PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

FABRAZYME® 5 mg powder for solution for infusion

FABRAZYME® 35 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FABRAZYME 5 mg:

Each vial of FABRAZYME 5 mg contains a nominal value of 5 mg of agalsidase beta. After reconstitution with 1,1 mL sterile water for injection, each vial contains 5 mg/mL of agalsidase beta. The reconstituted solution must be further diluted (see section 6.6).

Contains sugar alcohol (mannitol): Each vial contains 30 mg mannitol after reconstitution.

FABRAZYME 35 mg:

Each vial of FABRAZYME 35 mg contains a nominal value of 35 mg of agalsidase beta. After reconstitution with 7,2 mL sterile water for injection, each vial contains 5 mg/mL (35 mg/7 mL) of agalsidase beta. The reconstituted solution must be further diluted (see section 6.6).

Contains sugar alcohol (mannitol): Each vial contains 210 mg mannitol after reconstitution.

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 solution for infusion.

A sterile, non-pyrogenic, white to off-white lyophilised cake or powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FABRAZYME (agalsidase beta) is indicated for use in patients with Fabry disease.

4.2 Posology and method of administration

Posology

The recommended dose of FABRAZYME is 1,0 mg/kg body weight infused every 2 weeks as a slow IV infusion over 2 hours or longer.

The initial IV infusion rate should be no more than 0,25 mg/min or 15 mg/hour. The infusion rate may be slowed in the event of infusion-associated reactions. After patient tolerance has been established, the infusion rate may be increased gradually with subsequent infusions, as tolerated.

Overall, the safety and efficacy of FABRAZYME treatment administered at 1,0 mg/kg every 2 weeks in children between the ages of 8 and 16 years are consistent with that seen in adults. Patients younger than 8 years of age were not included in clinical studies.

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 specialist. Patients experiencing adverse events during the home infusion need to immediately **stop the infusion process** and seek the attention of a health care

provider. Subsequent infusions may need to occur in a clinical setting. Dose and infusion rate should remain constant while at home and should not be changed without supervision of a health care provider.

Special populations

Renal insufficiency:

No changes in dose are necessary for patients with renal insufficiency.

Hepatic insufficiency:

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.

Children younger than 8 years:

The safety and efficacy of FABRAZYME in patients younger than 8 years of age have not been evaluated.

Method of administration

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

4.3 Contraindications

Known hypersensitivity to agalsidase beta or to any of the other ingredients of FABRAZYME (see 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 titres (based on a ≥ 4-fold reduction in titre 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.

Antibody status should be regularly monitored.

In clinical trials, sixty-seven per cent (67 %) of the patients experienced at least one infusion-associated reaction. 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/hour) and/or pre-treatment with antihistamines, paracetamol, ibuprofen and/or corticosteroids.

Hypersensitivity:

Allergic-type hypersensitivity reactions are possible.

A small number of patients have experienced reactions suggestive of immediate (Type I) hypersensitivity.

In clinical trials, approximately 1 % of patients developed anaphylactic or severe allergic reactions during FABRAZYME infusion.

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.

The risks and benefits of re-administering FABRAZYME following a severe hypersensitivity or anaphylactoid reaction should be considered.

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 (0,5 mg/kg) at 1/25 the initial standard recommended rate (0,01 mg/min)].

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 kidney function may be limited in patients with advanced renal disease.

Useful laboratory tests for monitoring patients:

It is suggested that patients be monitored periodically for IgG antibody formation.

4.5 Interaction with other medicines and other forms of interaction

Interactions with food and drink are unlikely.

No formal medicine interaction studies have been performed.

No *in vitro* metabolism studies have been performed.

FABRAZYME should not be administered with chloroquine, amiodarone, benoquin or gentamycin due to a risk of inhibition of intracellular α-galactosidase A activity.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of FABRAZYME in pregnant women.

Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/fetal development.

FABRAZYME should not be used during pregnancy.

Breastfeeding

FABRAZYME may be excreted in breast milk. Because there are no data available on effects in neonates exposed to FABRAZYME via breast milk, it is recommended to stop breastfeeding 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 can cause side effects such as dizziness or somnolence (see section 4.8). Caution is advised when driving a vehicle or operating machinery until the effects of FABRAZYME are known.

4.8 Undesirable effects

Side effects have been reported according to the following categories:

Very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100). 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 below at a frequency category of “not known” (cannot be estimated from the available data).

Adverse reactions were mostly mild to moderate in severity:

Infections and infestations

Common: Nasopharyngitis

Uncommon: Rhinitis

Immune system disorders

Common: Anaphylaxis or severe allergic reactions, angioedema

Not known: Anaphylactoid reaction

Nervous system disorders

Very common: Headache, paraesthesia

Common: Dizziness, somnolence, hypoaesthesia, burning sensation, lethargy, syncope

Uncommon: Hyperaesthesia, tremor

Eye disorders

Common: Increased lacrimation

Uncommon: Eye pruritus, ocular hyperaemia

Ear and labyrinth disorders

Common: Tinnitus, vertigo

Uncommon: Auricular swelling, ear pain

Cardiac disorders

Common: Tachycardia, palpitations, bradycardia

Uncommon: Sinus bradycardia

Vascular disorders

Common:	Flushing, hypertension, pallor, hypotension, hot flushes
Uncommon:	Peripheral coldness

Respiratory, thoracic and mediastinal disorders

Common:	Dyspnoea, nasal congestion, throat tightness, wheezing, cough, exacerbated dyspnoea
Uncommon:	Bronchospasm, pharyngolaryngeal pain, rhinorrhoea, tachypnoea, upper respiratory tract congestion
Not known:	Hypoxia

Gastrointestinal disorders

Very common:	Nausea, vomiting
Common:	Abdominal pain, upper abdominal pain, abdominal discomfort, stomach discomfort, oral hypoaesthesia, diarrhoea
Uncommon:	Dyspepsia, dysphagia

Skin and subcutaneous tissue disorders

Common:	Pruritus, urticaria, rash, erythema, generalised pruritus, angioneurotic oedema, swelling face, maculopapular rash
Uncommon:	Livedo reticularis, erythematous rash, pruritic rash, skin discolouration, skin discomfort
Not known:	Leukocytoclastic vasculitis

Musculoskeletal, connective tissue and bone disorders

Common:	Pain in extremity, myalgia, back pain, muscle spasms, arthralgia, muscle tightness, musculoskeletal stiffness
Uncommon:	Musculoskeletal pain

General disorders and administration site conditions

Very common:	Chills, pyrexia, feeling cold
Common:	Fatigue, chest discomfort, feeling hot, peripheral oedema, pain, asthenia, chest pain, face oedema, hyperthermia
Uncommon:	Feeling hot and cold, influenza-like illness, infusion site pain, infusion site reaction, injection site thrombosis, malaise, oedema

Investigations

Not known:	Decreased oxygen saturation.

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, angioedema, 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 nonsteroidal anti-inflammatory medicines, antihistamines and/or corticosteroids. Pre-infusion administration of these medicines is advisable in some patients.

Sixty-seven per cent (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.

Post-marketing experience:

During the post-marketing period, the adverse reaction profile was generally similar to that seen during the clinical studies. Adverse effects seen during the post-marketing period included: feeling hot and cold, malaise, musculoskeletal pain, oedema, rhinitis, rhinorrhoea, and oxygen saturation decreased/hypoxia. Infusion site reaction was seen and not unexpected given the route of administration. One patient reported an event of leukocytoclastic vasculitis. One case of membranous glomerulonephritis has been reported.

A small number of patients have experienced anaphylactoid reactions which in some cases were considered life-threatening. Signs and symptoms of possible anaphylactoid reactions have included events of localised angioedema, generalised urticaria, bronchospasm and hypotension (see section 4.4).

Reporting of suspected adverse reactions

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

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

4.9 Overdose

See section 4.8. Treatment is symptomatic and supportive.

There have been no reports of overdose with FABRAZYME. In clinical trials, patients have received doses up to 3,0 mg/kg body weight.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.31 Enzymatic preparations.

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

ATC code: A16AB04

Fabry disease is characterised by the deficiency of α-galactosidase A, a lysosomal hydrolase which catalyses the hydrolysis of glycosphingolipids, in particular globotriaosylceramide (GL-3), to terminal galactose and ceramide dihexoside. Reduced or absent α-galactosidase activity results in the accumulation of GL-3 in many cell types, including the endothelial and parenchymal cells.
The rationale for enzyme replacement therapy is to restore a level of enzymatic activity sufficient to hydrolyse the accumulated substrate. 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.

5.2 Pharmacokinetic properties

Plasma profiles of agalsidase beta were studied at 0,3; 1,0 and 3,0 mg/kg in 15 adult patients with Fabry disease. The area under the plasma concentration-time curve (AUC_{∞}) and the clearance did not increase proportionately with increasing doses, demonstrating that the enzyme follows non-linear pharmacokinetics. Terminal half-life was dose independent with a range of 45 – 102 minutes.

Pharmacokinetics of agalsidase beta was evaluated in 11 adult Fabry patients in Europe. Following an intravenous infusion of 1 mg/kg of agalsidase beta over a period averaging 280 – 300 minutes, mean maximum plasma concentrations (C_{max}) ranged from 2,09 to 3,49 µg/mL. The mean AUC_{∞} ranged from 372 to 784 µg/mL•min. The mean volume of distribution (V_z) was 0,23 – 0,49 L/kg and the mean volume of distribution at steady state (V_{ss}) was 0,12 to 0,57 L/kg. Mean plasma clearance

ranged from 1,75 to 4,87 mL/min/kg and the mean elimination half-life ($t_{1/2}$) ranged from 82,3 to 119 minutes.

Pharmacokinetics of agalsidase beta was also evaluated in 13 Fabry patients in Japan. The results of these evaluations show that agalsidase beta pharmacokinetics is comparable in Caucasian and Japanese Fabry patients.

In 15 paediatric Fabry patients (ranging in age from 8 to 16 years old and weighing between 27,1 and 64,9 kg) who were dosed with 1,0 mg/kg every 14 days, agalsidase beta pharmacokinetics were not weight-dependent. After single dose administration, baseline clearance was 77 mL/min with a volume of distribution at steady state (V_{ss}) of 2,6 L; half-life was 55 minutes. After IgG seroconversion, clearance decreased to 35 mL/min, V_{ss} increased to 5,4 L, and half-life increased to 240 minutes. The net effect of these changes after IgG seroconversion was an increase in exposure of 2- to 3-fold based on AUC and C_{max}. As a result, agalsidase beta concentrations were about 5 times higher after IgG seroconversion, without any detectable impact on efficacy (GL-3 clearance). Between-subject variability was moderate: 37 % for clearance (CL) and 26 % for V_{ss}.

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/fetal 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.

6.2 Incompatibilities

In the absence of compatibility studies, FABRAZYME must not be mixed with other medicines in the same infusion.

6.3 Shelf life

Unopened vials:

3 years.

Reconstituted and diluted solutions:

FABRAZYME contains no preservatives. From a microbiological point of view, FABRAZYME reconstituted and diluted solution 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 may be stored for up to 24 hours at 2 °C – 8 °C.

6.4 Special precautions for storage

Store under refrigeration, between 2 °C and 8 °C.

DO NOT USE after the expiration date on the vial.

For storage conditions after reconstitution and dilution of FABRAZYME, see section 6.3.

6.5 Nature and contents of container

FABRAZYME 5 mg is supplied in a single-use, clear type I glass 5 mL vial (5 mg). The closure consists of a grey siliconised butyl stopper and an aluminium seal with a grey plastic flip-off cap.

Pack size: 1 vial per carton.

FABRAZYME 35 mg is supplied in a single-use, clear type I glass 20 mL vial (35 mg). The closure consists of a grey siliconised butyl stopper and an aluminium seal with a purple plastic flip-off cap.

Pack size: 1 vial per carton.

6.6 Special precautions for disposal and other handling

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

Prolonged exposure of FABRAZYME to the air/liquid interface, either through time or by agitation, may cause the formation of protein particles. Stress handling and forced particle formation studies have been performed to assess the impact of an in-line filter on drug product and dose in the presence of these particles. Following the admixture of FABRAZYME into 0,9 % sodium chloride infusion bags, and induction of particles, the use of an in-line low protein binding 0,2 µm filter led to the removal of the visible particles, with no detectible loss of protein or activity.

Each vial of FABRAZYME is intended for single use only.

Reconstitution and dilution (using aseptic technique):

1. FABRAZYME vials and diluent should be allowed to reach room temperature (23 °C to 27 °C) prior to reconstitution (approximately 30 minutes). The number of vials is based on the body weight (kg) of the patient and the recommended dose of 1,0 mg/kg.
2. Reconstitute each **FABRAZYME 5 mg** vial by slowly injecting 1,1 mL of sterile water for injection, to the inside wall of each vial and not directly onto the lyophilised cake. Roll and tilt each vial gently. Do not invert, swirl or shake the vial. Each vial will yield a 5,0 mg/mL clear, colourless solution (total extractable dose per vial is 5 mg, 1,0 mL).

Reconstitute each **FABRAZYME 35 mg** vial by slowly injecting 7,2 mL of sterile water for injection, down the inside wall of each vial and not directly onto the lyophilised cake. Roll and tilt each vial gently. Do not invert, swirl or shake the vial. Each vial will yield a 5,0 mg/mL clear, colourless solution (total extractable dose per vial is 35 mg, 7,0 mL).

3. Visually inspect the reconstituted vials for particulate matter and discolouration. Do not use the reconstituted solution if there is particulate matter or if it is discoloured.
4. After reconstitution, it is recommended to promptly dilute the vials. Failure to promptly dilute the vials could result in particle formation.
5. FABRAZYME should be diluted in 9 mg/mL (0,9 %) sodium chloride solution for infusion, immediately after reconstitution.

   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 minimise the air/liquid interface. Slowly withdraw 1,0 mL (equal to 5 mg) or 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.
6. Then slowly inject the reconstituted solution directly into the 0,9 % sodium chloride intravenous solution (not into any remaining airspace) to a final concentration between 0,05 mg/mL and 0,7 mg/mL. Determine the total volume of 0,9 % sodium chloride 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 of 35 to 70 mg use a minimum of 100 mL, for doses of 70 to 100 mg use a minimum of 250 mL and for doses greater than 100 mg use only 500 mL. Be sure to inject the reconstituted FABRAZYME solution directly into the 0,9 % sodium chloride solution.

   Discard any vial with unused reconstituted solution.
7. Gently invert or lightly massage the infusion bag to mix the solution, avoiding vigorous shaking and agitation.
8. FABRAZYME should not be infused in the same intravenous line with other products.

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. HOLDER OF CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd

Hertford Office Park, Building I, 5th Floor

90 Bekker Road, Vorna Valley

Midrand 2196

South Africa

8. REGISTRATION NUMBERS

FABRAZYME 5 mg: 46/31/0583

FABRAZYME 35 mg: 46/31/0584

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 December 2017

10. DATE OF REVISION OF THE TEXT

28 October 2022