

Fabrazyme® (agalsidase beta) Home Infusion Therapy:

Risk Minimisation Information for Healthcare Professionals

A Guide for Healthcare Professionals Treating

Patients with Fabry Disease

Essential Non-Promotional Information

Do not discard

Version No: 1.2 (Ireland): May 2015

(Based on EMA approved version No. 1.1: 19 September 2011)

The processes presented in this document serve as overall guidance but are subject to local medical practice and national rules and regulations

TABLE OF CONTENTS

1	OBJECTIVES AND GOALS.....	3
2	ASSESSING ELIGIBILITY FOR HOME INFUSION	4
3	REQUIREMENTS AND ORGANISATION OF HOME INFUSION	5
3.1	Patient	5
3.2	Treating Physician	5
3.3	Pharmacy and Infusion Equipment.....	6
3.4	Infusion Nurse	6
3.5	Pre-treatment and Emergency Treatment	7
3.6	The Logbook	8
4	TRAINING ON PREPARATION AND ADMINISTERING	
	FABRAZYME.....	9
5	ADMINISTRATION OF FABRAZYME.....	10
5.1	Prescription.....	10
5.2	Supplies	10
5.3	Preparations	11
5.4	Reconstituting Fabrazyme.....	11
5.5	Dilution	12
5.6	Filling the Infusion Line	13
5.7	Inserting the Needle in the Vein.....	13
5.8	Administration.....	14
5.9	Preparation of the Fabrazyme infusion in case of venous access device.....	14
6	FABRAZYME SAFETY INFORMATION	15
7	SAFETY REPORTING	15
8	FURTHER INFORMATION	16
9	APPENDICES	16
9.1	Fabrazyme Summary of Product Characteristics	17
9.2	Adverse Event Form	39
9.3	Logbook	40

1 OBJECTIVES AND GOALS

The objective of this document is to provide guidance to healthcare professionals for the management of patients receiving Fabrazyme® at home. The process (described in detail below) will start with patient evaluation and selection, and discussion of requirements for home infusion. This is followed by the organisation of home infusion and training.

Patients with Fabry disease may be offered home infusion therapy in order to reduce the burden of biweekly administration of infusions in the hospital setting. The objective of this document is to provide guidance on how to transfer Fabrazyme infusion therapy from the hospital setting to the patient's home. This process encompasses the selection of eligible patients and a careful evaluation of all specifics in relation to the organization of home infusion.

If the requirements can be fulfilled, the patient can receive treatment within the living environment which increases comfort and flexibility of infusion timing. It avoids spending time travelling to and from the hospital, and patients will be able to follow a normal schooling program and organise social and professional activities more easily. Moreover, it reduces the constraints of hospital resources.

Infusion of Fabrazyme at home may be considered for patients who are tolerating their infusions well. The decision to transfer Fabrazyme treatment to the patient's home setting is made by the treating physician and should take into account patient preferences and medical status.

The home infusion will take place under the responsibility of the treating physician. Distribution of the educational material should only be executed if the treating physician decides that the patient is eligible for home infusion treatment. It is the responsibility of the treating physician to ensure a safe administration to the patient. This should be checked and documented by the treating physician.

The processes presented in this document serve as overall guidance but are subject to local medical practice and national rules and regulations.

2 ASSESSING ELIGIBILITY FOR HOME INFUSION

Before making any arrangements, the physician overseeing the patient's clinical care must determine if the patient fulfils the following primary criteria for transfer of hospital-based infusion therapy to the patient's home setting:

- The patient is considered medically stable. A comprehensive evaluation must be completed before deciding on transfer of therapy.
- The patient must have received Fabrazyme infusions in a controlled setting for several months. Documentation of a pattern of well tolerated infusions with no infusion-associated reactions (IARs), or mild IARs that have been controlled with pre-medication, is a prerequisite for transfer of therapy to the home.
- The patient must have a history of adherence to the prescribed infusion schedule.

3 REQUIREMENTS AND ORGANISATION OF HOME INFUSION

Once the patient has been considered to be eligible for home infusion based on the primary criteria, a set of requirements must be considered to ensure that Fabrazyme infusions can be safely, efficiently, and reliably delivered at the patient's home.

3.1 Patient

General

- The patient and/or caregiver(s) have been informed by the treating physician about the treatment to be provided at home, the associated risks, and the provision of medical assistance at home, and must agree to the treatment at home.
- The patient and/or caregiver(s) have an understanding of the illness and are able to recognise adverse events and understand the procedure to be followed should these occur.
- The home environment must be conducive to home infusion therapy including a clean environment with electricity, water, telephone access, refrigeration, and physical space to support storage of Fabrazyme and other infusion supplies.
- The patient has been informed that the infusion should always be administered in the presence of an adult, i.e. the infusion nurse or, if self-infusion skills have been acquired, an adult knowledgeable about the infusion procedures and adequately trained on how to handle in case of an IAR and medication errors (as assessed by the treating physician or infusion nurse).

Medical

- The patient must be physically and mentally able to undergo the infusions at home. The treating physician is responsible for the recommendation to receive Fabrazyme infusions at home.
- The patient has venous access or a central venous access device that allows adequate infusion.

3.2 Treating Physician

- The treating physician is responsible for the initiation of all necessary administrative actions which will allow the other parties involved (patient and/or caregiver(s), infusion nurse, pharmacy) to proceed.
- The treating physician is responsible for selection of the infusion rate and dose. The infusion rate of Fabrazyme that was tolerated by the patient in a more controlled setting

(e.g., in the hospital or other medical setting) must not be changed in the home setting, unless necessary due to safety considerations. Any changes in Fabrazyme administration must be clearly documented in the Logbook (Appendix 3).

- The home infusion will take place under the responsibility of the treating physician. Distribution of the educational material should only be executed if the treating physician decides that the patient is eligible for home infusion treatment. It is the responsibility of the treating physician to ensure a safe administration to the patient. This should be checked and documented by the treating physician.
- Pre-infusion treatment, if administered in the hospital or other medical setting (e.g. antihistamines, paracetamol, ibuprofen, corticosteroids), must be provided based on the patient-specific prescription and should be described in the Logbook. This treatment must not be altered in the home setting, unless medically warranted at the discretion of the treating physician.
- Emergency treatment must be provided based on the patient-specific prescription and should be described in the Logbook.
- The treating physician must ensure that a rapid and reliable line of communication is available to expedite emergency response in case immediate medical attention is required.
- Patients experiencing adverse events need to contact the treating physician or his/her medical designate immediately. Subsequent infusions may need to occur in a hospital or other medical setting at the discretion of the treating physician or his/her medical designate.
- Regular disease monitoring of the home-infused patient is the responsibility of the treating physician.
- Appropriate scheduling and monitoring of the infusions is the responsibility of the treating physician and infusion nurse.

3.3 Pharmacy and Infusion Equipment

Treatment and all necessary equipment will be provided according to local arrangements and regulations.

3.4 Infusion Nurse

- The infusion nurse will have a coordinating role vis-à-vis the treating physician and the patient and/or caregiver(s) in organizing the treatment at home, and will establish with the treating physician, patient and/or caregiver(s) the level of support necessary in the

home.

- The infusion nurse is qualified to give IV infusions, has been appropriately trained on the administration of Fabrazyme, and is trained on the possible adverse events (including serious adverse events such as anaphylactoid reactions) and the actions to be taken should they occur.
- The infusion nurse will strictly follow the prescribed method of preparation and administration of Fabrazyme as stated in this Manual.
- The infusion nurse will strictly follow the prescribed dose and infusion rate of Fabrazyme as stated in the Logbook (Appendix 3).
- The infusion nurse records each administration of Fabrazyme in the Logbook (Appendix 3).
- Appropriate scheduling and monitoring of the infusions is the responsibility of the treating physician and infusion nurse.
- In the event of an IAR, the infusion nurse **must discontinue the infusion** and phone the treating physician and/or the country-specific national emergency number described in the Logbook. The treating physician and/or the country-specific national emergency number must also be phoned if an IAR occurs shortly after completion of the infusion. Any IAR must be recorded in the Logbook (Appendix 3).

3.5 Pre-treatment and Emergency Treatment

- Appropriate pre-treatment should be provided based on the patient-specific prescription. Treatment administered in the hospital or other medical setting should not be altered in the home setting unless medically warranted at the discretion of the treating physician.
- Medications must be available to respond to an emergency situation, if necessary. Proper education on the use of emergency medications must be provided by the treating physician to the patient and/or caregiver.
- In the event the patient experiences an adverse event during or shortly after the infusion, **the infusion should be discontinued immediately** and the treating physician or his/her medical designate should be contacted to seek advice. Subsequent infusions may need to occur in a hospital or other medical setting. All adverse events, including medication errors, should be reported to the Health Products Regulatory Authority (HPRA) and Genzyme's Pharmacovigilance Department by the treating physician (reporting instructions are provided in this Manual in Section 7 Safety Reporting).

3.6 The Logbook

- The Logbook serves as a means of communication for all involved in administering Fabrazyme in the home-setting.
- The infusion nurse/patient/caregiver(s) will record the findings and actions from the initial interview and all relevant information from subsequent visits in the Logbook.
- A resource contact list must be completed and available at home in the Logbook for the patient and/or caregiver(s) and the infusion nurse.
- The Logbook must be kept at the patient's home and will be updated by the infusion nurse/patient/caregiver(s) each time Fabrazyme is administered.
- The patient must take the Logbook along to the hospital at each appointment and bring it home afterwards.
- In the logbook, the treating physician clearly states the dose, the required reconstituted volume, infusion rate, as well as any changes. The treating physician clearly states what has to be done and which medications are to be administered in the event of a serious IAR in line with current medical standards for emergency treatment. The contact details of the treating physician and the country-specific national emergency number are documented in the logbook.

4 TRAINING ON PREPARATION AND ADMINISTERING FABRAZYME

In principle, the initial instructions will be given in the hospital and the level of support required from the infusion nurse in the home setting will be discussed and agreed by the treating physician and the patient and/or caregiver(s). The treating physician is responsible for the organization of the home infusion and needs to agree upon the home infusion procedure. The infusion nurse will carry out the entire procedure for the first infusions at the patient's home. Subsequently, should the patient then prefer to carry out the procedure him/herself, or with the assistance of a caregiver, the following conditions must be followed:

- The patient and/or caregiver(s) will receive adequate training from the infusion nurse on how the infusion is being prepared and administered. The infusion nurse will explain and demonstrate the complete infusion procedure to the patient and/or caregiver(s), including training in hand hygiene, proper disinfection and aseptic handling when preparing the infusion.
- At subsequent visits, the infusion nurse will be present to assist, if required, until the patient and/or caregiver(s) feels confident with the entire infusion procedure.
- While reconstituting and administering Fabrazyme, the procedures described in the Fabrazyme Summary of Product Characteristics (Appendix 1) and in section 5 “Administration of Fabrazyme infusions” of this document must be adhered to, and each administration of Fabrazyme should be recorded in the Logbook (see Appendix 3). In case of any problems with the reconstitution and administration of Fabrazyme, the patient or caregiver(s) should contact the nurse or treating physician to determine appropriate action before starting or continuing with the infusion. (details in Logbook (Appendix 3)).
- If self-infusion skills have been acquired, the infusion should always be administered in the presence of an adult knowledgeable about the infusion procedures and adequately trained on how to handle in case of an IAR and medication errors, as assessed by the treating physician or infusion nurse.
- In the event of any IAR, the **infusion must be immediately discontinued** and the patient or caregiver(s) must phone the treating physician or his/her medical designate. In the case of an emergency, refer to the emergency details in the Logbook (Appendix 3). The same procedure must be followed if an IAR occurs shortly after completion of the infusion.
- If the patient feels the treatment is not efficacious, he/she should consult the treating physician.

5 ADMINISTRATION OF FABRAZYME

Instructions for use relating to the reconstitution, dilution and administration can be found in the Summary of Product Characteristics (SmPC, Appendix 1). A detailed description is provided in this section.

5.1 Prescription

The Fabrazyme dose, required reconstituted volume, infusion rate, premedication, emergency medication, as well as any changes will be determined by the treating physician. The prescription must be written in the Logbook (Appendix 3). Any changes of this prescription (dose or infusion rate) must again be reported in the Logbook. It is important to keep this guide handy and review the method of administration regularly. This will ensure optimal practice.

5.2 Supplies

Supplied by the hospital/pharmacy to the patient or to a third party with the appropriate prescription:

- Vials of Fabrazyme (5 mg or 35 mg per vial); must be stored in a clean refrigerator at a temperature of between +2°C and +8°C.
- Sterile water for injections to reconstitute Fabrazyme.
- 0.9% sodium chloride (NaCl) intravenous solution, 2 x 250 ml for IV administration.
- 0.9% sodium chloride (NaCl) intravenous solution, 2 x 50 ml to flush infusion line pre- and post-infusion.
- Chlorhexidine 0.5% in alcohol 70% (antiseptic solution).
- Appropriate number of 2 ml, 10 ml and 50 ml syringes depending on dose of Fabrazyme.
- 3 x sterile hypodermic needles (1.1 x 40 mm).
- 1 x infusion needle.
- In-line low protein-binding 0.2 micron filter.
- Infusion-administration set (infusion line).
- Tape.
- Sterile skin cleansing swabs.
- Sharps bin.

- Hand wash.
- Tourniquet.
- Additional requisites if using a venous access device: heparin, NaCl 0.9% solution, needles, syringes, dressing pack, sterile gloves, Gripper needle.
- Pretreatment medication (if applicable)
- Emergency medication (as described in Logbook)

5.3 Preparations

NOTE: The instructions for use (reconstitution, dilution and administration) can be found in the SmPC (Appendix 1). A detailed description is provided in this section.

1. Prepare a clean work area and lay out the requisites.
2. The vials with Fabrazyme must be removed from the refrigerator to reach room temperature approximately 30 minutes before preparation.
3. Check the expiry date printed on the bottom of the vial pack (do not use Fabrazyme after the labelled expiry date).
4. Verify if the number of vials received is correct.
5. Prepare only the number of vials required for one infusion.
Note: The storage instructions as described in the instructions for use in the SmPC must be followed (Appendix 1).

5.4 Reconstituting Fabrazyme

1. Remove the flip-off cap from the Fabrazyme vial.
2. Disinfect the rubber stopper of the Fabrazyme vial with chlorhexidine and allow to air dry.
3. Open the sterile water for injections.
4. Draw the required amount (ml) of sterile water into the syringe.

For 35 mg vials, reconstitute each vial with 7.2 ml water for injection.

For 5 mg vials, reconstitute each vial with 1.1 ml water for injection.

5. Avoid forcefully ejecting the water for injections from the syringe onto the powder, to minimize foaming. This should be done by slow drop-wise addition of the water for injection down the inside of the vial. Roll and tilt each vial gently. Do not invert, swirl

or shake the vial.

6. Repeat the process for more Fabrazyme vials, if required.
7. Small bubbles may appear after the mixing.
8. Let the solution settle for a few minutes to allow any bubbles present to disappear and to ensure that the powder is properly reconstituted.
9. After reconstitution, Fabrazyme must be inspected visually before use. The reconstituted solution must be a clear, colourless liquid and free from foreign matter. Because this is a protein solution, slight flocculation/cloudiness (described as thin translucent fibres) may occur occasionally after dilution.
10. If foreign matter or discolouration of the liquid is noticed, the product must not be used and the infusion nurse and/or treating physician must be informed.
11. It is recommended that the vials be diluted promptly after reconstitution to minimize protein particle formation over time.
12. Any unused product or waste material must be disposed of in accordance with local requirements.

5.5 Dilution

1. Disinfect the cap/opening of 1 or 2 bags of NaCl 0.9% solution using chlorhexidine and allow to air dry.
2. The volume of reconstituted Fabrazyme solution must be the same as the prescribed volume in the Logbook (Appendix 3).
3. Insert the needle in the cap of the infusion bag and slowly withdraw a volume of NaCl 0.9% solution, equivalent to the volume of the reconstituted Fabrazyme solution to be added.
For instance, if the prescribed reconstituted volume is 14 ml, remove 14 ml (2 x 7 ml) from the bag of NaCl solution. Never remove more than half the content of the bag of NaCl solution to ensure that at least half the diluted solution consists of NaCl solution.
4. Remove the airspace within the infusion bag by withdrawing the air into a 50 ml syringe.
5. Slowly withdraw the reconstituted solution from each vial up to the total volume required. Do not use filter needles.
At the point when these quantities have been drawn, the reconstituted product should not contain any foam.

6. Gently inject the total volume of the reconstituted Fabrazyme solution into the bag of NaCl 0.9% solution.
7. Carefully mix this Fabrazyme solution by gently inverting or lightly massaging the infusion bag. Do not shake or excessively agitate the infusion bag.
8. The diluted solution should be filtered through an in-line low protein-binding 0.2 micron filter during administration.

5.6 Filling the Infusion Line

1. Remove the infusion system from the package and close it using the roller clamp. Connect the in-line filter to the infusion line.
2. Connect the spike in the NaCl 0.9% solution bag that does not contain Fabrazyme and fill the infusion system by holding the drip chamber upside down and opening the clamp.
3. Fill the entire system, remove any air bubbles that may be present and close the roller clamp.
4. Connect the infusion bag containing Fabrazyme to the y-system. Keep the clamp closed.

5.7 Inserting the Needle in the Vein

In case of self-infusion, the adult person present during the infusion session should have been adequately trained (by the infusion nurse, treating physician, or his/her medical designate) on the technique of needle insertion.

1. Ensure that some strips of tape are hanging ready for use and that the start of the infusion system is within reach. Place the chlorhexidine close by along with some gauzes.
2. Remove the infusion needle from the packaging.
3. Have the patient sit down and rest one arm on the table (preferably on a clean cloth).
4. Apply the tourniquet and disinfect the area where the needle is to be inserted and allow it to dry.
5. Pull the skin tight and insert the needle (with its eye facing upward) at a slight angle through the skin and into the vein. When the needle has entered the vein, a 'flash' of blood will be visible at the start of the tubing.
6. Insert the needle approximately 0.5 cm in the vein to ensure that it does not

immediately pop out again. Use tape to keep the needle into place. Connect the system with filter to the needle.

7. Remove the tourniquet; the tube will now fill up with blood. If this does not happen, the needle is not positioned correctly in the vein. The process must then be repeated using a new needle. Open the clamp for NaCl 0.9% solution.
8. Adjust the infusion rate according to the prescription (Logbook, Appendix 3) and open the valve. Sit down and relax while the infusion takes place.

5.8 Administration

- 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 product diluted in NaCl 0.9% solution will retain chemical stability if stored up to 24 hours at a temperature between 2°C and 8°C and away from light.
- The Fabrazyme dose, infusion rate, as well as any changes, will be determined by the treating physician. The treatment must not be altered in the home setting, unless medically warranted at the discretion of the treating physician.
- After the Fabrazyme infusion has been completed, the system is flushed with NaCl 0.9% solution at the same rate and the needle removed.

5.9 Preparation of the Fabrazyme infusion in case of venous access device

When the patient has a venous access device for the delivery of Fabrazyme, the patient and/or caregiver(s) will be shown how to care for the device by the infusion nurse, if this has not already been demonstrated during hospital-based infusions.

Proper home care of a venous access device involves regular irrigation with heparin to prevent clotting and attention to a sterile technique to keep the device free of infectious agents.

The patient and/or caregiver(s) will be informed of the following necessary steps:

- When in use, cover site with transparent occlusive dressing. No dressing is required when not in use.
- Flush with 5 ml NaCl 0.9% solution before and after each use.
- Flush with 5 ml heparin (100 U/ml) after each use.

6 FABRAZYME SAFETY INFORMATION

Please refer to section 4 of the current Summary of Product Characteristics (Appendix 1) for complete information on the safety of Fabrazyme.

7 SAFETY REPORTING

An adverse event (AE) is defined as any untoward physical, psychological or behavioral occurrence in a patient administered a medicinal product which does not necessarily have to have a causal relationship with this treatment. A serious adverse event (SAE) involves an occurrence defined as having at least one of the following outcomes or characteristics:

- Results in death.
- Is life-threatening (any event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Required in-patient hospitalisation or prolongation of an existing hospitalisation.
- Results in persistent or significant disability/incapacity (any adverse event that resulted in a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is an important medical event (any event that, based upon appropriate medical judgement, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above).

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

Suspected adverse reactions should also be reported to Genzyme: Tel: + 44 (0)1865 405 200. Alternatively, please complete an Adverse Event Form (Appendix 2) and send via E-mail to (IEPharmacovigilance@sanofi.com).

If the patient becomes aware that a mistake was made in the preparation and/or administration of the drug, the patient or infusion nurse should inform the treating physician to determine appropriate action. Any medication errors should be reported as a spontaneous report to Genzyme by the treating physician.

8 FURTHER INFORMATION

Please refer to the Summary of Product Characteristic (Appendix 1) for complete indication statements and further information about the approved use of Fabrazyme. Other detailed information on Fabrazyme is available at the following website: The European Medicines Agency (EMA) (see <http://www.ema.europa.eu>).

9 APPENDICES

1. Fabrazyme Summary of Product Characteristics
2. Adverse Event Form
3. Logbook

9.1 Fabrazyme Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Fabrazyme 35 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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).

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.

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.

Alternative dosing regimens have been used in clinical studies. In one of these studies, 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

Patients with renal impairment

No dose adjustment is necessary for patients with renal insufficiency.

Patients with hepatic impairment

Studies in patients with hepatic insufficiency have not been performed.

Elderly patients

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

Studies in children 0-7 years have not been performed and no dosage regimen can presently be recommended in patients in this paediatric age group as safety and efficacy have not yet been established. 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 radioimmunoprecipitation (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 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 $\geq 1/10$; common $\geq 1/100$ to $< 1/10$ and uncommon $\geq 1/1000$ 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, rhinorrhoea, 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, $\geq 1\%$ 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 suggests that the safety profile of Fabrazyme treatment in paediatric patients (above the age of 7) is not different with that seen in adults.

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 below:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

Ireland

HPRA Pharmacovigilance

Earlsfort Terrace

IRL - Dublin 2

Tel: +353 1 6764971

Fax: +353 1 6762517

Website: www.hpra.ie

e-mail: medsafety@hpra.ie

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 one study 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 the open-label paediatric study, sixteen patients with Fabry disease (8-16 years old; 14 males, 2 females) had been treated for one year. 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.

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 dependent 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 $\mu g \text{ min/ml}$. V_{ss} 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 15 paediatric patients (8.5 to 16 years old weighing 27.1 to 64.9 kg). Agalsidase clearance was not influenced by weight in this population. Baseline clearance was 77 ml/min with a volume of distribution at steady-state (V_{ss}) of 2.6 l; half-life was 55 min. After IgG seroconversion, clearance decreased to 35 ml/min, V_{ss} 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.

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 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.

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

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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/188/001-003

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

06/2014

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

1. NAME OF THE MEDICINAL PRODUCT

Fabrazyme 5 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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.

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.

Alternative dosing regimens have been used in clinical studies. In one of these studies, 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

Patients with renal impairment

No dose adjustment is necessary for patients with renal insufficiency.

Patients with hepatic impairment

Studies in patients with hepatic insufficiency have not been performed.

Elderly patients

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

Studies in children 0-7 years have not been performed and no dosage regimen can presently be recommended in patients in this paediatric age group as safety and efficacy have not yet been established. 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 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-haGAL) 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-haGAL 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 $\geq 1/10$; common $\geq 1/100$ to $< 1/10$ and uncommon $\geq 1/1000$ 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, rhinorrhoea, 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, $\geq 1\%$ 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 suggests that the safety profile of Fabrazyme treatment in paediatric patients (above the age of 7) is not different with that seen in adults.

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 below:

United Kingdom

Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard

Ireland

HPRA Pharmacovigilance

Earlsfort Terrace

IRL - Dublin 2

Tel: +353 1 6764971

Fax: +353 1 6762517

Website: www.hpra.ie

e-mail: medsafety@hpra.ie

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 one study 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 the open-label paediatric study, sixteen patients with Fabry disease (8-16 years old; 14 males, 2 females) had been treated for one year. 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.

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 dependent 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 $\mu\text{g min/ml}$. V_{ss} 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 15 paediatric patients (8.5 to 16 years old weighing 27.1 to 64.9 kg). Agalsidase clearance was not influenced by weight in this population. Baseline clearance was 77 ml/min with a volume of distribution at steady-state (V_{ss}) of 2.6 l; half-life was 55 min. After IgG seroconversion, clearance decreased to 35 ml/min, V_{ss} 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.

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 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

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.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/188/004-006

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

06/2014

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

9.2 Adverse Event Form



Enzyme Replacement Therapies* Adverse Event Reporting Form (*Cerezyme, Fabrazyme, Aldurazyme, Myozyme, Lumizyme)					
GENZYME ERT Adverse Event Report Form					
Report Date: DD-MMM-YYYY	Report Type: <input type="checkbox"/> Initial <input type="checkbox"/> Follow-up	Registry ID (if applicable):	Patient Initials:	Drug/Biologic: (select ONE) <input type="checkbox"/> Cerezyme <input type="checkbox"/> Fabrazyme <input type="checkbox"/> Aldurazyme <input type="checkbox"/> Myozyme <input type="checkbox"/> Lumizyme <input type="checkbox"/> NONE Reason: _____	Lot Number & Expiration Date:
Reporter Name, Institution, Address:		Age:	Gender: <input type="checkbox"/> Male <input type="checkbox"/> Female	Indication: Gaucher Phenotype: <input type="checkbox"/> Type 1 <input type="checkbox"/> Type 2 <input type="checkbox"/> Type 3 Pompe Phenotype: <input type="checkbox"/> Infantile-onset <input type="checkbox"/> Late-onset	
		Country:	Dose: _____ Units: _____ Frequency: _____		
		Date of Birth: DD-MMM-YYYY	Administration schedule (including rate ramp schedule):		
Reporter's Telephone Number:		Height: <input type="checkbox"/> cm <input type="checkbox"/> in	Weight: <input type="checkbox"/> kg <input type="checkbox"/> lb	Route: <input type="checkbox"/> I.V. <input type="checkbox"/> Other _____	
Reporter's Fax Number:		Pregnant? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA If yes, please complete pregnancy forms		Therapy Start Date: DD-MMM-YYYY	
Please provide the patient's medical history.				Date of Last Dose (prior to event): DD-MMM-YYYY	
				Therapy Stop Date: DD-MMM-YYYY <input type="checkbox"/> continuing	
Event term(s): (List one term per column) Provide Diagnosis, if known	Event #1	Event #2		Event #3	Event #4
	Event Start Date & Time: DD-MMM-YYYY	Event Start Date & Time: DD-MMM-YYYY		Event Start Date & Time: DD-MMM-YYYY	Event Start Date & Time: DD-MMM-YYYY
	Event Stop Date & Time: DD-MMM-YYYY <input type="checkbox"/> Ongoing	Event Stop Date & Time: DD-MMM-YYYY <input type="checkbox"/> Ongoing		Event Stop Date & Time: DD-MMM-YYYY <input type="checkbox"/> Ongoing	Event Stop Date & Time: DD-MMM-YYYY <input type="checkbox"/> Ongoing
Event Serious:	<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> YES <input type="checkbox"/> NO		<input type="checkbox"/> YES <input type="checkbox"/> NO	<input type="checkbox"/> YES <input type="checkbox"/> NO
Infusion Associated Reaction?: If yes, please include time to onset	<input type="checkbox"/> YES <input type="checkbox"/> NO Time to onset: _____	<input type="checkbox"/> YES <input type="checkbox"/> NO Time to onset: _____		<input type="checkbox"/> YES <input type="checkbox"/> NO Time to onset: _____	<input type="checkbox"/> YES <input type="checkbox"/> NO Time to onset: _____
Severity:	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe		<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe	<input type="checkbox"/> Mild <input type="checkbox"/> Moderate <input type="checkbox"/> Severe
Outcome of the Event:	<input type="checkbox"/> Recovered <input type="checkbox"/> Recovered with sequelae Specify: _____ <input type="checkbox"/> Recovering <input type="checkbox"/> Not recovered <input type="checkbox"/> Fatal Cause of death: _____ <input type="checkbox"/> Unknown	<input type="checkbox"/> Recovered <input type="checkbox"/> Recovered with sequelae Specify: _____ <input type="checkbox"/> Recovering <input type="checkbox"/> Not recovered <input type="checkbox"/> Fatal Cause of death: _____ <input type="checkbox"/> Unknown		<input type="checkbox"/> Recovered <input type="checkbox"/> Recovered with sequelae Specify: _____ <input type="checkbox"/> Recovering <input type="checkbox"/> Not recovered <input type="checkbox"/> Fatal Cause of death: _____ <input type="checkbox"/> Unknown	<input type="checkbox"/> Recovered <input type="checkbox"/> Recovered with sequelae Specify: _____ <input type="checkbox"/> Recovering <input type="checkbox"/> Not recovered <input type="checkbox"/> Fatal Cause of death: _____ <input type="checkbox"/> Unknown
Serious Criteria:	<input type="checkbox"/> Not applicable (non-serious) <input type="checkbox"/> Life-threatening <input type="checkbox"/> Fatal <input type="checkbox"/> Inpatient/prolonged hospitalization <input type="checkbox"/> Persistent or significant disability/incapacity <input type="checkbox"/> Important medical event <input type="checkbox"/> Congenital anomaly/birth defect	<input type="checkbox"/> Not applicable (non-serious) <input type="checkbox"/> Life-threatening <input type="checkbox"/> Fatal <input type="checkbox"/> Inpatient/prolonged hospitalization <input type="checkbox"/> Persistent or significant disability/incapacity <input type="checkbox"/> Important medical event <input type="checkbox"/> Congenital anomaly/birth defect		<input type="checkbox"/> Not applicable (non-serious) <input type="checkbox"/> Life-threatening <input type="checkbox"/> Fatal <input type="checkbox"/> Inpatient/prolonged hospitalization <input type="checkbox"/> Persistent or significant disability/incapacity <input type="checkbox"/> Important medical event <input type="checkbox"/> Congenital anomaly/birth defect	<input type="checkbox"/> Not applicable (non-serious) <input type="checkbox"/> Life-threatening <input type="checkbox"/> Fatal <input type="checkbox"/> Inpatient/prolonged hospitalization <input type="checkbox"/> Persistent or significant disability/incapacity <input type="checkbox"/> Important medical event <input type="checkbox"/> Congenital anomaly/birth defect
Action Taken with Suspect Drug:	<input type="checkbox"/> Discontinued <input type="checkbox"/> Dose changed Specify: _____ <input type="checkbox"/> None Did event abate after drug was stopped or dose changed? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown Date Stopped: DD-MMM-YYYY Did event reoccur after drug was restarted? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA <input type="checkbox"/> Unknown Date Re-started: DD-MMM-YYYY	<input type="checkbox"/> Discontinued <input type="checkbox"/> Dose changed Specify: _____ <input type="checkbox"/> None Did event abate after drug was stopped or dose changed? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown Date Stopped: DD-MMM-YYYY Did event reoccur after drug was restarted? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA <input type="checkbox"/> Unknown Date Re-started: DD-MMM-YYYY		<input type="checkbox"/> Discontinued <input type="checkbox"/> Dose changed Specify: _____ <input type="checkbox"/> None Did event abate after drug was stopped or dose changed? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown Date Stopped: DD-MMM-YYYY Did event reoccur after drug was restarted? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA <input type="checkbox"/> Unknown Date Re-started: DD-MMM-YYYY	<input type="checkbox"/> Discontinued <input type="checkbox"/> Dose changed Specify: _____ <input type="checkbox"/> None Did event abate after drug was stopped or dose changed? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown Date Stopped: DD-MMM-YYYY Did event reoccur after drug was restarted? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> NA <input type="checkbox"/> Unknown Date Re-started: DD-MMM-YYYY

Property of Sanofi – Enzyme Replacement Therapies Adverse Event Reporting Form: version 2.0 Apr-2015

9.3 Logbook

Logbook for Fabrazyme[®] Home Infusion

General data (to be completed by treating physician)

Emergency number:

CONTACT DETAILS		
Patient	Name:	
	Birth Date:	
	Address:	
	Zip / City:	
	Telephone:	
Contact details of patient's caregiver	Name:	
	Address:	
	Zip / City:	
	Telephone:	
Nurse	Name:	
	Organisation:	
	Address:	
	Zip / City:	
	Telephone:	
Treating physician	Name:	
	Hospital:	
	Address:	
	Zip / City:	
	Telephone:	
	Emergency number	
Pharmacy	Name:	
	Address:	
	Zip / City:	
	Telephone:	

Administration details *(to be completed by treating physician)*

Fabrazyme administered since	Date (dd-mmm-yyyy):
First infusion at home	Date (dd-mmm-yyyy):
Fabrazyme dosing regimen - Dose	
- Frequency	
- Rate of infusion	
- Required reconstituted volume (ml)	
- Total volume in infusion bag (ml)	
Pre-treatment medication (if applicable)	
Reasons for Fabrazyme infusion at home	
Findings and actions from the initial interview	
Indicate support to be provided by infusion nurse at home	

Necessary actions in the event of a serious infusion-associated reaction

(to be completed by treating physician)

1. Stop the infusion	
2. Call the national emergency number - Telephone number	
3. Call the physician - Telephone number - Telephone number (24hr) - Name of physician - Name of clinic - Address	
Emergency medication, including dose	
Patient's contact person to be notified - Name - Telephone number	

Complete this form for every infusion session

- The patient and/or caregiver(s) have been informed about the associated risks of home infusion of Fabrazyme, and proper education on the use of emergency medications has been provided.
- In the event of any infusion-associated reaction, the **infusion must be immediately discontinued**
- Necessary actions in the event of a serious infusion-associated reaction, **including emergency contact details**, are described in the Logbook. Keep this information readily available during the infusion procedure.

Infusion data

Date of infusion	Date (dd-mmm-yyyy):
Patient's general health status - Describe any new health issues that you are currently experiencing prior to infusion, if any	
Dose	
Required reconstituted volume (ml)	
Number of vials used	5 mg vials: 35 mg vials:
Duration of administration	
Rate of administration	
Problems/Remarks related to the infusion, if any (including infusion-associated reaction(s), action taken, and outcome)	
Name of person responsible for infusion, and date - Nurse - Caregiver (if different from above)	