PRODUCT MONOGRAPH

Pr Fabrazyme®

Agalsidase Beta
(Recombinant human α-galactosidase A)

Lyophilized Powder
5 mg and 35 mg

Enzyme Replacement Therapy

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FABRAZYME®

Agalsidase Beta
Recombinant human α-galactosidase A

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Lyophilized powder for reconstitution and intravenous infusion 5 mg 35 mg	There are no clinically relevant nonmedicinal ingredients. For a complete listing of nonmedicinal ingredients, see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.

DESCRIPTION

Fabrazyme® (agalsidase beta) is a recombinant enzyme intended for use as replacement for the human enzyme, α-galactosidase A, (α-GAL). The characteristics of Fabrazyme® were consistent with the limited data (molecular weight, pH optimum and isoelectric focusing [IEF] patterns) available about the enzyme isolated from human sources (plasma, placenta, liver and spleen). α-GAL catalyzes the hydrolysis to ceramide dihexoside and galactose of globotriaosylceramide (GL-3) and other α-galactyl-terminated neutral glycosphingolipids, such as galabiosylceramide and blood group B substances. Accumulation of undegraded forms of these glycosphingolipids is the primary pathological process in Fabry disease.

INDICATIONS AND CLINICAL USE

Fabrazyme® (agalsidase beta) is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease. Fabrazyme® reduces globotriaosylceramide (GL-3) levels in the vascular endothelium and slows the rate of clinical progression in Fabry disease as manifested by renal, cardiac and cerebrovascular outcomes (see CLINICAL TRIALS).

Pediatrics (≥ 8 years of age):
The safety and efficacy of Fabrazyme® has been demonstrated in Fabry patients at least 8 years of age. The safety and efficacy of Fabrazyme® have not been studied in children below the age of 8 years. (see WARNINGS AND PRECAUTIONS, Pediatrics and CLINICAL TRIALS)

CONTRAINDICATIONS

Treatment with Fabrazyme® (agalsidase beta) is contraindicated if there is clinical evidence of anaphylaxis to agalsidase beta or any of the excipients.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

As with any intravenous protein product, allergic-type hypersensitivity reactions have been observed in patients receiving Fabrazyme® infusions including anaphylaxis or anaphylaxis-like reactions. [see Anaphylaxis and Allergic Reactions, Infusion Reactions and Immunogenicity and Rechallenge]

Overall, during the double-blind, placebo-controlled period of the study, 23 of 48 (47.9 %) patients in the Fabrazyme® (agalsidase beta)-treated group compared to 8 of 29 (27.6 %) in the placebo-treated group had centrally-read QT/QTc prolongations (defined as any QTc interval >450 msec) at any time point during the study, including prior to treatment. Of these patients with QT/QTc intervals > 450 msec, 7 of 23 (30%) patients in the Fabrazyme®-treated group compared to 1 of 8 (13%) patients in the placebo-treated group had a QTc interval increase from baseline ≥ 60 msec.

Anaphylaxis and Allergic Reactions

Life-threatening anaphylactic and severe allergic reactions have been observed in patients during Fabrazyme® infusions. Reactions have included localized angioedema (including swelling of the face, mouth, and throat), bronchospasm, hypotension, generalized urticaria, dysphagia, rash, dyspnea, flushing, chest discomfort, pruritus, and nasal congestion. Interventions have included cardiopulmonary resuscitation, oxygen supplementation, IV fluids, hospitalization, and treatment with inhaled beta-adrenergic agonists, epinephrine, and IV corticosteroids.

If anaphylactic or severe allergic reactions occur, immediately discontinue the administration of Fabrazyme® and initiate necessary emergency treatment. Because of the potential for severe allergic reactions, appropriate medical support measures should be readily available when Fabrazyme® is administered.

The risks and benefits of re-administering Fabrazyme® following an anaphylactic or severe allergic reaction should be considered. Extreme care should be exercised, with appropriate medical support measures readily available, if the decision is made to re-administer the product. (see WARNINGS AND PRECAUTIONS–Immunogenicity and Rechallenge and CLINICAL TRIALS).

Infusion Reactions

Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions, and these patients should be monitored closely during Fabrazyme® administration.

Most Fabry patients have no detectable α-GAL protein levels or activity; therefore, it is expected that the majority of patients will develop IgG antibodies (seroconvert) upon treatment. Patients with antibodies to Fabrazyme® have a higher risk of infusion-associated reactions (IARs). The mean time to seroconversion was within 3 months of the first infusion with Fabrazyme®. The percentage of patients with IARs peaked early in the treatment period and coincided with IgG seroconversion. (see WARNINGS AND PRECAUTIONS, Immunogenicity and Rechallenge and ADVERSE REACTIONS)

In clinical trials, infusion-associated reactions were the most frequently reported related adverse events occurring in patients treated with Fabrazyme®. 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), and pruritus (pruritus generalized). The majority of these infusion-associated reactions were assessed as mild or moderate in intensity.

Infusion site reactions and catheter complications (including pain, infiltration at the IV site, bleeding and infection) would not be unexpected given the route of drug administration.

As a preventive measure, it is recommended that patients are treated with antipyretics prior to an infusion. If an infusion-associated reaction occurs, regardless of pretreatment, the adverse events have been successfully managed by decreasing the infusion rate, temporarily stopping the infusion, and/or administering non-steroidal anti-inflammatory drugs, antipyretics, antihistamines and/or corticosteroids to ameliorate the symptoms. IARs have occurred in some patients after receiving pretreatment with antipyretics, antihistamines, and/or oral steroids. IARs

declined in frequency with continued use of Fabrazyme®. However, IARs may still occur despite extended duration of Fabrazyme® treatment.

The initial IV infusion rate should be no more than 0.25 mg/min (15 mg/hr). The infusion rate may be slowed in the event of infusion-associated reactions. After patient tolerance to the infusion is well established, the infusion rate may be increased gradually in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hr) with each subsequent infusion. For patients weighing < 30 kg, the maximum infusion rate should remain at 0.25 mg/min (15 mg/hr). For patients weighing ≥ 30 kg, the administration duration should not be less than 1.5 hours (based on individual patient tolerability).

Immunogenicity and Rechallenge

Most patients develop IgG antibodies to Fabrazyme® (see ADVERSE REACTIONS and ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics). IgG seroconversion in pediatric patients was associated with prolonged half-life of Fabrazyme®, a phenomenon rarely observed in adult patients [see ACTION AND CLINICAL PHARMACOLOGY - Pharmacokinetics]. A possible cause for this prolongation likely pertains to the ability of antibodies to act as "carriers" for their antigens. Among patients treated with Fabrazyme® in clinical trials, approximately 4% of patients developed IgE or skin test reactivity specific to Fabrazyme®. Physicians should consider testing for IgE (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests) in patients who experienced suspected allergic reactions and consider the risks and benefits of continued treatment in patients with anti-Fabrazyme® IgE. Skin testing can be considered based on the patient's clinical presentation of symptoms.

Patients who have had a positive skin test to Fabrazyme® or who have tested positive for Fabrazyme®-specific IgE antibody have been rechallenged with Fabrazyme® using a rechallenge protocol (see CLINICAL TRIALS). Two of six patients in the open-label rechallenge study (AGAL-019-01) discontinued treatment with Fabrazyme® prematurely due to recurrent infusion reactions. Following voluntary withdrawal from the study, one of these patients transitioned to treatment with commercially available Fabrazyme®. Four serious infusion reactions occurred in three patients during Fabrazyme® infusions, including bronchospasm, urticaria, hypotension, and development of Fabrazyme®-specific antibodies. Other infusion-related reactions occurring in more than one patient during the study included rigors, hypertension, nausea, vomiting, and pruritus. Rechallenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available.

Patients who have had a positive skin test to Fabrazyme® or who have tested positive for anti-Fabrazyme® IgE may be successfully rechallenged with Fabrazyme®. The initial re-challenge administration should be a low dose at a lower infusion rate, e.g., 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 approved dose of 1.0 mg/kg and the infusion rate may be increased by slowly titrating upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/min), as tolerated.

During the rechallenge with Fabrazyme®, particular attention must be taken for a patient with severe congestive heart failure or severe ischemic heart disease requiring beta-adrenergic blocking agents as these patients did not participate in the trial.

Special Populations

The Fabry Registry, sponsored by Genzyme Corporation, is an ongoing, observational database that tracks natural history and outcomes of patients with Fabry disease. Participation is open to all physicians managing patients with Fabry disease. Physicians are encouraged to collaborate, share observations, and generate hypotheses for evaluation, as well as assist in the collection of clinical data in an effort to guide and assess future therapeutic interventions.

The primary objectives of the Registry are:

- To enhance the understanding of the variability, progression and natural history of Fabry disease, including heterozygous females with the disease;
- To assist the Fabry medical community with the development of recommendations for monitoring patients and reports on patient outcomes to help optimize patient care;
- To characterize and describe the Fabry population as a whole; and
- To evaluate the long-term safety and effectiveness of Fabrazyme[7].

For a more detailed description of the Fabry Registry, please refer to the Fabry Registry Protocol, or contact The Fabry Registry team at 1-800-745-4447 or refer to the website, www.LSDregistry.net.

Pregnant Women:

Reproduction studies have been performed in rats at daily doses up to 30 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Fabrazyme®. However, since clinical trials have not been carried out in pregnant women with Fabry disease and there is no other clinical data to indicate safety in pregnancy, caution should be exercised if Fabrazyme® is to be used during pregnancy.

Nursing Mothers:

It is not known whether Fabrazyme® is secreted in human milk. However, since clinical trials have not been carried out in nursing women with Fabry disease and there is no other clinical data to indicate safety in this clinical situation, caution should be exercised if Fabrazyme® is to be administered to nursing women.

Pediatrics (≥ 8 years of age):

The safety and efficacy of Fabrazyme® in patients less than 8 years old have not been studied. The safety and efficacy of Fabrazyme® were assessed in an open-label study (AGAL-016-01) of 16 pediatric patients with Fabry disease who were ages 8 to 16 years at first treatment. The safety profile was found to be consistent with that seen in adults (see ADVERSE REACTIONS).

The safety and efficacy of Fabrazyme® has been demonstrated in Fabry patients at least 8 years of age.

Geriatrics:

Clinical studies of Fabrazyme® did not include sufficient number of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Monitoring and Laboratory Tests

There are no marketed tests for antibodies against Fabrazyme®. It is suggested that patients be monitored periodically for IgG antibody formation. If testing is warranted, contact your local Genzyme representative or Genzyme Corporation at 1-800-589-6215.

Effects on Ability to Drive or Handle Heavy Machinery

No studies on the ability to drive or use heavy machinery have been conducted with Fabrazyme®.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most frequently reported related adverse events in the clinical trials are infusion-associated and include: 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), and pruritus (pruritus generalized).

The most common serious adverse drug reactions requiring intervention [interruption or discontinuation of Fabrazyme® (agalsidase beta)], hospitalization or medical treatment were also IARs, including urticaria, fever, chills, tachycardia, tightness in chest/throat, or hypertension/hypotension (see **WARNINGS AND PRECAUTIONS, Infusion Reactions**). Most patients develop IgG antibodies to Fabrazyme® (see WARNINGS AND PRECAUTIONS, Infusion Reactions). Some patients developed IgE or skin test reactivity specific to Fabrazyme® see **WARNINGS AND PRECAUTIONS, Immunogenicity and Rechallenge**).

The adverse events associated with Fabrazyme® infusion have been successfully managed using standard medical practices, such as reduction in infusion rate and/or premedication with, or additional administration of non-steroidal anti-inflammatory drugs, antipyretics, antihistamines and/or corticosteroids.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

In clinical studies, Fabrazyme® (agalsidase beta) infusions were generally well tolerated.

The data described below reflect exposure of 80 patients, ages 16 to 61 years, to 1.0 mg/kg Fabrazyme® every two weeks in two separate randomized, double-blind, placebo-controlled clinical trials (AGAL-1-002-98 and AGAL-008-00) for periods ranging from 1 to 35 months (mean 15.5 months). Table 1 enumerates treatment-emergent adverse events (regardless of relationship) that occurred during the double-blind treatment periods of the two placebo-controlled trials. Reported adverse events have been classified by Medical Dictionary for Regulatory Activities (MedDRA) terminology System Organ Class and Preferred Term.

Table 1

Summary of Adverse Events Occurring in at least 5% of Patients treated with Fabrazyme® in Randomized, Double-Blind, Placebo Controlled Studies AGAL-1-002-98 and AGAL-008-00

MedDRA System Organ Class/ Preferred Term	**Fabrazyme® n=80 (%)**	**Placebo n=60 (%)**
Blood and Lymphatic System Disorders		
Anaemia	11 (14)	8 (13)
Cardiac Disorders		
Tachycardia	4 (5)	2 (3)
Ventricular Wall Thickening	4 (5)	1 (2)
Ear and Labyrinth Disorders		
Hypoacusis	4 (5)	0
Tinnitus	6 (8)	2 (3)
Gastrointestinal Disorders		
Stomach discomfort	5 (6)	1 (2)
Toothache	5 (6)	2 (3)
Vomiting	19 (24)	14 (23)
General Disorders and Administration Site Conditions		
Adverse event	8 (10)	3 (5)
Chest discomfort	4 (5)	1 (2)
Chills	34 (43)	8 (13)
Fatigue	20 (25)	10 (17)
Feeling cold	8 (10)	1 (2)
Oedema peripheral	17 (21)	4 (7)
Pain	13 (16)	8 (13)
Pyrexia	29 (36)	12 (20)
Infections and Infestations		
Bronchitis	6 (8)	3 (5)
Fungal infection	4 (5)	0
Lower respiratory tract infection	9 (11)	1 (2)
Nasopharyngitis	22 (28)	9 (15)
Pharyngitis	5 (6)	1 (2)
Sinusitis	7 (9)	2 (3)
Upper respiratory tract infection	15 (19)	6 (10)
Viral infection	4 (5)	0
Viral upper respiratory infection	5 (6)	1 (2)
Injury, Poisoning and Procedural Complications		
Excoriation	7 (9)	1 (2)
Fall	5 (6)	2 (3)
Post-procedural hemorrhage	4 (5)	1 (2)
Procedural pain	20 (25)	12 (20)
Investigations		
Blood bicarbonate decreased	7 (9)	4 (7)
Blood creatinine increased	7 (9)	3 (5)
Blood pressure increased	8 (10)	2 (3)
Body temperature increased	5 (6)	1 (2)
Musculoskeletal and Connective Tissue Disorders		

Back pain	13 (16)	6 (10)
Muscle spasms	4 (5)	1 (2)
Myalgia	6 (8)	2 (3)
Neck pain	4 (5)	1 (2)
Pain in extremity	15 (19)	5 (8)
Nervous System Disorders		
Burning sensation	5 (6)	0
Dizziness	17 (21)	6 (10)
Headache	31 (39)	17 (28)
Hypoaesthesia	7 (9)	5 (8)
Paraesthesia	25 (31)	11 (18)
Psychiatric Disorders		
Anxiety	6 (8)	3 (5)
Depression	5 (6)	1 (2)
Insomnia	7 (9)	4 (7)
Renal and Urinary Disorders		
Proteinuria	4 (5)	2 (3)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	26 (33)	15 (25)
Dyspnoea	6 (8)	1 (2)
Nasal congestion	15 (19)	9 (15)
Pharyngolaryngeal pain	13 (16)	9 (15)
Respiratory tract congestion	6 (8)	1 (2)
Wheezing	5 (6)	0
Skin and Subcutaneous Tissue Disorders		
Dermatitis contact	4 (5)	1 (2)
Pruritus	6 (8)	3 (5)
Rash	8 (10)	5 (8)
Vascular Disorders		
Hypertension	4 (5)	2 (3)

During clinical studies with Fabrazyme® (AGAL-1-002-98, AGAL-005-99, AGAL-007-99, and AGAL-008-00), the following adverse events were considered to be related by the reporting investigator and occurred with the frequency of < 5%: anemia, eosinophilia, leukopenia, aortic valve incompetence, arrhythmia, bradycardia/sinus bradycardia, bundle branch block right, cardiac arrest, cardiac valve disease, dilatation atrial, dilatation ventricular, heart valve insufficiency, mitral valve incompetence, mitral valve sclerosis, palpitations, pulmonary valve incompetence, supraventricular extrasystoles, ventricular extrasystoles, auricular swelling, ear discomfort, ear pain, tinnitus, vertigo, diplopia, eye pruritus, lacrimation increased, night blindness, ocular hyperaemia, vision blurred, vision acuity reduced, visual disturbance, abdominal discomfort, abdominal pain, abdominal pain upper, diarrhoea, dyspepsia, dysphagia, gingivitis, hypoaesthesia oral, stomach discomfort, asthenia, axillary pain, catheter-related complication, discomfort, chest pain, face oedema/face swelling, feeling hot and cold, gait disturbance, hyperthermia, influenza-like illness, infusion site pain, infusion site reaction, injection site thrombosis, malaise, oedema, pain, thirst, seasonal allergy, gastroenteritis, gingival infection, infection, nasopharyngitis, rhinitis, tooth infection, excoriation, fall, laceration, post-

procedural nausea, alanine aminotransferase increased, albumin urine present, blood alkaline phosphatase increased, blood pressure decreased, 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, hemoglobin decreased, heart rate increased, hepatic enzymes increased, intraocular pressure increased, protein urine present, right ventricular systolic pressure increased, skin test positive, hypocalcaemia, arthralgia, back pain, chest wall pain, flank pain, groin pain, joint stiffness, muscle spasms, muscle tightness, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, pain in jaw, shoulder pain, balance disorder, burning sensation, cerebrovascular accident, dyskinesia, hyperaesthesia, hypoaesthesia, ischaemic stroke, lethargy, migraine, sinus headache, syncope, syncope vasovagal, tremor, agitation, anxiety, confusional state, depression, visual hallucination, haematuria, proteinuria, renal failure, renal impairment, benign prostatic hyperplasia, dysmenorrhea, erectile dysfunction, bronchospasm, cough, dyspnoea exacerbated, pharyngolaryngeal pain, productive cough, pulmonary oedema, respiratory distress, rhinorrhoea, rhonchi, tachypnoea, throat tightness, upper respiratory tract congestion, wheezing, acne, angioneurotic oedema, eczema, erythema, livedo reticularis, pruritus generalized, rash, rash erythematous, rash maculo-papular, rash pruritic, skin discoloration, skin discomfort, hot flush, hypotension, orthostatic hypotension, pallor, peripheral coldness, poor venous access, and vasospasm.

Overall, during the double-blind, placebo-controlled period of the study, 23 of 48 (47.9 %) patients in the Fabrazyme®-treated group compared to 8 of 29 (27.6 %) in the placebo-treated group had centrally-read QT/QTc prolongations (defined as any QTc interval >450 msec) at any time point during the study, including prior to treatment. Of these patients with QT/QTc intervals > 450 msec, 7 of 23 (30%) patients in the Fabrazyme®-treated group compared to 1 of 8 (13%) patients in the placebo-treated group had a QTc interval increase from baseline ≥ 60 msec.

Infusion associated reactions were the most frequently reported related adverse events in the double-blind, placebo-controlled (AGAL-1-002-98), open-label extension (AGAL-005-99), double-blind placebo-controlled (AGAL-008-00), and open-label Japan (AGAL-007-99) studies. 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), and pruritus (pruritus generalized).

The majority of these IARs are thought to be due to the formation of IgG antibodies and/or complement activation. Ninety-five of 121 (79%) adult patients and 11 of 16 (69%) pediatric patients (106 of 137, 77% of all patients) treated with Fabrazyme® in clinical studies have developed IgG antibodies to Fabrazyme®. Most patients who develop IgG antibodies do so within the first 3 months of exposure. Among the 14 female patients exposed to Fabrazyme® in

clinical studies [2 in the double-blind, placebo-controlled (AGAL-1-002-98)/open-label extension (AGAL-005-99) studies, 10 in the double-blind placebo-controlled study (AGAL-008-00), 2 in the pediatric (AGAL-016-01)], six adult patients developed IgG antibodies to Fabrazyme®. There was no evidence that IgG seroconversion had any impact on the efficacy of Fabrazyme®.

No patient experienced anaphylaxis. Only a small number of patients have experienced reactions suggestive of immediate (Type 1) hypersensitivity. The adverse events associated with Fabrazyme® infusion have been successfully managed using standard medical practices, such as reduction in infusion rate and/or premedication with, or additional administration of non-steroidal anti-inflammatory drugs, antipyretics, antihistamines and corticosteroids.

Out of 165 patients treated with Fabrazyme® in clinical trials, 60 were tested for IgE because they experienced reactions suggestive of Type 1 hypersensitivity. Fabrazyme®-specific IgE antibodies or a positive skin test to Fabrazyme® were found in 4% of all treated patients and 12% of tested patients. (see CLINICAL TRIALS, WARNINGS AND PRECAUTIONS, Immunogenicity and Rechallenge and DOSAGE AND ADMINISTRATION sections).

The safety profile of Fabrazyme® was assessed in an open-label study (AGAL-016-01) of pediatric patients with Fabry disease who were ages 8 to 16 years at first treatment. Fifteen of the 16 patients (94%) experienced a treatment-emergent adverse event and the most common AEs were headache (56%), abdominal pain (56%), pharyngitis (56%), fever (50%), nausea (50%), vomiting (44%), pain (38%), rhinitis (38%), and diarrhea (31%). Six of the 16 patients (38%) experienced infusion-associated reactions (IARs) and the most common IARs were rigors/chills (19%), headache (19%), nausea (19%), fever (13%), and temperature changed sensation/feeling hot and/or feeling cold (13%). The majority of IARs were mild or moderate in intensity and managed by infusion rate adjustments and/or medications. No new safety concerns were identified and the overall safety and efficacy profile of Fabrazyme® treatment in pediatric patients was found to be consistent with that seen in adults.

Post-Market Adverse Drug Reactions

In addition to the adverse reactions reported in Clinical Trial Adverse Drug Reactions, the following adverse reactions have been reported during postmarketing use of Fabrazyme®: arthralgia, asthenia, erythema, hyperhidrosis, infusion site reaction, lacrimation increased, lymphadenopathy, oral hypoesthesa, palpitations, feeling hot and cold, malaise, musculoskeletal pain, oedema, rhinitis, rhinorrhea 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.

A small number of patients have experienced severe infusion-related reactions which in some cases were considered life-threatening, including anaphylaxis. Reactions have included events

of localized angioedema (including auricular swelling, eye swelling, dysphagia, lip swelling, edema, pharyngeal edema, face swelling, and swollen tongue), generalized urticaria, bronchospasm and hypotension (see **WARNINGS AND PRECAUTIONS, Infusion Reactions and Anaphylaxis and Allergic Reactions**).

DRUG INTERACTIONS

Drug-Drug Interactions: Interactions with other drugs have not been established.
No *in vitro* metabolism studies have been carried out. Because it is a protein, Fabrazyme® (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 theorectical risk of inhibition of intra-cellular a-galactosidase activity.

Drug-Food Interactions: Interactions with food and drink are unlikely. Interactions with food have not been established.

Drug-Herb Interactions: Interactions with herbal products have not been established.

Drug-Laboratory Interactions: Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Renal Disease: No changes in dose are necessary for patients with renal insufficiency.
- Liver Disease: Studies in patients with hepatic insufficiency were not performed.

Recommended Dose and Dosage Adjustment

The recommended dosage of Fabrazyme® (agalsidase beta) is 1.0 mg/kg body weight infused every 2 weeks as an IV infusion.

The initial IV infusion rate should be no more than 0.25 mg/min (15 mg/hr). The infusion rate may be slowed in the event of infusion-associated reactions. After patient tolerance to the infusion is well established, the infusion rate may be increased gradually in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hr) with each subsequent infusion. For patients weighing < 30 kg, the maximum infusion rate should remain at 0.25 mg/min (15 mg/hr). For patients weighing ≥ 30 kg, the administration duration should not be less than 1.5 hours (based on individual patient tolerability).

In clinical trials, pretreatment with an antipyretic and/or an antihistamine was used to manage a single or recurrent mild-moderate infusion-associated reaction(s). Pretreatment with an antihistamine, antipyretic and/or corticosteroid was used to manage a single severe or recurrent moderate-severe infusion-associated reaction(s). The selection of pretreatment medication and dose should be based on the patient=s age, weight and severity of the reaction. The time of administration should be based on the onset of action of the medication selected. A decrease in infusion rate should also be considered. If the infusion proceeds without incident, consideration may be given to increasing infusion rates in a stepwise manner and to reducing premedication.

Patients who have had a positive skin test to Fabrazyme® or who have tested positive for anti-Fabrazyme® IgE may be successfully rechallenged with Fabrazyme®. The initial re-challenge administration should be a low dose at a lower infusion rate, e.g., 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 approved dose of 1.0 mg/kg and the infusion rate may be increased by slowly titrating upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/min), as tolerated.

Administration

Instructions for Use

Fabrazyme® does not contain any preservatives.

Vials are for single use only. Any unused product should be discarded. Pneumatic tube systems should not be used for transport of this product.

Excessive agitation of this product should be avoided. Do not use filter needles during the preparation of the 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 0.2µm filter led to the removal of the visible particles with no detectable loss of protein or activity.

Materials Inventory

The following items are suggested for the reconstitution and administration of Fabrazyme®:

$ Fabrazyme® (Vials)

$ Sterile Water for Injection, USP
$ 0.9% Sodium Chloride Injection, USP (Normal Saline)
$ Tape
$ Two syringes for reconstitution and dilution
$ Two needles
$ In-line low protein-binding particulate filter (0.2 μm)
$ Administration set with flow-regulating device or intravenous infusion pump and tubing
$ IV kit
$ Anaphylaxis kit
$ Angiocatheter
$ Gloves
$ Alcohol wipes
$ Arm board
$ Medication label

Reconstitution and Dilution (using Aseptic Technique)

1. Fabrazyme® vials and diluent should be allowed to reach room temperature prior to reconstitution (approximately 30 minutes). The number of vials needed is based on the patient's body weight (kg) and the recommended dose of 1.0 mg/kg. Select the appropriate number of vials so that the total number of mg is equal to or greater than the patient's number of kg of body weight.

2. Reconstitute each 35 mg vial of Fabrazyme® by **slowly** injecting 7.2 mL of Sterile Water for Injection, USP down the inside wall of each vial and not directly onto the lyophilized 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, colorless solution (total extractable dose per vial is 35 mg, 7.0 mL).

Reconstitute each 5 mg vial of Fabrazyme® by **slowly** injecting 1.1 mL of Sterile Water for Injection, USP down the inside wall of each vial and not directly onto the lyophilized 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, colorless solution (total extractable dose per vial is 5 mg, 1.0 mL).

3. Visually inspect the reconstituted vials for particulate matter and discoloration. Do not use vials exhibiting particulate matter or discoloration. Report lot number to hospital pharmacist for vials exhibiting particulate matter or discoloration.

4. After reconstitution, it is recommended to promptly dilute the vials. Failure to promptly dilute the vials could result in particle formation.).

5. Slowly withdraw the reconstituted solution from each vial and further dilute with 0.9 % Sodium Chloride Injection, USP to a **total volume based on patient weight specified in Table**

2 below. To minimize the air/liquid interface, remove the airspace within the infusion bag prior to adding the reconstituted Fabrazyme®. Be sure to inject the reconstituted Fabrazyme® solution directly into the sodium chloride solution. Total infusion volumes as low as 50 mL have been used in a clinical trial. Discard any vial with unused reconstituted solution.).

Table 2

Patient Weight (kg)	Minimum Total Volume
≤ 35	**50**
35.1 – 70	100
70.1 – 100	250
> 100	500

6. Gently invert infusion bag to mix the solution, avoiding vigorous shaking and agitation. Use immediately.

7. Fabrazyme® should not be infused in the same intravenous line with other products.

8. The diluted solution should be filtered through an in-line low protein binding 0.2 μm filter during administration.

OVERDOSAGE

There have been no reports of overdose with Fabrazyme® (agalsidase beta). In clinical trials, patients received doses up to 3.0 mg/kg body weight.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

In Fabry disease, deficiency of the lysosomal enzyme α-GAL leads to progressive accumulation of glycosphingolipids, predominantly GL-3, in most body tissues and fluids. This excessive accumulation of GL-3 is the primary pathological process which, starting early in life and continuing over decades, triggers a cascade of events that results in disease expression.

GL-3 buildup 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. The most significant clinical manifestations of Fabry disease are renal failure, cardiomyopathy, and cerebrovascular accidents resulting in chronic morbidity and premature death.

Fabrazyme® is intended as an enzyme replacement therapy to provide an exogenous source of α-GAL in Fabry disease patients. This recombinant human α-GAL (r-hαGAL) will catalyze the hydrolysis of glycosphingolipids including GL-3 in the lysosomes of multiple cell types and tissues.

Pharmacodynamics

The rationale for enzyme replacement therapy is to restore a level of enzymatic activity sufficient to hydrolyse the accumulated substrate. After intravenous infusion, Fabrazyme® 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. In a placebo-controlled study conducted in patients with Fabry disease after intravenous administration of 1 mg/kg of Fabrazyme® every two weeks for 20 weeks, a reduction of GL-3 was observed in the capillary endothelium (vasculature) of kidney, heart and skin as determined by histological assessment, and in plasma as determined by ELISA.

Pharmacokinetics

Plasma pharmacokinetic profiles of Fabrazyme® were characterized at 0.3, 1.0 and 3.0 mg/kg in adult patients with Fabry disease (open-label, dose-finding study FB9702-01). 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 (Table 3). Plasma pharmacokinetics of Fabrazyme® was evaluated in adult Fabry patients in Europe participating in a double-blind clinical trial (AGAL-1-002-98). Patients were given Fabrazyme® every 14 days for a total of 11 infusions. Refer to Table 3 below for more details.

Results from the open-label study (AGAL-016-01) of 15 pediatric Fabry patients (ranging in age from 8 to 16 years old and weighing between 27.1 to 64.9 kg) who were dosed with 1.0 mg/kg every 14 days showed that Fabrazyme® exposure was about 5-times higher after IgG seroconversion **(Table 3)**, without any detectable impact on GL-3 clearance in plasma (see **Figures 1, 2,** and **3**) and skin. IgG seroconversion in pediatric patients was associated with prolonged half-life and plasma concentrations of Fabrazyme®, a phenomenon rarely observed in adult patients. A possible cause for this prolongation likely pertains to the ability of antibodies to potentially act as "carriers" for their antigens. The Fabrazyme® pharmacokinetics were not weight-dependent.

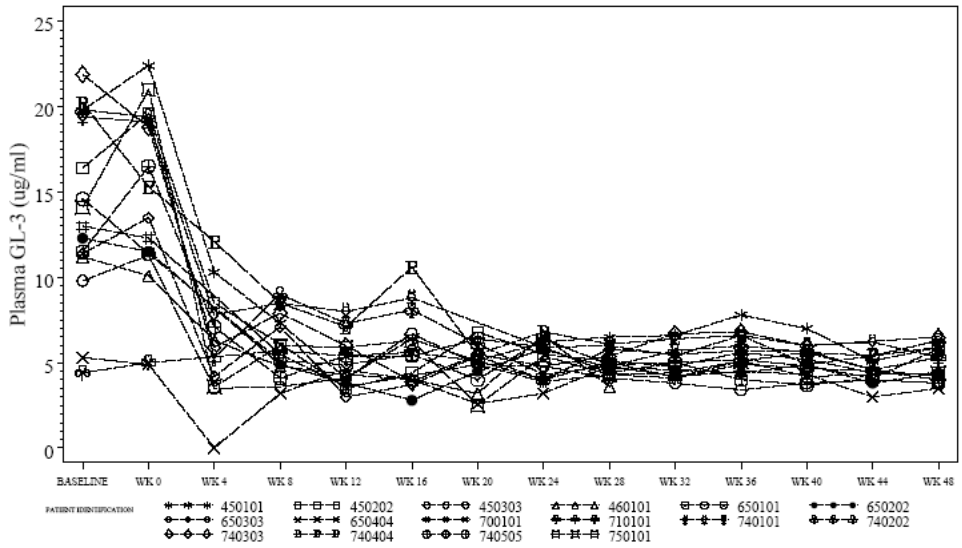
Pharmacokinetics of Fabrazyme® was also evaluated in 13 Fabry patients in Japan participating in an open-label clinical trial (AGAL-007-99). The results of these evaluations show that Fabrazyme® pharmacokinetics are comparable in Caucasian and Japanese Fabry patients.

Table 3
Fabrazyme® Pharmacokinetic Summary

Dose	Regimen	Mean Infusion Length (min)	Serum Antibody Titre	Infusion Number	N	$AUC_{(0-\infty)}$ µg min/mL	C_{max} µg/mL	Half-life min	CL mL/min/kg	Vss* mL/kg
Study FB9702-01: Open-Label Study in Adult Patients with Fabry Disease – same cohort, weight range: 56-88 kg										
0.3 mg/kg	q14 days ×5	132	NA	1	3	79 ± 24	0.6 ± 0.2	92 ± 27	4.1 ± 1.2	225 ± 62
		128	NA	5	3	74 ± 30	0.6 ± 0.2	78 ± 67	4.6 ± 2.2	330 ± 231
1.0 mg/kg	q14 days × 5	115	NA	1	3	496 ± 137	5.0 ± 1.1	67 ± 12	2.1 ± 0.7	112 ± 13
		120	NA	5	2	466 ± 382	4.74 ± 4.3	45 ± 3	3.2 ± 2.6	243 ± 236
3.0 mg/kg	q14 days × 5	129	NA	1	2	4168 ± 1401	29.7 ± 14.6	102 ± 4	0.8 ± 0.3	81 ± 45
		300	NA	5	2	4327 ± 2074	19.8 ± 5.8	87 ± 21	0.8 ± 0.4	165 ± 80
Study AGAL-1-002-98: Double-Blind, Placebo-Controlled Study in Adult Patients with Fabry Disease - same cohort, weight range: 50-81 kg										
1.0 mg/kg	q14 days x 11	280	0-6400	1-3	11	649 ± 226	3.5 ± 1.6	89 ± 20	1.8 ± 0.8	120 ± 80
		280	0-51200	7	11	372 ± 223	2.1 ± 1.14	82 ± 25	4.9 ± 5.6	570 ± 710
		300	0-25600	11	11	784 ± 521	3.5 ± 2.2	119 ± 49	2.3 ± 2.2	280 ± 230
Study AGAL-016-01: Open-Label Study in Pediatric Patients with Fabry Disease - same cohort, weight range: 28-66 kg										
1.0 mg/kg	q14 days × 24	208	0	1	8-9	344 ± 307	2.2 ± 1.9	86 ± 27	5.8 ± 4.6	1097 ± 912
		111	0-3200	12	15	1007 ± 688	4.9 ± 2.4	130 ± 41	1.6 ± 1.2	292 ± 185
		108	0-6400	24	9-10	1238 ± 547	7.1 ± 4.3	151 ± 59	1.1 ± 0.8	247 ± 145

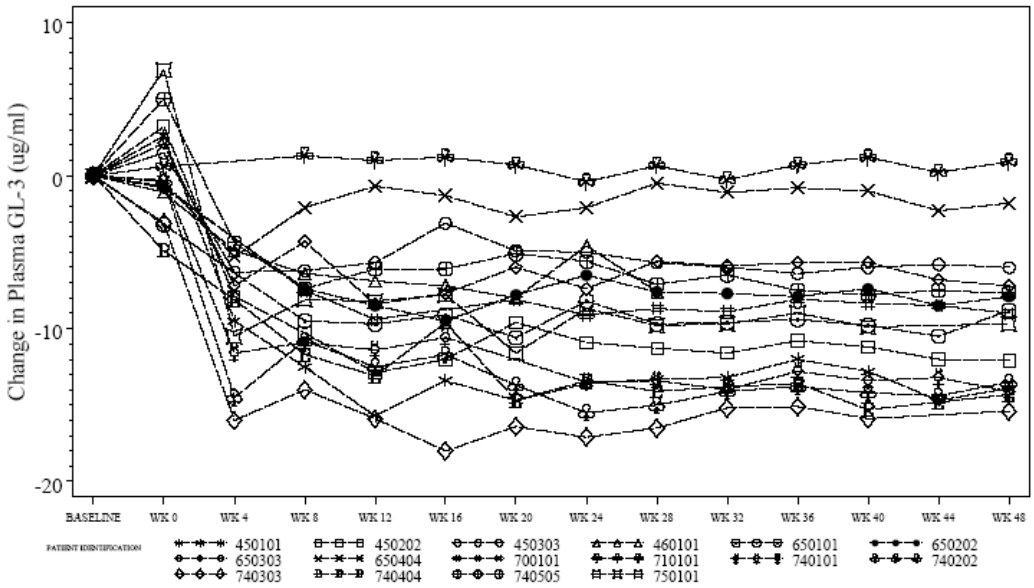
All data reported as the mean ± standard deviation, unless a range is indicated.
*Vss = volume of distribution at steady state
N = number of patients
NA = No serum antibody titre level data available

Figure 1
Patient Plasma GL-3 Values Over Time



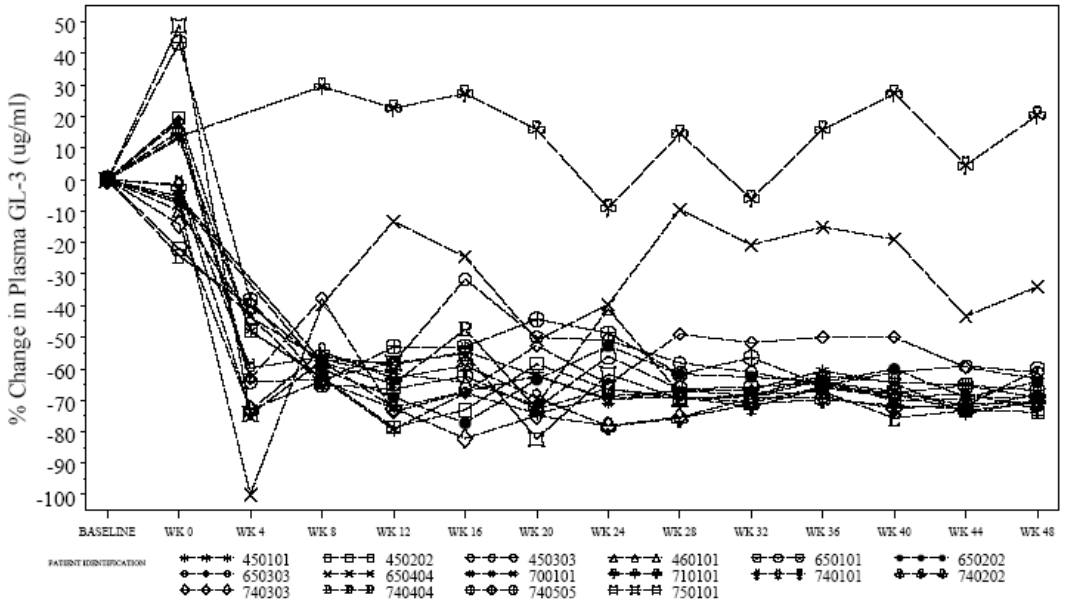
Note: Values below quantitation limit (BQL) are set to 0 for calculations.

Figure 2
Change from Baseline in Plasma GL-3 Over Time



Note: Values below quantitation limit (BQL) are set to 0 for calculations.

Figure 3
Percent Change from Baseline in Plasma GL-3 Over Time



Note: Values below quantitation limit (BQL) are set to 0 for calculations.

STORAGE AND STABILITY

Store Fabrazyme® (agalsidase beta) under refrigeration between 2° - 8°C (36° - 46°F). DO NOT USE Fabrazyme® after the expiration date on the vial.

Reconstituted and diluted solutions of Fabrazyme® should be used immediately. This product contains no preservatives. If immediate use is not possible, the reconstituted and diluted solution may be stored for up to 24 hours at 2° - 8°C (36° - 46°F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Fabrazyme® (agalsidase beta), lyophilized powder for intravenous infusion, is supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder.

The quantitative composition of the lyophilized drug is provided as follows:

- 35 mg vial is composed of agalsidase beta (37 mg total amount, which allows for an extractable dose of 35 mg/vial), mannitol (222 mg), sodium phosphate monobasic, monohydrate (20.4 mg), sodium phosphate dibasic, heptahydrate (59.2 mg)
- 5 mg vial is composed of agalsidase beta (5.5 mg total amount, which allows for an extractable dose of 5 mg/vial), mannitol (33 mg), sodium phosphate monobasic,

monohydrate (3.0 mg), sodium phosphate dibasic, heptahydrate (8.8 mg)

Fabrazyme® contains no preservatives.

Fabrazyme® 35 mg vials are supplied in single-use, clear Type I glass 20 mL (cc) vials. The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic purple flip-off cap. Fabrazyme® 5 mg vials are supplied in single-use, clear Type I glass 5 mL (cc) vials. The closure consists of a siliconized butyl stopper and an aluminum seal with a plastic grey flip-off cap.

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: agalsidase beta

Chemical Name: recombinant human α-galactosidase A (r-hαGAL)

Molecular Formula and molecular mass: $C_{2029}H_{3080}N_{544}O_{587}S_{27}$

Molecular Weight: approximately 100 kD

Structural formula:

Amino acid sequence of r-hαGAL

```
1                   11                  21                  31
LDNGL ARTPT   MGWLH   WERFM   CNLDC   QEEPD   SCISE   KLFME
41                  51                  61                  71
MAELM VSEGW       KDAGY EYLCI DDCWM   APQRD   SEGRL   QADPQ
81                  91                  101                 111
RFPHG IRQLA       NYVHS KGLKL GIYAD   VGNKT   CAGFP   GSFGY
121                 131                 141                 151
YDIDA QTFAD       WGVDL LKFDG CYCDS   LENLA   DGYKH   MSLAL
161                 171                 181                 191
NRTGR SIVYS       CEWPL YMWPF QKPNY   TEIRQ   YCNHW   RNFAD
201                 211                 221                 231
IDDSW KSIKS       ILDWT SFNQE RIVDV   AGPGG   WNDPD   MLVIG
241                 251                 261                 271
NFGLS WNQQV       TQMAL WAIMA APLFM   SNDLR   HISPQ   AKALL
281                 291                 301                 311
QDKDV IAINQ       DPLGK QGYQL RQGDN   FEVWE   RPLSG   LAWAV
321                 331                 341                 351
AMINR QEIGG       PRSYT IAVAS LGKGV   ACNPA   CFITQ   LLPVK
361                 371                 381                 391
RKLGF YEWTS       RLRSH INPTG TVLLQ   LENTM   QMSLK   DLL
```

Physicochemical properties:

r-hαGAL is a non-covalently linked homodimer with an approximate molecular weight of 100 kD, comprised of two subunits of approximately 51 kD each. The full-length cDNA for each subunit encodes a polypeptide of 429 amino acids and the mature subunit is a polypeptide of 398 amino acids. Each monomer has three N-linked glycosylation sites at asparagines 108, 161 and 184. The theoretical mass of the peptide is 45,349 daltons (excluding the mass of the carbohydrate chains).

Solubility: Soluble in Water

Product Characteristics

Fabrazyme®, lyophilized powder for intravenous infusion, is supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder. The lyophilized powder is reconstituted with Sterile Water for Injection, USP for intravenous administration.

Viral Inactivation

The viral safety of Fabrazyme® is confirmed by a combination of selection and qualification of vendors, raw material testing, cell bank characterization studies, validation of the viral removal and inactivation capacity of the purification process, and routine in-process testing.

CLINICAL TRIALS

Study demographics and trial design

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
FB9702-01 Phase 1/2 Study	Open-label, non-randomized, dose-finding	Fabrazyme® (r-hαGAL) at: 0.3, 1.0 or 3.0 mg/kg every two weeks; or 1.0 or 3.0 mg/kg every two days	Fabry patients (n = 15)	34.4 years (18-45)	15 M/ 0 F
AGAL-1-002-98 Phase 3 Study	Randomized, double-blind, placebo-controlled, parallel-group	Fabrazyme® (r-hαGAL) at 1.0 mg/kg OR placebo every two weeks for two weeks for five months (20 weeks) for a total of 11 infusions	Fabry patients (n = 58)	30.2 years (16-48)	56 M/ 2 F
AGAL-005-99 Phase 3 Extension	Open-label extension study (patients rolled over from Study AGAL-1-002-98)	Fabrazyme® (r-hαGAL) at 1.0 mg/kg every two weeks for 54 months	Fabry patients (n = 58)	Fz/Fz Treatment Group: 33.0 years (17-49) Placebo/ Fz Treatment Group: 29.3 years (18-62)	56 M 2 F
AGAL-007-99 Phase 2 Japan Bridging Study	Open-label	Fabrazyme® (r-hαGAL) at 1 mg/kg every two weeks for 20 weeks	Fabry patients (n = 13)	26.0 years (16-34)	13 M 0 F
AGAL-008-00 Double Blind Study	Randomized, double-blind, placebo-controlled study of safety and efficacy	Fabrazyme® (r-hαGAL) at 1 mg/kg OR placebo every two weeks for a maximum of 35 months	Fabry patients (n = 82)	45.9 years (20-72)	72 M 10 F

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
AGAL-019-01	Open-label, multi-centre, safety study	Fabrazyme® (r-hαGAL) at 0.5 mg/kg. Following successful completion of the first 2 graded infusion with no moderate, severe, or life-threatening infusion-associated reaction, dose increased to 1 mg/kg every 2 weeks for the duration of the study for a maximum of 52 weeks	Fabry patients (n = 6)	44.0 years (27-67)	6 M
AGAL-016-01	Multi-centre, open-label study	Fabrazyme® (r-hαGAL) at 1 mg/kg every two weeks for up to 48 weeks	Fabry pediatric patients (n = 16)	12.1 years (8-16)	14 M 2 F

Study results

The safety and efficacy of Fabrazyme® (agalsidase beta) have been assessed in seven clinical studies involving a total of 184 male and female patients.

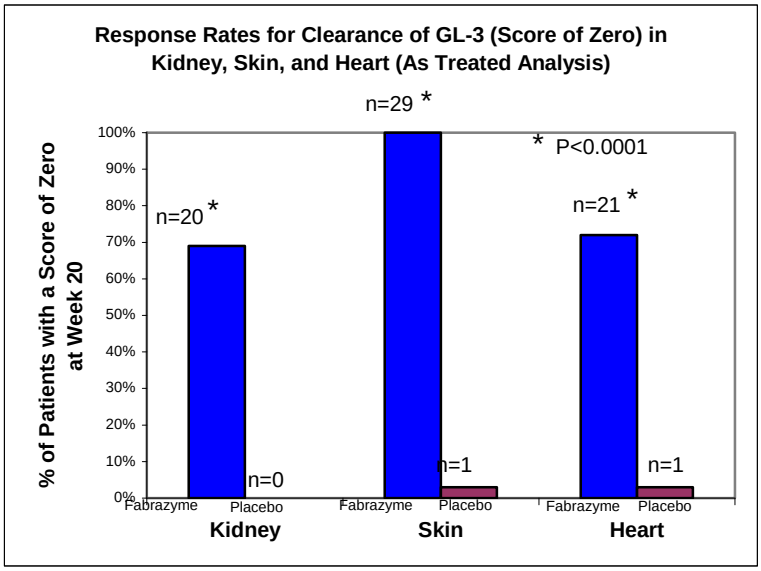
The safety and efficacy of Fabrazyme® were assessed in a open-label dose finding study (FB9702-01) of 15 patients evaluated at five dosing regimens: 0.3, 1.0 or 3.0 mg/kg every two weeks or 1.0 or 3.0 mg/kg every two days. Fabrazyme® administration achieved rapid and marked reductions in plasma and tissue GL-3 observed biochemically and histologically by light and electron microscopy at doses of 0.3, 1.0 and 3.0 mg/kg. Patients reported decreased pain, increased ability to perspire and improved quality of life. The 1.0 mg/kg dose every two weeks demonstrated the most favorable safety and efficacy profile at the end of this dose-finding study.

The safety and efficacy of Fabrazyme® were further assessed in a randomized, double-blind, placebo-controlled, multinational, multicenter study (AGAL-1-002-98) of 58 Fabry patients (56 males and 2 females), ages 16 to 61 years, all naïve to enzyme replacement therapy. Patients received either 1.0 mg/kg of Fabrazyme® or placebo every two weeks for five months (20 weeks) for a total of 11 infusions. The primary efficacy endpoint, GL-3 clearance from renal vascular endothelium, was assessed by light microscopy and was graded on an inclusion severity score

ranging from 0 (normal-near normal) to 3 (severe inclusions). Pathology evaluations were performed by a blinded panel of three expert pathologists examining an average of approximately 195 capillaries per biopsy specimen. The primary endpoint (score of 0) was reached when greater than 50% of the renal interstitial capillaries in each specimen had a score of 0, less than 5% had a score of 1, 2 or 3, and the remainder had zero or trace (single small granule) evidence of deposits of GL-3.

The prospectively defined renal efficacy endpoint (score of 0) was achieved in 20 of 29 (69%) patients treated with Fabrazyme® ($p<0.0001$). In contrast, no patients receiving placebo attained this efficacy endpoint. Similar results were achieved in the capillary endothelium of the heart and skin (Figure 4).

Figure 4:



The adverse reactions were generally similar between the Fabrazyme® treatment group compared to the placebo treatment group with three exceptions including rigors (52% vs. 14%), fever (48% vs. 17%), and skeletal pain (21% vs. 0%), respectively. All reports of skeletal pain were reported as mild to moderate, none were related to treatment and did not occur during an infusion. No serious adverse events were reported related to treatment.

The safety and efficacy of Fabrazyme® were further investigated in an open-label, multicenter extension of the placebo-controlled clinical trial (AGAL-005-99), in which Fabrazyme® therapy was administered to all 58 original participants. Fabrazyme® was administered at 1.0 mg/kg every two weeks and continued for an additional 54 months. After six months of treatment with Fabrazyme®, all former placebo patients achieved clearance of GL-3 (score of 0) in the vascular endothelium of the kidney ($p<0.001$). At the end of six months of the open label extension study, a score of 0 was achieved or maintained in the vascular endothelium of the kidney, heart

and skin in 96%, 80% and 96% of patients with available biopsies, respectively. Additionally, a retrospective histological review of other renal cell types (> 3000 individual cell type assessments) confirmed that GL-3 is cleared 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). Forty-four of the 58 patients completed 54 months of the open-label extension study (AGAL-005-99). Thirty-six of these 44 patients underwent follow-up skin biopsy, and 31 of these patients showed sustained GL-3 clearance in the capillary endothelium of the skin. Follow-up heart and kidney biopsies were assessed in only 8 of the 44 patients, which showed sustained GL-3 clearance in the capillary endothelium of the kidney in 8 patients, and sustained GL-3 clearance in the capillary endothelium of the heart in 6 patients. Plasma GL-3 levels were reduced to normal levels (≤ 7.03 μg/mL) and remained at normal levels after up to 60 months of treatment.

The most common adverse events in open-label extension (AGAL-005-99) patients treated with Fabrazyme® for up to 60 months continue to be infusion-associated reactions. The number of patients experiencing these types of reactions has decreased over time. Serious adverse events considered related to Fabrazyme® also primarily consist of infusion-associated reactions (see ADVERSE REACTIONS SECTION).

Improvement was also observed in other efficacy measurements. Improvement in pain as assessed by the Short Form McGill questionnaire was seen in the first five months of the double-blind placebo-controlled study (AGAL-1-002-98), both in the placebo and Fabrazyme® groups, and was maintained with treatment for up to 60 months in the open-label extension study (AGAL-005-99). Improvement in other efficacy measurements was also observed for the SF- 36 Health Survey (Quality of Life). Renal function as measured by glomerular filtration rate and serum creatinine remained stable and normal in the majority of the patients up to 60 months. However, the effect of Fabrazyme® treatment on kidney function was limited in some patients with advanced renal disease. Mean plasma GL-3 levels normalized within 3 months with treatment and remained normal for up to 60 months.

Safety and efficacy of Fabrazyme® were also assessed in an open-label study (AGAL-007-99) of 13 Japanese patients who were treated with 1 mg/kg of Fabrazyme® every two weeks for 20 weeks. The open-label Japan study results were similar to the results of the double-blind placebo-controlled study (AGAL-1-002-98).

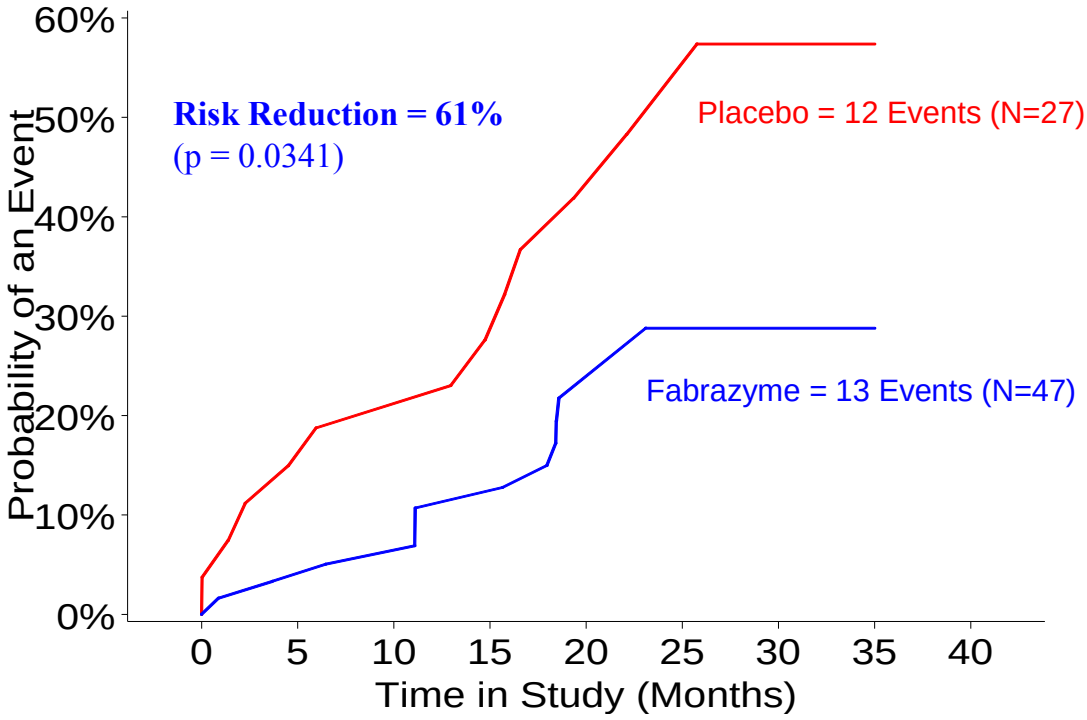
The safety and clinical efficacy of Fabrazyme® were also assessed in a randomized (2:1), double-blind, placebo-controlled study (AGAL-008-00) of 82 Fabry patients (72 males and 10 females). Patients received either 1.0 mg/kg of Fabrazyme® or placebo every two weeks for up to a maximum of 35 months. The primary efficacy endpoint was the time to clinically significant progression of the composite outcomes of renal, cardiac and cerebrovascular disease and/or death and was assessed by a log-rank test comparing the Fabrazyme® and placebo treatment

groups. Among the 82 patients enrolled, 13 patients (42%) in the placebo group and 14 patients (27%) in the Fabrazyme® group met the predefined clinical endpoint (progression of clinical symptoms).

There was a strong trend favoring Fabrazyme® in the intent-to-treat (ITT) population with a reduction of 43 % (Hazard Ratio=0.57, CI=0.27, 1.22; p=0.1449) of the occurrence of the primary endpoint (progression of renal, cardiac or cerebrovascular disease or death). The favorable and consistent trend was noted across the renal, cardiac and cerebrovascular components of the primary endpoint. There was a 46% risk reduction in the per protocol (PP) population (Hazard Ratio 0.54; 95% confidence interval 0.25, 1.19, p=0.1229).

To correct for an imbalance in baseline proteinuria between the Fabrazyme® and placebo groups, a Cox proportional hazards model was performed with treatment group and baseline proteinuria as covariates in the model. This analysis demonstrated a risk reduction of 53% for the intent-to-treat (ITT) population (Risk Ratio 0.47, 95% C.I. 0.21, 1.03, p = 0.0577). In the per protocol (PP) population (n=74), Fabrazyme® demonstrated a 61% risk reduction (Risk Ratio 0.39; 95% C.I. 0.16, 0.93, p = 0.0341) (refer to Figure 5).

Figure 5
Proteinuria Ratio-Adjusted Predicted Probability of a Primary Endpoint: Per-Protocol Population



The first quartile (25%) time to first clinical event for the Fabrazyme® treatment group was 18.59 months and 14.74 months for the placebo group.

Therefore, results from this double-blind placebo-controlled study (AGAL-008-00) demonstrate that Fabrazyme® therapy administered at 1mg/kg slows the rate of clinical progression in Fabry disease as manifested by renal, cardiac and cerebrovascular outcomes. While benefit was demonstrated in patients with varying severity of disease, the most pronounced benefit was observed among patients who have less severe renal disease at baseline.

Proteinuria is an independent risk factor for progression of renal, cardiovascular and cerebrovascular events among Fabry patients.

The safety and efficacy of Fabrazyme® were assessed in a multinational, multicenter, uncontrolled, open-label study (AGAL-016-01) to evaluate safety, pharmacokinetics, and pharmacodynamics in 16 pediatric patients with Fabry disease (14 males, 2 females) who were ages 8 to 16 years at first treatment. All patients received Fabrazyme® 1 mg/kg every 2 weeks for up to 48 weeks. At Baseline, all 14 males had elevated plasma GL-3 levels (i.e., > 7.03

μg/mL), whereas the two female patients had normal plasma GL-3 levels. Twelve of the 14 male patients, and no female patients, had GL-3 inclusions observed in the capillary endothelium on skin biopsies at Baseline. At Weeks 24 and 48 of treatment, all 14 males had plasma GL-3 within the normal range. The 12 male patients with GL-3 inclusions in capillary endothelium at Baseline achieved GL-3 inclusion scores of 0 at Week 24 of treatment. The two female patients' plasma GL-3 levels remained normal through study Week 48. No new safety concerns were identified in pediatric patients in this study, and the overall safety and efficacy profile of Fabrazyme® treatment in pediatric patients was found to be consistent with that seen in adults.

The safety of Fabrazyme® was evaluated in an open-label, rechallenge study (AGAL-019-01) in patients who had a positive skin test to Fabrazyme® or who had tested positive for Fabrazyme®-specific IgE antibodies. In this study, 6 adult male patients, who had experienced multiple or recurrent infusion reactions during previous clinical trials with Fabrazyme®, were rechallenged with Fabrazyme® administered as a graded infusion, for up to 52 weeks of treatment (see WARNINGS AND PRECAUTIONS, Immunogenicity and Rechallenge). The initial two rechallenge doses of Fabrazyme® were administered as a 0.5 mg/kg dose per week at an initial infusion rate of 0.01 mg/min for the first 30 minutes (1/25th the usually recommended maximum infusion rate). The infusion rate was doubled every 30 minutes thereafter, as tolerated, for the remainder of the infusion up to a maximum rate of 0.25 mg/min. If the patient tolerated the infusion, the dose was increased to 1.0 mg/kg every two weeks (usually recommended dose), and the infusion rate was increased by slow titration upwards (see DOSAGE AND ADMINISTRATION).

Four of the six patients treated in this open-label rechallenge study (AGAL-019-01) received at least 26 weeks of study medication, and two patients discontinued prematurely due to recurrent infusion reactions (see WARNINGS AND PRECAUTIONS, Immunogenicity and Rechallenge). Following voluntary withdrawal from the study, one of these patients transitioned to treatment with commercially available Fabrazyme®.

Patients with severe congestive heart failure or severe ischemic heart disease requiring beta-adrenergic blocking agents did not participate in the trial.

A total of twelve women were enrolled in the clinical studies, 10 of whom received Fabrazyme® (2 in the double-blind placebo-controlled (AGAL-1-002-98)/open-label extension (AGAL-005-99) and 8 in the double blind placebo-controlled (AGAL-008-00) studies). Two female pediatric patients with Fabry disease, ages 11 years, were also evaluated in an open-label, pediatric study (AGAL-016-01) (see **WARNINGS AND PRECAUTIONS, Pediatrics**). In the double-blind, randomized, placebo-controlled clinical study (AGAL-008-00), female and male patients appeared to have a similar risk of a primary endpoint event based on their baseline proteinuria value. Although the safety and efficacy data available in female patients in these clinical studies are limited, there is no indication that the clinical response of Fabrazyme® is different between

males and females (see WARNINGS AND PRECAUTIONS, Infusion Reactions and ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions).

DETAILED PHARMACOLOGY

A series of studies were performed to evaluate the effect of Fabrazyme® on GL-3 in plasma and tissue of α-GAL SV129 Knock-out Mice. Additionally, one safety pharmacology study was conducted in Beagle dogs. The effects of single and multiple doses were investigated.

The studies conducted using α-GAL Knock-out SV129 mice demonstrated that intravenous (IV) administration of Fabrazyme® at the levels to be used clinically (1.0 mg/kg), did reduce GL-3 levels. Significant reduction in GL-3 was observed at all doses tested, in a time and dose dependent manner. Reductions were most pronounced in the liver, heart and spleen. Cumulative doses of 0.5 - 0.6 mg/kg of Fabrazyme® completely reduced GL-3 in the liver after 1-2 days, whereas cumulative doses of 5-6 mg/kg were required for complete reductions in the heart and spleen. No undesirable pharmacodynamic effects were identified. These studies support the hypothesis that IV administration of Fabrazyme® will have an effect on the accumulation and depletion of GL-3 in the tissues and confirm the biochemistry supporting the use of Fabrazyme® as a replacement therapy. These studies indicate that the proposed clinical dose (1.0 mg/kg) is of the correct order of magnitude to produce a decrease in the levels of GL-3.

A study was conducted to evaluate the effects of a single bolus IV administration of r-hαGAL on cardiac function in Beagle dogs. Doses used in this study were 0, 3, 9 and 27 mg/kg. Administration of escalating doses of Fabrazyme® to Beagle dogs showed no cardiac effects at doses of 3 and 9 mg/kg. A transient hypotension was observed in 5 of 6 dogs administered r-hαGAL at a dose of 27 mg/kg. Heart rate, respiration rate and central venous pressure were not significantly affected.

Results from all nonclinical pharmacology studies of Fabrazyme® present no evidence of safety concerns at the dose of 1.0 mg/kg administered intravenously.

TOXICOLOGY

Preclinical data reveal no special hazard from humans based on studies of safety pharmacology, single dose and repeated dose toxicity. Reproduction studies performed on rats (at doses up to 30 times the human dose) revealed no evidence of impaired fertility or harm to the fetus due to Fabrazyme® (agalsidase beta).

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PART III: CONSUMER INFORMATION

Fabrazyme®
Agalsidase Beta

This leaflet is part III of a three-part "Product Monograph" published when Fabrazyme® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Fabrazyme®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Fabrazyme® is used to treat individuals with a confirmed diagnosis of Fabry Disease. Fabrazyme® reduces levels of globotriaosylceramide or GL-3, a fat substance, and slows the rate of progression of Fabry disease in the kidney, heart and brain.

The safety and efficacy of Fabrazyme® have not been studied in children below the age of 8 years.

What it does:

Fabry disease is a genetic disorder where the level of α-galactosidase activity [an enzyme that breaks down complex lipids (fats)] is absent or lower than normal. If you suffer from Fabry disease, GL-3 is not removed from the cells of your body and starts to accumulate in the walls of the blood vessels of your organs. Fabrazyme® is a form of human enzyme, α-galactosidase, produced by recombinant DNA technology. Fabrazyme® can help to treat some of the symptoms of Fabry Disease by replacing the deficient enzyme.

When it should not be used:
Do not use Fabrazyme® if you have experienced any life-threatening allergic reaction to agalsidase beta or to any ingredient in the medication.

What the medicinal ingredient is:
Agalsidase beta

What the important nonmedicinal ingredients are:
Mannitol, Sodium Phosphate Monobasic Monohydrate, Sodium Phosphate Dibasic Heptahydrate
For a full listing of nonmedicinal ingredients, see Part 1 of the product monograph.

What dosage forms it comes in:
Fabrazyme® is supplied as a sterile dry powder for intravenous infusion.

Fabrazyme® is supplied in a 20 mL vial containing either 35 mg (purple cap) or 5 mg (grey cap) of agalsidase.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
As with any medication of this type, severe allergic reactions, including life-threatening ones, have been seen in patients receiving Fabrazyme.

Serious Warnings and Precautions:
As with any intravenous protein product, severe allergic reactions have been seen in patients receiving Fabrazyme® infusions. Reactions have included swelling of the face, mouth and throat, wheezing, low blood pressure, hives, difficulty swallowing, rash, shortness of breath, flushing, chest discomfort, itchiness, and nasal congestion. Interventions have included cardiopulmonary resuscitation (CPR), oxygen, fluids given through a catheter in a vein (intravenously), hospitalization and treatment with epinephrine, beta-adrenergic medicines to help with breathing, and steroids. Because of the potential for severe allergic reactions, appropriate medical support measures should be readily available when Fabrazyme® is administered.

It is expected that most individuals will develop antibodies upon treatment with enzyme replacement therapy. If you develop antibodies to agalsidase beta, you have a higher risk of allergic side effects (see SIDE EFFECTS AND WHAT TO DO ABOUT THEM). The antibodies are not likely to stop Fabrazyme® working and will decrease with time.

If you experience an allergic side effect following the administration of Fabrazyme®, you should immediately contact your physician. Your doctor can decrease the infusion rate and/or treat the symptoms with other medicines (antihistamines, ibuprofen, paracetamol and/or corticosteroids) to help reduce some of the side effects. If infusions proceed without further incident, consideration may be given to increasing the infusion rate in a stepwise manner and to reducing premedication.

If severe allergic or life-threatening reactions occur, immediate discontinuation of the administration of Fabrazyme® may be considered and an appropriate treatment will have to be initiated by your physician.

BEFORE you use Fabrazyme®, talk to your doctor or pharmacist if:

- $ You have had a severe allergic or life-threatening reaction to the administration of Fabrazyme®
- $ You have any allergies to this drug or its ingredients or components of the container
- $ You are pregnant or plan to become pregnant or are breast-feeding

INTERACTIONS WITH THIS MEDICATION

No formal interaction studies have been conducted. Please inform your doctor if you are using any other medicinal products, due to the potential risk of interference with the uptake of agalsidase beta. Fabrazyme® should not be administered with certain medications including chloroquine, amiodarone, benoquin or gentamycin because of a theoretical risk that they may interfere with the activity of Fabrazyme®.

PROPER USE OF THIS MEDICATION

Usual dose:
The recommended dosage of Fabrazyme® is 1.0 mg/kg body weight administered every 2 weeks as an intravenous infusion.

Overdose:

There have been no reports of overdose with Fabrazyme®. Doses up to 3.0 mg/kg body weight have been tested in clinical trials.

Missed Dose:
If you have missed a Fabrazyme® infusion, please contact your doctor. The next dose will not be doubled to make up for the missed or partially administered dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Fabrazyme® can have side effects. Patients with advanced Fabry disease may have heart problems, which may put them to a higher risk of severe complications from infusion reactions. These patients should be monitored closely during Fabrazyme® infusions.

In clinical trials, the following side effects were reported as being related to Fabrazyme® in a total of 134 patients by greater than 10% of individuals treated for a minimum of one infusion up to a maximum of 5 years: chills, temperature changed feeling, runny nose or seasonal allergies, fever, headache, tremor, nausea, pain of the extremities, swelling of the extremities, vomiting, high blood pressure, muscle pain, shortness of breath. Side effects were mostly mild or moderate in severity.

Approximately half of the individuals treated at 1 mg/kg initially experienced related side effects, on the day of the infusion. After up to 2 years of treatment, less than 37% of patients experienced infusion-associated reactions. These reactions consisted most often of fever and chills. Additional symptoms included allergic-like reactions with mild to moderate shortness of breath, throat tightness, chest tightness, difficulty in breathing, red face, itching, hives, runny nose or seasonal allergies, rapid breathing and/or wheezing, swelling of the face, swelling of the lips and throat, heart and blood vessel symptoms including high blood pressure, decreased blood pressure, increased heart rate, palpitations, stomach and bowel symptoms including abdominal pain, nausea, vomiting, infusion-related pain including pain of extremities and muscle pain, and headache.

Since Fabrazyme® has been released on the market, side effects which have been seen include: joint pain, weakness, redness of the skin, excessive sweating, increased tear production, reduced sensation of the mouth, palpitations, feeling hot and cold, fatigue (a lack of energy), musculoskeletal (muscle and bone) pain, swelling, runny nose and decreased oxygen. Since Fabrazyme® is administered into a vein (intravenously), some patients have had reactions at the site where Fabrazyme® was given. There was one report of a skin reaction due to inflammation of the small blood vessels of the skin.

A small number of patients have experienced allergic reactions which in some cases were considered life-threatening. Signs and symptoms of possible allergic reactions include localized rapid swelling often of the mouth and throat, hives, difficulty breathing and low blood pressure.

If you exhibit such a reaction following the administration of Fabrazyme®, you should immediately contact your doctor.

Pre-treatment with antihistamines, antipyretics, and/or corticosteroids can be used to manage infusion-associated reactions. A slower infusion rate should also be considered.

This is not a complete list of side effects. For any unexpected effects while taking Fabrazyme®, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of reach and sight of children.
Store under refrigeration at 2 ºC to 8 ºC. Do not use after the expiration date on the vial.

Since Fabrazyme® does not contain any preservatives, vials must be used immediately after reconstitution.

The Fabry Registry, sponsored by Genzyme Corporation, has been established in order to better understand the variability and progression of Fabry disease, and to continue to monitor and evaluate safety and effectiveness of Fabrazyme®. You are encouraged to participate. Information regarding the registry program may be found at www.LSDregistry.net or by calling 1-800-745-4447. If you are interested in participating, please contact your doctor. You can only participate in the Registry through your doctor.

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug, you may notify Canada Vigilance:

Online: www.healthcanada.gc.ca/medeffect
Toll free phone: 1-866-234-2345
Toll free fax: 1-866-678-6789
Postage Paid Mail: Canada Vigilance Program
Health Canada
AL 0701C
Ottawa, Ontario K1A 0K9

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be found at: http://www.genzyme.ca or by contacting the sponsor, Genzyme Canada Inc., at: 1-877-220-8918.

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