AUSTRALIAN PRODUCT INFORMATION – FABRAZYME (AGALSIDASE BETA - RCH)

1 NAME OF THE MEDICINE

Fabrazyme, agalsidase beta-rch mg powder for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Fabrazyme 5 mg – each vial contains a nominal value of 5 mg of agalsidase beta.

Fabrazyme 35 mg – each vial contains a nominal value of 35 mg of agalsidase beta.

After reconstitution with Sterile Water for Injection (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Instructions for Use) the resulting solution has an agalsidase beta concentration of 5 mg/mL and a pH of approximately 7. The reconstituted solution must be diluted further. The diluted solution may be filtered through an in-line low protein-binding 0.2 μm filter during administration.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Fabrazyme is supplied as a sterile, non-pyrogenic, white to off-white lyophilised powder in a clear glass vial. Fabrazyme is a powder for injection.

Fabrazyme is intended for intravenous infusion.

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 deficiency).

4.2 DOSE AND METHOD OF ADMINISTRATION

Therapy with FABRAZYME should only be initiated or continued by a physician with expertise in the treatment of Fabry disease (see Section 4.4 SPECIAL WARNING AND PRECAUTIONS FOR USE).

If an infusion-associated reaction occurs during a FABRAZYME infusion, decreasing the infusion rate, temporarily stopping the infusion and/or administration of antipyretics, antihistamines and/or steroids may ameliorate the symptoms. Patients who experience an infusion -associated reaction during a FABRAZYME infusion should be treated with caution when FABRAZYME is re-administered. If severe allergic or anaphylactoid reactions occur,

immediate discontinuation of the administration of FABRAZYME and current medical standards for emergency treatment are to be observed.

Table 1 - Managing Therapy for Patients Experiencing Infusion-Associated Reactions

Event Severity and Frequency	Single Mild to Moderate Event or Recurrent Mild to Moderate Event	Single Severe Event or Recurrent Moderate to Severe Event
Pre-Treatment Regimen	Approximately 1 hr prior to infusion: - Antihistamines - Paracetamol/Ibuprofen	Approximately 13 hrs, 7 hrs, and 1 hr prior to infusion: - Corticosteroids* Approximately 1 hr prior to infusion: - Antihistamines - Paracetamol/Ibuprofen
Infusion Rate	~ 0.15 mg/min (10 mg/hr)*	~ 0.15 mg/min (10 mg/hr)*
*If infusion proceeds without incident, consideration may be given to increasing infusion rates in a stepwise manner and to reducing premedication.		

The recommended dosage is 1 mg/kg of FABRAZYME per dose, infused every 2 weeks. Dosage should be individualised for each patient and small adjustments can be made to avoid discarding partially used vials.

No dose adjustment is necessary for paediatric patients 8 - 16 years old. The safety and efficacy in patients younger than 8 years of age have not been evaluated. However, patients with Fabry disease younger than 8 years old may be treated with FABRAZYME when clearly needed and after a careful risk/benefit analysis has been conducted by the physician.

The initial infusion rate should be no more than 0.25 mg/min (15 mg/hr) 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. Home infusions will be administered by an appropriately trained healthcare professional. 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.

A Home Infusion Guide for HCPs and Patients/Carers is available to provide home infusion information related to Fabrazyme.

INSTRUCTIONS FOR USE

1 Determine the number of vials for reconstitution based on the patient's body weight (kg) and the recommended dose of 1 mg/kg.

2 Using aseptic technique, reconstitute each vial with Sterile Water for Injection to yield a 5 mg/mL clear, colourless solution. The final concentration and administration volumes are provided in Table 2 below:

Table 2 - Final Concentration and Administration Volumes

	5 mg Presentation	35 mg Presentation
Sterile water for reconstitution	1.1 mL	7.2 mL
Final volume of reconstituted product	1.1 mL	7.4 mL
Concentration after reconstitution	5 mg/mL	5 mg/mL
Extractable volume	1.0 mL	7.0 mL
Amount (mg) of enzyme within extractable volume	5 mg	35 mg

3 Visually inspect the reconstituted vials for particulate matter and discolouration. Do not use vials exhibiting particulate matter or discolouration. FABRAZYME does not contain preservatives. Vials are for single use only.

4 Immediately withdraw reconstituted solution from each vial, and using aseptic technique, further dilute with 0.9% Sodium Chloride for Injection to a total volume based on the individual dose dispensed (see Table 3 below). Total infusion volumes as low as 50 mL were used in the Phase 1/2 trial.

Table 3 - Minimum Total Volume for Infusion Based on Individual Dose

Individual Patient Dose Dispensed (mg)	Minimum Total Volume
<35	50
35.1 to 70	100
70.1 to 100	250
>100	500

5 Administer the solution intravenously at an initial rate of no more than 0.25 mg/min. The diluted solution may be filtered through an in-line low protein-binding 0.2 µm filter during administration.

6 FABRAZYME should not be infused in the same intravenous line with other products.

FABRAZYME does not contain any preservatives; therefore after dilution with saline in the infusion bag, the unused product should be discarded.

4.3 CONTRAINDICATIONS

Treatment with FABRAZYME is contraindicated if there is clinical evidence of anaphylaxis to agalsidase beta or any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The diagnosis, assessment and management of Fabry disease should only be undertaken by physicians with experience and training in the treatment of inherited diseases of metabolism. FABRAZYME therapy should only be initiated or continued under the ongoing supervision of a physician with such expertise in the treatment of Fabry disease.

As with any intravenously administered protein product, patients may develop IgG antibodies to FABRAZYME (see Section 4.8 ADVERSE EFFECTS). Some patients develop IgE or skin reactivity specific to FABRAZYME. Patients with antibodies to FABRAZYME have a higher risk of infusion -associated reactions (see Section 4.8 ADVERSE EFFECTS).

Physicians should consider testing for IgE (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE: Laboratory Tests) in patients who experienced suspected allergic reactions and consider the risks and benefits of continued treatment in patients with anti-FABRAZYME IgE.

Patients treated with FABRAZYME may develop infusion-associated reactions, the majority of which are mild to moderate in intensity. If an infusion-associated reaction occurs during a FABRAZYME infusion, decreasing the infusion rate, temporarily stopping the infusion and/or administration of antipyretics, antihistamines, and/or steroids may ameliorate the symptoms (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Patients who experience an infusion-associated reaction during a FABRAZYME infusion should be treated with caution when FABRAZYME is re-administered. If severe allergic or anaphylactoid reactions occur, immediate discontinuation of the administration of FABRAZYME and 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. Patients who have had a positive skin test or who have tested positive for IgE antibodies to r-hαGAL have been successfully rechallenged with FABRAZYME. The initial rechallenge administration should be at a low dose and a lower infusion rate [1/2 the therapeutic dose (0.5mg/kg) at 1/25 the initial standard recommended rate (0.01mg/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.

Studies in humans have not been conducted to assess the potential effects of FABRAZYME on impairment of fertility.

FABRAZYME at the proposed clinical use may not produce significant hepatic toxicity, but caution should be exercised in patients with hepatic impairment.

Laboratory tests

It is suggested that patients be monitored routinely for IgG antibody formation. The recommendation for long-term routine antibody monitoring should be as follows: samples should be drawn at baseline, every 3 months until month 18 and then every 6 months until the results are negative. Once one negative result has been obtained, an additional sample will be collected to confirm the patient has tolerised. Clinicians may submit a sample at any time for

immediate testing in the event a patient experiences a reaction that is suspected to be immune-mediated.

Use in the elderly

Clinical studies did not include any subjects aged 65 and over and therefore did not determine whether they respond differently from younger subjects.

Paediatric use

Safety and efficacy of FABRAZYME have been investigated in children aged 8 - 16 years (see PHARMACOLOGY, Pharmacokinetics and CLINICAL TRIALS). Patients younger than 8 years of age were not included in clinical studies. The safety and efficacy in patients younger than 8 years of age have not been evaluated. Patients younger than 8 years of age with Fabry disease may be treated with FABRAZYME when clearly needed and after a careful risk/benefit analysis has been conducted by the physician.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal drug/drug interaction studies were performed. In the absence of drug interaction studies, FABRAZYME must not be mixed with other medicinal products in the same infusion.

No in vitro metabolism studies have been carried out. Based on its metabolism, agalsidase beta is an unlikely candidate for cytochrome P450-mediated drug/drug interactions. FABRAZYME is not recommended to be administered with chloroquine, amiodarone, benoquin or gentamicin due to a theoretical risk of inhibited intracellular α-galactosidase activity.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There have been no studies conducted to assess the potential effect of FABRAZYME on fertility.

Use in pregnancy (Category B2)

Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

There are limited data from the use of agalsidase beta in pregnant women.

A study to evaluate the effects of agalsidase beta on embryofetal development in rats was conducted. Agalsidase beta did not affect embryofetal development in rats at IV doses up to 30 mg/kg/day during organogenesis, associated with maternal plasma AUC about 45 times that expected in humans.

As a precautionary measure, it is preferable to avoid the use of FABRAZYME during pregnancy.

Use in lactation

Agalsidase beta is excreted in human milk. The effect of agalsidase beta on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from FABRAZYME therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the ability to drive and use machines have been conducted with FABRAZYME.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

Table 4 below presents the incidence of adverse drug reactions, related to FABRAZYME, in a total of 181 patients treated with FABRAZYME in the Phase 1/2 Extension study, the Phase 3 Double–Blind/Open-Label Extension studies, the Phase 2 Japan Bridging study, the Phase 4 Double-Blind study/Open-Label Extension and the Phase 2 Paediatric studies for a minimum of one infusion to a maximum of 5 years. The majority of these product-related adverse events were judged to be mild to moderate in severity. Currently available data demonstrate that the total number of FABRAZYME-treated patients experiencing any related adverse event on the same day as infusion has decreased over time. Observed adverse events in the Phase 1/2 study and the open-label treatment period following the controlled study were not different in nature or severity.

In the Phase 2 paediatric study (AGA-016-01), the safety profile of FABRAZYME treatment in paediatric Fabry disease patients, ages 8 to 16 years, was found to be consistent with that seen in adults. The safety of FABRAZYME in patients younger than 8 years of age has not been evaluated.

Table 4 - Incidence of Adverse Drug Reactions with FABRAZYME® Treatment (Seven Studies Combined: Phase 1/2 Extension, Phase 3 Double-Blind, Phase 3 Extension, Phase 2 Japan, Phase 4 Double-Blind, Phase 4 Extension and Phase 2 Paediatric)

System Organ Class	≥10% of Patients	≥5% up to 10% of Patients	≥1% up to 5% of Patients[a]
Cardiac disorders	---	tachycardia	palpitations
Eye disorders	---	---	lacrimation increased
Gastrointestinal disorders	nausea, vomiting	abdominal pain	abdominal pain upper, abdominal discomfort, stomach discomfort, hypoaesthesia oral

System Organ Class	≥10% of Patients	≥5% up to 10% of Patients	≥1% up to 5% of Patients[a]
General disorders and administration site conditions	chills, pyrexia, feeling cold	fatigue, chest discomfort, feeling hot	oedema peripheral, pain, asthenia, chest pain, malaise, face oedema, hyperthermia
Investigations	---	blood pressure increased, body temperature increased	heart rate increased, blood pressure decreased
Musculoskeletal and connective tissue disorders	---	pain in extremity	myalgia, back pain, muscle spasms, arthralgia, muscle tightness, musculoskeletal stiffness
Nervous system disorders	headache, paraesthesia	dizziness, somnolence	hypoaesthesia, burning sensation, lethargy
Respiratory, thoracic and mediastinal disorders	---	Dyspnoea, nasal congestion	throat tightness, wheezing, cough, dyspnoea exacerbated
Skin and subcutaneous tissue disorders	---	pruritus, urticaria	rash, erythema, pruritus generalised, angioneurotic oedema, swelling face
Vascular disorders	---	flushing	hypertension, pallor; hypotension, hot flush

Reference: TAEREL.SAS

[a] For the purpose of this table, ≥1% is defined as events occurring in 2 or more patients.

The occurrence of somnolence can be attributed to clinical trial specified pre-treatment with antihistamines. Most of the patients had experienced one or more infusion-associated events during the long-term treatment.

One hundred and twenty eight (128) of 181 patients in the 7 clinical studies combined experienced at least one adverse event (AE) that was considered related to FABRAZYME treatment. Additional drug-related AEs as assessed by the investigator seen in ≥1% of patients in clinical trials include (≥1% defined as occurring in at least one patient):

Blood and Lymphatic System Disorders: anaemia, eosinophilia, leucopoenia.

Cardiac Disorders: aortic valve incompetence, arrhythmia, bradycardia, arrhythmia supraventricular, bundle branch block right, cardiac arrest, cardiac valve disease, dilatation atrial, dilation ventricular, mitral valve disease, mitral valve incompetence, mitral valve sclerosis, pulmonary valve incompetence, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles, ventricular hypokinesia.

Ear and Labyrinth Disorders: auricular swelling, ear discomfort, ear pain, tinnitus, vertigo.

Eye Disorders: diplopia, eye oedema, eye pruritus, night blindness, ocular hyperaemia, vision blurred, visual acuity reduced, visual disturbance.

General Disorders and Administration Site Conditions: axillary pain, catheter site rash, catheter site related reaction, discomfort, feeling cold and hot, feeling jittery, gait disturbance, influenza-like illness, infusion site pain, infusion site reaction, injection site thrombosis, oedema, sluggishness, thirst.

Gastrointestinal Disorders: dysphagia, dyspepsia, gastroenteritis, gingivitis, retching.

Immune System Disorders: seasonal allergy.

Infections and Infestations: gingival infection, infection, rash pustular, nasopharyngitis, rhinitis, tooth infection.

Injury, Poisoning and Procedural Complications: excoriation, fall, post-procedural nausea, vascular access complication.

Musculoskeletal and Connective Tissue Disorders: chest wall pain, flank pain, groin pain, joint stiffness, musculoskeletal chest pain, musculoskeletal pain, pain in jaw, shoulder pain.

Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, cardiac imaging procedure abnormal, cardiac output decreased, creatinine renal clearance decreased, cystatin C increased, ejection fraction decreased, electrocardiogram PR shortened, electrocardiogram ST segment abnormal, electrocardiogram T wave abnormal, haematocrit decreased, haemoglobin decreased, heart rate irregular, hepatic enzyme increased, prostate examination abnormal, intraocular pressure increased, right ventricular systolic pressure increased, albumin urine present/protein urine present, skin test positive.

Metabolism and Nutrition Disorders: hypocalcaemia.

Nervous System Disorders: cerebrovascular accident/ischaemic stroke, migraine, psychomotor hyperactivity, sinus headache, syncope/syncope vasovagal, restless legs syndrome, tremor, balance disorder, dyskinesia, hyperaesthesia.

Psychiatric Disorders: agitation, anxiety, confusional state, depression, hallucination visual, flat effect, restlessness.

Renal and Urinary Disorders: dysuria, haematuria, renal failure, renal impairment, benign prostatic hyperplasia, proteinuria.

Reproductive System and Breast Disorders: dysmenorrhoea, nipple pain, erectile dysfunction.

Respiratory, Thoracic and Mediastinal Disorders: bronchospasm, productive cough, pharyngolaryngeal pain, pulmonary oedema, respiratory distress, rhinitis allergic, rhinorrhea, rhonchi, tachypnoea, throat irritation, upper respiratory tract congestion.

Skin and Subcutaneous Tissue Disorders: acne, eczema, generalised erythema, hair growth abnormal, rash erythematous, rash maculo-papular, rash pruritic, livedo reticularis, skin discolouration, skin discomfort, urticaria localised.

Vascular Disorders: orthostatic hypotension, peripheral coldness, poor peripheral circulation, poor venous access, vasoconstriction and vasospasm.

The safety profile of FABRAZYME treatment in paediatric patients was consistent with that seen in adults.

Infusion-associated reactions (IARs) (defined as product-related adverse events occurring on the same day as the infusion) were the most frequently reported related adverse events in the 7 clinical studies discussed in Table 4. The majority (65%) of patients ever on

FABRAZYME experienced at least one infusion-associated event during the long-term treatment. These IARs included events of chills, fever (pyrexia/body temperature increased/hyperthermia), temperature change sensation (feeling cold/feeling hot), hypertension (blood pressure increased), nausea, vomiting, flushing (hot flush), paraesthesia (burning sensation), fatigue (lethargy/malaise/asthenia), pain (pain in extremity), headache, chest pain (chest discomfort), pruritus (pruritus generalised), urticaria, dyspnoea (dyspnoea exacerbated), dizziness, pallor, somnolence and tachycardia.

In the majority of patients, the adverse events associated with FABRAZYME infusions have been successfully managed using standard medical practices, such as reduction in infusion rate and/or pre-medication with, or additional administration of non-steroidal anti-inflammatory drugs, antipyretics, antihistamines and/or corticosteroids.

The majority of these IARs are thought to be associated with the formation of IgG antibodies and/or complement activation. The majority of patients developed IgG antibodies to r-hαGAL, which is not unexpected (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). The mean time to seroconversion was within three months of the first infusion of treatment with FABRAZYME. The majority of 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) or tolerised (no detectable antibody by radioimmunoprecipitation (RIP)). There was no evidence that IgG seroconversion inhibited or neutralised the activity of FABRAZYME.

Post-Marketing Adverse Drug Reactions

During the post-marketing period, the adverse drug reaction profile was generally similar to that seen during the clinical studies. Adverse drug reactions 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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Alimentary tract and metabolism, ATC code: A16AB04

Mechanism of action

Fabry disease is a rare genetic disorder of glycosphingolipid metabolism. Deficiency of the lysosomal enzyme α-galactosidase leads to progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide (GL-3), in most body tissues and fluids. Progressive accumulation of GL-3 occurs predominantly in the lysosomes of endothelial, perithelial and smooth-muscle cells of blood vessels. GL-3 accumulation also occurs in ganglion cells of the autonomic nervous system, cardiomyocytes of the heart, epithelial cells of glomeruli and tubules in the kidney, epithelial cells of the cornea, and cells of many other tissues.

Excessive accumulation of GL-3 in the vascular wall results in narrowing and thrombosis of arteries and arterioles. This derangement of the vascular architecture often involves capillaries and has been implicated in the development of peripheral neuritis, angiokeratoma corporis diffusum universale, renal failure, myocardial infarction and cerebral infarction. Ultimately, premature death results from renal disease, cardiac disease or cerebrovascular disease.

FABRAZYME is intended as an enzyme replacement therapy to provide an exogenous source of α-galactosidase in Fabry disease patients who are deficient or lacking endogenous enzyme. This recombinant human α-galactosidase (r-hαGAL) will catalyse the hydrolysis of glycosphingolipids including GL-3. The clinical studies conducted with FABRAZYME support this mechanism of action.

Histological analysis of tissues from patients in the Phase 1/2 trial showed that treatment with FABRAZYME at all dose regimens tested resulted in reduction of GL-3 from the vasculature of the kidney, heart and skin. GL-3 was cleared from the plasma in a dose-dependent manner (also refer to Section 5.1 PHARMACODYNAMIC PROPERTIES, CLINICAL TRIALS).

Clinical trials

The safety and efficacy of FABRAZYME were assessed in a randomised, double-blind, placebocontrolled, multicentre study of 58 patients (56 males and 2 females), 16 to 61 years of age. Patients received 1 mg/kg of FABRAZYME or placebo every other week for 5 months (20 weeks) for a total of 11 infusions. The primary efficacy variable, GL-3 clearance from renal vascular endothelium, was assessed by light microscopy and was graded on an inclusion severity score ranging from 0 (near normal) to 3 (severe). The prospectively defined renal efficacy endpoint (score of 0) was achieved in 20 of 29 (69%) patients treated with FABRAZYME. In contrast, no patients receiving placebo attained this efficacy endpoint ($p<0.0001$). Similar results were achieved in the capillary endothelium of the heart and skin (refer to

Table 5).

The safety and efficacy of FABRAZYME were further investigated in an open-label, multicentre extension study, in which FABRAZYME therapy was administered at 1 mg/kg to all 58 participants of the original pivotal trial for an additional 54 months of treatment.

Table 5 - Reduction of GL-3 Inclusions to Normal or Near - Normal Levels (0 Score) in the Capillary Endothelium of the Kidney, Heart and Skin

	5 Months of the Placebo-Controlled Study (AGAL-1-002-98)		6 Months of the Open-Label Extension Study (AGAL-005-99)		54 Months of the Open-Label Extension Study (AGAL-005-99)
	Placebo (n=29)	FABRAZYME® (n=29)	Placebo/ FABRAZYME® (n=29)*	FABRAZYME®/ FABRAZYME® (n=29)*	All Patients (n=58)*
Kidney	0/29	20/29	24/24	23/25	8/8**
Heart	1/29	21/29	13/18	19/22	6/8**
Skin	1/29	29/29	25/26	26/27	31/36

* Results reported where biopsies were available.

** Biopsies at the 54-month time point were optional in the AGAL-005-99 study.

Mean plasma GL-3 levels showed a rapid decrease and return to normal levels (i.e., <7.03 µg/mL) within 6 months (i.e., first time point tested) of treatment with FABRAZYME. Importantly, mean plasma GL-3 levels remained normal through Month 54 (end of the study). Additionally, a retrospective histological review of other renal cell types confirmed that GL-3 is cleared to normal or near normal levels from mesangial cells, glomerular capillary endothelium, interstitial cells and non-capillary endothelium**,** and reduced in cell types with the highest substrate burden (vascular smooth muscle cells, tubular epithelium and podocytes).

During the extended follow-up, the kidney function, as measured by estimated GFR and serum creatinine, remained stable throughout the study.

The safety and clinical efficacy of FABRAZYME were also assessed in a randomised (2:1), Phase 4 double-blind, placebo-controlled, multinational, multicentre study of 82 Fabry patients (72 males and 10 females). Patients received either 1 mg/kg of FABRAZYME or placebo every other week for up to a maximum of 35 months. The primary efficacy endpoint was the time to clinically significant progression of the composite outcomes of renal, cardiac and cerebrovascular disease and/or death. Among the 82 patients enrolled, 13 patients (42%) in the placebo group and 14 patients (27%) in the FABRAZYME group met the pre-defined clinical endpoint (progression of clinical symptoms). The results are summarised in Table 6 and Figure 1**.**

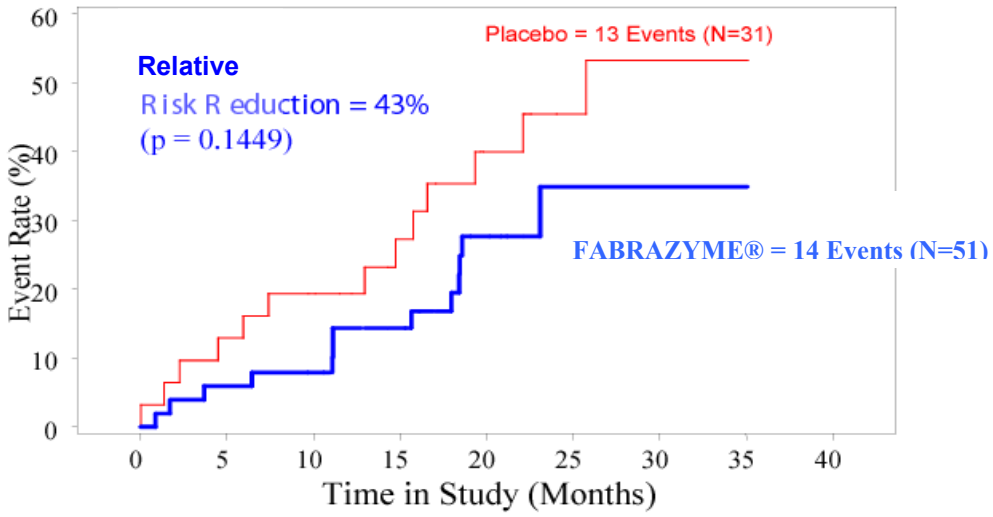
Table 6 - Summary of Primary Efficacy Endpoint: Intent - to - Treat Population

FABRAZYME® (n=51)	Placebo (n=31)	Hazard Ratio (95% CI)	*p*-Value[1]	Absolute Difference (95% CI)	NNT[2]
14 (27%)	13 (42%)	0.57 (0.27-1.22)	0.145	14.5% (-6.1-34.6%)	7

[1] 2-sided log-rank procedure

[2] Numbers needed to treat for 22 months to prevent one composite outcome event

Figure 1 - Kaplan-Meier Estimate of Time to First Occurrence of a Primary Endpoint: Intent-to-Treat Population



While benefit was seen in patients with varying severity of disease, the most pronounced benefit was observed among patients who had less severe disease at baseline.

Paediatric Use

Efficacy and safety of FABRAZYME were studied in an open-label paediatric study. In this 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 skin vascular endothelium was achieved in all patients who had accumulated GL-3 at baseline. Since FABRAZYME treats the underlying pathology of Fabry disease by significantly clearing GL-3 from vascular endothelium of the kidney, heart and skin, paediatric patients younger than 8 years old would be expected to benefit from treatment with FABRAZYME.

Use in the Elderly

Clinical studies did not include any subjects aged 65 and over and therefore did not determine whether they respond differently from younger subjects.

5.2 PHARMACOKINETIC PROPERTIES

Plasma profiles of agalsidase beta were studied in adults at 0.3, 1 and 3 mg/kg. The area under the plasma concentration-time curve (AUC_∞) did not increase proportionately with increasing dose, demonstrating that the drug displays non-linear pharmacokinetics. Terminal half-life was dose independent with a range of 45 to 102 minutes.

Pharmacokinetics of agalsidase beta were also evaluated in 11 adult Fabry patients participating in a Phase 3 pivotal clinical trial. Following an intravenous infusion of 1 mg/kg FABRAZYME over a period averaging 280 to 300 minutes, mean maximum plasma concentrations (C_{max}) ranged from 2000 to 3500 ng/mL. The mean AUC_{∞} ranged from 372 to 784 min•µg/mL. The mean volume of distribution (V_z) was 0.23 to 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.

FABRAZYME pharmacokinetics were also evaluated in 15 paediatric patients (8.5 to 16 years old weighing 27.1 to 64.9 kg). Weight did not influence FABRAZYME pharmacokinetics in this population. Baseline clearance was 129 mL/min with a volume of distribution at steady-state (Vd_{ss}) of 21.4 L; half-life was 84 min. After seroconversion, clearance decreased to 37 mL/min, Vd_{ss} decreased to 8.6 L, and half-life increased to 156 min. The net effect of these changes after seroconversion was an increase in exposure of 2 to 4-fold based on AUC and C_{max}. This increase in exposure after seroconversion was not correlated with an increased incidence of adverse events nor did it result in a change in efficacy.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

There have been no studies conducted to assess the mutagenic potential of FABRAZYME.

Carcinogenicity

There have been no studies conducted to assess the carcinogenic potential of FABRAZYME.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol

Monobasic sodium phosphate monohydrate

Dibasic sodium phosphate heptahydrate

FABRAZYME does not contain preservatives. Vials are for single use only.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

To reduce microbiological hazard, use as soon as practicable after reconstitution/dilution.

FABRAZYME diluted for infusion in 0.9% Sodium Chloride for Injection is stable for up to 24 hours when stored at 2°C to 8°C (36°F to 46°F), without microbial contamination. The diluted solution may be filtered through an in-line low protein-binding 0.2 μm filter during administration.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store FABRAZYME under refrigeration between 2°C to 8°C (36°F to 46°F). DO NOT USE FABRAZYME after the expiration date on the vial. This product contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

6.5 NATURE AND CONTENTS OF CONTAINER

Fabrazyme 5 mg is supplied in clear Type I glass 5 ml vials. 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.

Pack size: 1 vial per carton.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

FABRAZYME is produced by recombinant DNA technology and is an enzyme replacement for the human enzyme, α-galactosidase A enzyme with the same amino acid sequence as the native enzyme. Alpha-galactosidase catalyses the hydrolysis of globotriaosylceramide (GL-3) and other α-galactyl-terminated neutral glycosphingolipids, such as galabiosylceramide and blood group B substances. GL-3 is hydrolysed to ceramide dihexoside and galactose. Purified agalsidase beta is a homodimeric glycoprotein with a molecular weight of approximately 100 kD. The mature protein is comprised of two subunits of 398 amino acids (approximately 51 kD), each of which contains three N-linked glycosylation sites. Agalsidase beta is produced by recombinant DNA technology in a Chinese hamster ovary cell line. The protein is purified by a column chromatography process that includes measures to inactivate and remove potential viruses, resulting in a highly purified, active protein.

CAS number

104138-64-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
E-mail: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

11 July 2006

10 DATE OF REVISION

8 April 2026

FABRAZYME® is a registered trademark of Genzyme Corporation, USA.

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8	Post marketing reporting section added
4.9	Poisons Information Centre statement reworded
8	Sponsor details updated