for concentrate for solution for infusion
EU/1/01/188/002 5 vials of powder for concentrate for solution for infusion
EU/1/01/188/003 10 vials of powder for concentrate for solution for infusion

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fabrazyme 35 mg

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

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Fabrazyme 35 mg powder for concentrate for solution for infusion
agalsidase beta
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Genzyme Europe B.V.-NL

Store in a refrigerator (2°C – 8°C).

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (1 VIAL, 5 VIALS, 10 VIALS)

1. NAME OF THE MEDICINAL PRODUCT

Fabrazyme 5 mg powder for concentrate for solution for infusion
agalsidase beta

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 5 mg of agalsidase beta.

3. LIST OF EXCIPIENTS

Excipients:
mannitol
sodium phosphate monobasic, monohydrate
sodium phosphate dibasic, heptahydrate
See the leaflet for further information.

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.
10 vials of powder for concentrate for solution for infusion.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous 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

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).

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

Genzyme Europe B.V.
Gooimeer 10
1411DD Naarden - NL

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/188/004 1 vial of powder for concentrate for solution for infusion
EU/1/01/188/005 5 vials of powder for concentrate for solution for infusion
EU/1/01/188/006 10 vials of powder for concentrate for solution for infusion

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Fabrazyme 5 mg

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

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Fabrazyme 5 mg powder for concentrate for solution for infusion
agalsidase beta
Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Genzyme Europe B.V.- NL

Store in a refrigerator (2°C – 8°C)

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Fabrazyme 35 mg powder for concentrate for solution for infusion
Agalsidase beta

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 Fabrazyme is and what it is used for

Fabrazyme contains the active substance agalsidase beta and is used as enzyme replacement therapy in Fabry disease, where the level of α-galactosidase enzyme activity is absent or lower than normal. If you suffer from Fabry disease a fat substance, called globotriaosylceramide (GL-3), is not removed from the cells of your body and starts to accumulate in the walls of the blood vessels of your organs.

Fabrazyme is indicated for use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease.

Fabrazyme is indicated in adults, children and adolescents aged 8 years and older.

2. What you need to know before you use Fabrazyme

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

Warnings and precautions
Talk to your doctor or pharmacist before using Fabrazyme.

If you are treated with Fabrazyme, you may develop infusion associated reactions. An infusion-associated 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.

Children and adolescents
No clinical studies have been performed in children 0-4 years old. The risks and benefits of Fabrazyme in children aged 5 to 7 years have not yet been established and therefore no dose can be recommended for this age group.

Other medicines and Fabrazyme
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Tell your doctor if you use any medicines containing chloroquine, amiodarone, benoquin or gentamicin. There is a theoretical risk of decreased agalsidase beta activity.

Pregnancy, breast-feeding and fertility
Use of Fabrazyme during pregnancy is not recommended. There is no experience with the use of Fabrazyme in pregnant women. Fabrazyme may get into breast milk. Use of Fabrazyme during breast-feeding is not recommended. Studies have not been performed to examine the effects of Fabrazyme on fertility.

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.

Driving and using machines
Do not drive or use machines if you experience dizziness, sleepiness, vertigo or fainting during or shortly after administration of Fabrazyme (see section 4). Talk to your doctor first.

3. How to use Fabrazyme

Fabrazyme 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 (see information for Health Care Professionals at the end of this leaflet).
Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Fabrazyme is only used under the supervision of a doctor who is knowledgeable in the treatment of Fabry 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.

The recommended dose of Fabrazyme for adults is 1 mg/kg body weight, once every 2 weeks. No changes in dose are necessary for patients with kidney disease.

Use in children and adolescents
The recommended dose of Fabrazyme for children and adolescents 8 – 16 years is 1 mg/kg body weight, once every 2 weeks. No changes in dose are necessary for patients with kidney disease.

If you use more Fabrazyme than you should
Doses up to 3 mg/kg body weight have shown to be safe.

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

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

4. Possible side effects

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

In clinical studies side effects were mainly seen while patients were being given the medicine or shortly after (“infusion related reactions”). Severe life-threatening allergic reactions (“anaphylactoid reactions”) have been reported in some patients. If you experience any serious side effect, you should **contact your doctor immediately**.

Very common symptoms (may affect more than 1 in 10 people) include chills, fever, feeling cold, nausea, vomiting, headache and abnormal feelings in the skin such as burning or tingling. Your doctor may decide to lower the infusion rate or give you additional medicines to prevent such reactions from occurring.

List of other side effects:

Common (may affect up to 1 in 10 people):

- chest pain
- difficulty in breathing
- pallor
- itching
- abnormal tear secretion
- feeling weak
- tinnitus
- nasal congestion
- diarrhoea
- redness
- muscle pain
- increased blood pressure
- sudden swelling of the face or throat
- oedema in extremities
- vertigo
- stomach discomfort
- muscle spasms
- sleepiness
- increased heart beat
- abdominal pain
- back pain
- rash
- low heart rate
- lethargy
- syncope
- cough
- abdominal discomfort
- swelling face
- joint pain
- decreased blood pressure
- chest discomfort
- face oedema
- exacerbated difficulty in breathing
- muscle tightness
- fatigue
- flushing
- pain
- throat tightness
- dizziness
- palpitations
- decreased sensitivity to pain
- burning sensation
- wheezing
- urticaria
- pain at the extremities
- nasopharyngitis
- hot flush
- feeling hot
- hyperthermia
- decreased mouth sensitivity
- musculoskeletal stiffness

Uncommon (may affect up to 1 in 100 people):

- tremor
- red eyes
- ear pain
- throat pain
- fast breathing
- itchy rash
- feeling hot and cold
- difficulty swallowing
- infusion site pain
- infusion site reaction
- itching eyes
- ear swelling
- bronchospasm
- runny nose
- heart burn
- skin discomfort
- musculoskeletal pain
- rhinitis
- influenza-like illness
- malaise
- low heart rate due to conduction disturbances
- increased sensitivity to pain
- upper respiratory tract congestion
- red rash
- (mottled purplish) skin discoloration
- coldness of the extremities
- injection site blood clotting
- skin discoloration
- oedema

Not known (frequency cannot be estimated from the available data):

- lower blood oxygen levels
- serious inflammation of the vessels

In some patients initially treated at the recommended dose, and whose dose was later reduced for an extended period, some symptoms of Fabry disease were reported more frequently.

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 to store Fabrazyme

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

Do not use this medicine after the expiry date which is stated on the label after 'EXP'. The expiry date refers to the last day of that month.

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

Reconstituted and diluted solutions
The reconstituted solution cannot be stored and should be promptly diluted. The diluted solution can be held for up to 24 hours at 2°C – 8°C.

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 Fabrazyme contains
- The active substance is agalsidase beta, one vial contains 35 mg.
- The other ingredients are:
  - Mannitol
  - Sodium phosphate monobasic, monohydrate
  - Sodium phosphate dibasic, heptahydrate.

What Fabrazyme looks like and contents of the pack
Fabrazyme 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.
Package sizes: 1, 5 and 10 vials per carton. Not all pack sizes may be marketed.

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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This leaflet was last revised in

Other sources of information

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.

The following information is intended for healthcare professionals only:

Instructions for use – reconstitution, dilution and administration

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.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage and conditions are the responsibility of the user. The reconstituted solution cannot be stored and should be promptly diluted; only the diluted solution can be held for up to 24 hours at 2ºC -8ºC.

Use Aseptic Technique

1. Determine the number of vials to be reconstituted based on the individual patient's weight and remove the required vials from the refrigerator in order to allow them to reach room temperature (in approximately 30 minutes). Each vial of Fabrazyme is intended for single use only.

Reconstitution

2. Reconstitute each vial of Fabrazyme 35 mg with 7.2 ml water for injections. Avoid forceful impact of the water for injections on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilized cake. Roll and tilt each vial gently. Do not invert, swirl or shake the vial.

3. The reconstituted solution contains 5 mg agalsidase beta per ml, and appears as a clear colourless solution. The pH of the reconstituted solution is approximately 7.0. Before further dilution, visually inspect the reconstituted solution in each vial for particulate matter and discoloration. Do not use the solution if foreign particles are observed or if the solution is discoloured.

4. After reconstitution it is recommended to promptly dilute the vials, to minimise protein particle formation over time.

5. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Dilution

6. Prior to adding the reconstituted volume of Fabrazyme required for the patient dose, it is recommended to remove an equal volume of 0.9% sodium chloride intravenous solution, from the infusion bag.

7. Remove the airspace within the infusion bag to minimize the air/liquid interface.

8. Slowly, withdraw 7.0 ml (equal to 35 mg) of the reconstituted solution from each vial up to the total volume required for the patient dose. Do not use filter needles and avoid foaming.

9. Then slowly inject the reconstituted solution directly into the 0.9% sodium chloride intravenous solution (not in any remaining airspace) to a final concentration between 0.05 mg/ml and 0.7 mg/ml. Determine the total volume of sodium chloride 0.9% solution for infusion (between 50 and 500 ml) based on the individual dose. For doses lower than 35 mg use a minimum of 50 ml, for doses 35 to 70 mg use a minimum of 100 ml, for doses 70 to 100 mg use a minimum of 250 ml and for doses greater than 100 mg use only 500 ml. Gently invert or lightly massage the infusion bag to mix the diluted solution. Do not shake or excessively agitate the infusion bag.

Administration

10. It is recommended to administer the diluted solution through an in-line low protein-binding 0.2 µm filter to remove any protein particles which will not lead to any loss of agalsidase beta activity. The initial infusion rate should be no more than 0.25 mg/min (15 mg/hour) to minimise the potential occurrence of infusion-associated reactions. After patient tolerance is established, the infusion rate may be increased gradually with subsequent infusions.

Package leaflet: Information for the user

Fabrazyme 5 mg powder for concentrate for solution for infusion
Agalsidase beta

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 Fabrazyme is and what it is used for

Fabrazyme contains the active substance agalsidase beta and is used as enzyme replacement therapy in Fabry disease, where the level of α-galactosidase enzyme activity is absent or lower than normal. If you suffer from Fabry disease a fat substance, called globotriaosylceramide (GL-3), is not removed from the cells of your body and starts to accumulate in the walls of the blood vessels of your organs.

Fabrazyme is indicated for use as long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease.

Fabrazyme is indicated in adults, children and adolescents aged 8 years and older.

2. What you need to know before you use Fabrazyme

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

Warnings and precautions
Talk to your doctor or pharmacist before using Fabrazyme.

If you are treated with Fabrazyme, you may develop infusion associated reactions. An infusion-associated 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.

Children and adolescents
No clinical studies have been performed in children 0-4 years old. The risks and benefits of Fabrazyme in children aged 5 to 7 years have not yet been established and therefore no dose can be recommended for this age group.

Other medicines and Fabrazyme
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.
Tell your doctor if you use any medicines containing chloroquine, amiodarone, benoquin or gentamicin. There is a theoretical risk of decreased agalsidase beta activity.

Pregnancy, breast-feeding and fertility
Use of Fabrazyme during pregnancy is not recommended. There is no experience with the use of Fabrazyme in pregnant women. Fabrazyme may get into breast milk. Use of Fabrazyme during breast-feeding is not recommended. Studies have not been performed to examine the effects of Fabrazyme on fertility.

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.

Driving and using machines
Do not drive or use machines if you experience dizziness, sleepiness, vertigo or fainting during or shortly after administration of Fabrazyme (see section 4). Talk to your doctor first.

3. How to use Fabrazyme

Fabrazyme 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 (see information for Health Care Professionals at the end of this leaflet).
Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Fabrazyme is only used under the supervision of a doctor who is knowledgeable in the treatment of Fabry 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.

The recommended dose of Fabrazyme for adults is 1 mg/kg body weight, once every 2 weeks. No changes in dose are necessary for patients with kidney disease.

Use in children and adolescents
The recommended dose of Fabrazyme for children and adolescents 8 – 16 years is 1 mg/kg body weight, once every 2 weeks. No changes in dose are necessary for patients with kidney disease.

If you use more Fabrazyme than you should
Doses up to 3 mg/kg body weight have shown to be safe.

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

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

4. Possible side effects

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

In clinical studies side effects were mainly seen while patients were being given the medicine or shortly after (“infusion related reactions”). Severe life-threatening allergic reactions (“anaphylactoid reactions”) have been reported in some patients. If you experience any serious side effect, you should **contact your doctor immediately.**

Very common symptoms (may affect more than 1 in 10 people) include chills, fever, feeling cold, nausea, vomiting, headache and abnormal feelings in the skin such as burning or tingling. Your doctor may decide to lower the infusion rate or give you additional medicines to prevent such reactions from occurring.

List of other side effects:

Common (may affect up to 1 in 10 people):

- chest pain
- difficulty in breathing
- pallor
- itching
- abnormal tear secretion
- feeling weak
- tinnitus
- nasal congestion
- diarrhoea
- redness
- muscle pain
- increased blood pressure
- sudden swelling of the face or throat
- oedema in extremities
- vertigo
- stomach discomfort
- muscle spasms
- sleepiness
- increased heart beat
- abdominal pain
- back pain
- rash
- low heart rate
- lethargy
- syncope
- cough
- abdominal discomfort
- swelling face
- joint pain
- decreased blood pressure
- chest discomfort
- face oedema
- exacerbated difficulty in breathing
- muscle tightness
- fatigue
- flushing
- pain
- throat tightness
- dizziness
- palpitations
- decreased sensitivity to pain
- burning sensation
- wheezing
- urticaria
- pain at the extremities
- nasopharyngitis
- hot flush
- feeling hot
- hyperthermia
- decreased mouth sensitivity
- musculoskeletal stiffness

Uncommon (may affect up to 1 in 100 people):

- tremor
- red eyes
- ear pain
- throat pain
- fast breathing
- itchy rash
- feeling hot and cold
- difficulty swallowing
- infusion site pain
- infusion site reaction
- itching eyes
- ear swelling
- bronchospasm
- runny nose
- heart burn
- skin discomfort
- musculoskeletal pain
- rhinitis
- influenza-like illness
- malaise
- low heart rate due to conduction disturbances
- increased sensitivity to pain
- upper respiratory tract congestion
- red rash
- (mottled purplish) skin discoloration
- coldness of the extremities
- injection site blood clotting
- skin discoloration
- oedema

Not known (frequency cannot be estimated from the available data):

- lower blood oxygen levels
- serious inflammation of the vessels

In some patients initially treated at the recommended dose, and whose dose was later reduced for an extended period, some symptoms of Fabry disease were reported more frequently.

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 to store Fabrazyme

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

Do not use this medicine after the expiry date which is stated on the label after 'EXP'. The expiry date refers to the last day of that month.

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

Reconstituted and diluted solutions
The reconstituted solution cannot be stored and should be promptly diluted. The diluted solution can be held for up to 24 hours at 2°C – 8°C.

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 Fabrazyme contains
- The active substance is agalsidase beta, one vial contains 5 mg.
- The other ingredients are:
  - Mannitol
  - Sodium phosphate monobasic, monohydrate
  - Sodium phosphate dibasic, heptahydrate.

What Fabrazyme looks like and contents of the pack
Fabrazyme 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.
Package sizes: 1, 5 and 10 vials per carton. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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Manufacturer
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Other sources of information

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.

The following information is intended for healthcare professionals only:

Instructions for use – reconstitution, dilution and administration

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.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage and conditions are the responsibility of the user. The reconstituted solution cannot be stored and should be promptly diluted; only the diluted solution can be held for up to 24 hours at 2ºC -8ºC.

Use Aseptic Technique

1. Determine the number of vials to be reconstituted based on the individual patient's weight and remove the required vials from the refrigerator in order to allow them to reach room temperature (in approximately 30 minutes). Each vial of Fabrazyme is intended for single use only.

Reconstitution

2. Reconstitute each vial of Fabrazyme 5 mg with 1.1 ml water for injections. Avoid forceful impact of the water for injections on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilized cake. Roll and tilt each vial gently. Do not invert, swirl or shake the vial.

3. The reconstituted solution contains 5 mg agalsidase beta per ml, and appears as a clear colourless solution. The pH of the reconstituted solution is approximately 7.0. Before further dilution, visually inspect the reconstituted solution in each vial for particulate matter and discoloration. Do not use the solution if foreign particles are observed or if the solution is discoloured.

4. After reconstitution it is recommended to promptly dilute the vials, to minimise protein particle formation over time.

5. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Dilution

6. Prior to adding the reconstituted volume of Fabrazyme required for the patient dose, it is recommended to remove an equal volume of 0.9% sodium chloride intravenous solution, from the infusion bag.

7. Remove the airspace within the infusion bag to minimize the air/liquid interface.

8. Slowly, withdraw 1.0 ml (equal to 5 mg) of the reconstituted solution from each vial up to the total volume required for the patient dose. Do not use filter needles and avoid foaming.

9. Then slowly inject the reconstituted solution directly into the 0.9% sodium chloride intravenous solution (not in any remaining airspace) to a final concentration between 0.05 mg/ml and 0.7 mg/ml. Determine the total volume of sodium chloride 0.9% solution for infusion (between 50 and 500 ml) based on the individual dose. For doses lower than 35 mg use a minimum of 50 ml, for doses 35 to 70 mg use a minimum of 100 ml, for doses 70 to 100 mg use a minimum of 250 ml and for doses greater than 100 mg use only 500 ml. Gently invert or lightly massage the infusion bag to mix the diluted solution. Do not shake or excessively agitate the infusion bag.

Administration

10. It is recommended to administer the diluted solution through an in-line low protein-binding 0.2 µm filter to remove any protein particles which will not lead to any loss of agalsidase beta activity. The initial infusion rate should be no more than 0.25 mg/min (15 mg/hour) to minimise the potential occurrence of infusion-associated reactions. After patient tolerance is established, the infusion rate may be increased gradually with subsequent infusions.