

FABRAZYME- agalsidase beta injection, powder, lyophilized, for solution

Genzyme Corporation

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FABRAZYME® safely and effectively. See full prescribing information for FABRAZYME®.

FABRAZYME® (agalsidase beta) for injection, for intravenous use

Initial U.S. Approval: 2003

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

See full prescribing information for complete boxed warning

- Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. (5.1)
- Initiate FABRAZYME in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. (5.1)
- If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue FABRAZYME and immediately initiate appropriate medical treatment, including use of epinephrine. (5.1)

RECENT MAJOR CHANGES

Boxed Warning	7/2024
Dosage and Administration (2.1)	7/2024
Warnings and Precautions (5.1)	7/2024

INDICATIONS AND USAGE

FABRAZYME is a hydrolytic lysosomal neutral glycosphingolipid-specific enzyme indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease. (1)

DOSAGE AND ADMINISTRATION

- Administration of FABRAZYME should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. (2.1)
- The recommended dosage is 1 mg/kg body weight given every two weeks as an intravenous infusion. (2.2)
- Patients who have had a positive skin test to FABRAZYME or who have tested positive for anti-FABRAZYME IgE may be rechallenged with FABRAZYME. (2.3)
- See the full prescribing information for preparation, storage, and administration instructions. (2.4, 2.5, 2.6)

DOSAGE FORMS AND STRENGTHS

For injection: 5 mg or 35 mg of agalsidase beta as a lyophilized cake or powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Infusion-Associated Reactions: If a severe infusion-associated reaction occurs, discontinue FABRAZYME immediately and initiate appropriate medical treatment. (5.2)

ADVERSE REACTIONS

Most common adverse reactions ($\geq 20\%$) are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

Patients treated with enzyme replacement therapies have experienced life-threatening hypersensitivity reactions, including anaphylaxis. Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. Initiate FABRAZYME in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue FABRAZYME and immediately initiate appropriate medical treatment, including use of epinephrine. Inform patients of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and to seek immediate medical care should symptoms occur [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

FABRAZYME® is indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease.

2 DOSAGE AND ADMINISTRATION

2.1 Recommendations Prior to FABRAZYME Treatment

- Administration of FABRAZYME should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis [see Warnings and Precautions (5.1)].
- Initiate FABRAZYME in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment [see Warnings and Precautions (5.1)].
- Prior to FABRAZYME administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids [see Warnings and Precautions (5.1, 5.2)].
- FABRAZYME must be reconstituted and diluted prior to use [see Dosage and Administration (2.4)]

2.2 Recommended Dosage and Administration

- The recommended dosage of FABRAZYME is 1 mg/kg body weight infused every two weeks as an intravenous infusion.
- The initial recommended infusion rate is 0.25 mg/min (15 mg/hour) [see Dosage and Administration (2.6)].

2.3 Rechallenge Instructions

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 rechallenge administration should be a low dose at a lower infusion rate, e.g., one-half the therapeutic dose (0.5 mg/kg) at 1/25th of the initial standard recommended rate (0.01 mg/min or 0.6 mg/hr). Once a patient tolerates the infusion, the dose may be increased to reach the approved dose of 1 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/minute), as tolerated [see *Adverse Reactions* (6.2)].

2.4 Preparation Instructions

Use aseptic technique during preparation. Reconstitute and dilute FABRAZYME in the following manner:

Reconstitution Instructions

1. Determine the number of 35 mg and 5 mg FABRAZYME vials to be reconstituted based on actual body weight (kg) and the recommended dose [see *Dosage and Administration* (2.2)].
2. Remove the required number of 35 mg and 5 mg FABRAZYME vials from the refrigerator and allow the vials to sit for approximately 30 minutes at room temperature 20°C to 25°C (68°F to 77°F) before use.
3. Reconstitute each vial by directing the diluent down the inside wall of each vial then gently tilt and roll each vial. Use the following volumes for reconstitution:
 - 7.2 mL of FABRAZYME Sterile Water for Injection into the 35 mg vial. Total extractable amount per vial is 35 mg, 7 mL.
 - 1.1 mL of Sterile Water for Injection into the 5 mg vial. Total extractable amount per vial is 5 mg, 1 mL.
4. Each reconstituted vial will yield a concentration of 5 mg/mL of agalsidase beta.
5. Do not shake or agitate the product.
6. Visually inspect the reconstituted solution in the vials for particulate matter and discoloration. The reconstituted solution should be clear and colorless. Discard if visible particulate matter is present or the solution is discolored.

Dilution Instructions

7. Select an appropriate size 0.9% Sodium Chloride Injection infusion bag and prepare by removing a volume equal to the required FABRAZYME volume to achieve a total volume per Table 1.
8. Slowly withdraw the required volume of reconstituted solution from the FABRAZYME vial(s). Discard any unused reconstituted solution remaining in the vial.

Table 1: Total Infusion Volume Based on Patient Weight

Patient Weight (kg)	Total Volume (mL)
≤35	50
35.1 to 70	100
70.1 to 100	250
>100	500

9. Gently inject the FABRAZYME reconstituted solution into the port of the 0.9% Sodium Chloride Injection infusion bag. Do not inject into the airspace within the infusion bag.
10. Gently invert the infusion bag to mix the solution. Do not shake or agitate the product. After dilution, the solution will have a final concentration of 0.2 to 0.7

mg/mL of agalsidase beta.

2.5 Storage Instructions for the Reconstituted and Diluted Product

- Dilute the reconstituted solution without delay and use immediately. If immediate use is not possible, the reconstituted and diluted solution may be stored at 2°C to 8°C (36°F to 46°F) for up to 24 hours.

2.6 Administration Instructions

- The initial recommended infusion rate is 0.25 mg/min (15 mg/hour). For patients weighing:
 - 30 kg or more, in the absence of hypersensitivity and/or infusion-associated reactions (IARs), increase the infusion rate in increments of 0.05 to 0.08 mg/min (3 to 5 mg/hour) with each subsequent infusion. The minimum infusion duration is 1.5 hours (based on individual patient tolerability) [see *Dosage and Administration* (2.6)].
 - Less than 30 kg, the maximum infusion rate is 0.25 mg/minute (15 mg/hour) [see *Dosage and Administration* (2.6)].
- Do not infuse FABRAZYME in the same intravenous line with other products. Administer FABRAZYME using an in-line low protein binding 0.2 µm filter.

3 DOSAGE FORMS AND STRENGTHS

For injection: 5 mg or 35 mg of agalsidase beta as a white to off-white, lyophilized cake or powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions Including Anaphylaxis

Life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients treated with enzyme replacement therapies, including FABRAZYME. In clinical trials and postmarketing safety experience with FABRAZYME, approximately 1% of patients developed anaphylaxis or severe hypersensitivity reactions. 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.

In clinical trials with FABRAZYME, 10 of 238 patients developed IgE antibodies or skin test reactivity specific to FABRAZYME. Two of six patients in the rechallenge study discontinued treatment with FABRAZYME prematurely due to recurrent infusion-associated reactions. Four serious infusion-associated reactions occurred in three patients during FABRAZYME infusions, including bronchospasm, urticaria, hypotension, and development of FABRAZYME-specific antibodies. Other infusion-associated reactions occurring in more than one patient during the study included rigors, hypertension, nausea, vomiting, and pruritus.

Higher incidences of hypersensitivity reactions were observed in adult patients with persistent anti-FABRAZYME antibodies and in adult patients with high antibody titer compared to that in antibody-negative adult patients [see *Adverse Reactions* (6.2)].

Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. Administration of FABRAZYME should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. Prior to FABRAZYME administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids. Initiate FABRAZYME in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment.

- If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue FABRAZYME and immediately initiate appropriate medical treatment, including use of epinephrine. Consider the risks and benefits of re-administering FABRAZYME following severe hypersensitivity reactions (including anaphylaxis). Inform patients of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and to seek immediate medical care should symptoms occur.
 - Consider testing for IgE antibodies in FABRAZYME-treated patients who experienced severe hypersensitivity reactions, including anaphylaxis and consider the risks and benefits of continued treatment in patients with anti-FABRAZYME IgE antibodies. There are no marketed tests for antibodies against FABRAZYME. If testing is warranted, contact Genzyme Corporation at 1-800-745-4447 [see *Adverse Reactions* (6.2)].
 - Patients who have had a positive skin test to FABRAZYME or who have tested positive for FABRAZYME-specific IgE antibodies have been rechallenged with FABRAZYME using a rechallenge protocol. Rechallenge of these patients should only occur under the direct supervision of qualified personnel with appropriate medical monitoring and support measures readily available [see *Dosage and Administration* (2.3) and *Adverse Reactions* (6.2)].

5.2 Infusion-Associated Reactions

In clinical trials of FABRAZYME, 59% of patients experienced infusion-associated reactions (IARs) during FABRAZYME administration, some of which were severe. Infusion-associated reactions are defined as adverse reactions occurring on the same day as the infusion. The incidence of infusion-associated reactions was higher in patients who were positive for anti-FABRAZYME antibodies than in patients who were negative for anti-FABRAZYME antibodies [see *Adverse Reactions* (6.2)].

Severe infusion-associated reactions experienced by more than one patient in clinical trials of FABRAZYME included chills, vomiting, hypotension, and paresthesia. Other infusion-associated reactions included pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, urticaria, bradycardia, and somnolence [see *Adverse Reactions* (6.1)].

Prior to FABRAZYME administration, consider pre-treatment with antihistamines, antipyretics, and/or corticosteroids to reduce the risk of infusion-associated reactions (IARs). However, IARs may still occur in patients after receiving pre-treatment. IARs tended to decline in frequency with continued use of FABRAZYME. However, IARs may still occur despite extended duration of FABRAZYME treatment. Appropriate medical

monitoring and support measures, including cardiopulmonary resuscitation equipment, should be readily during FABRAZYME administration.

- If a severe IAR occurs, discontinue FABRAZYME immediately and initiate appropriate medical treatment. Consider the risks and benefits of re-administering FABRAZYME following a severe IAR and monitor patients closely upon re-administration of FABRAZYME.
- If a *mild or moderate* IAR occurs, consider temporarily holding the infusion, slowing the infusion rate, and/or reducing the FABRAZYME dosage.

Patients with advanced Fabry disease may have compromised cardiac function which may predispose them to a higher risk of severe complications from IARs. Closely monitor patients with compromised cardiac function if FABRAZYME is administered to these patients.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Hypersensitivity Reactions Including Anaphylaxis [*see Warnings and Precautions (5.1)*]
- Infusion-Associated Reactions [*see Warnings and Precautions (5.2)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in patients in clinical practice.

The data described below reflect exposure of 80 patients, ages 16 to 61 years, to 1 mg/kg FABRAZYME every two weeks in two separate double-blind, placebo-controlled clinical trials, for periods ranging from 1 to 35 months (mean 15.5 months). All 58 patients enrolled in one of the two studies continued into an open-label extension study of FABRAZYME treatment for up to 54 additional months. Patients were treated with antipyretics and antihistamines prior to the infusions.

Most Common Adverse Reactions

Table 2 enumerates adverse reactions that occurred during the double-blind treatment periods of the two placebo-controlled trials (Study 1 and Study 2) [*see Clinical Studies (14)*]. The most common adverse reactions reported with FABRAZYME were infusion-associated reactions, (FABRAZYME 59% vs placebo 27%) some of which were severe (FABRAZYME 5.0% vs placebo 1.7%). Infusion-associated reactions are defined as adverse reactions occurring on the same day as the infusion.

Common adverse reactions which occurred in $\geq 20\%$ of patients treated with FABRAZYME and $>2.5\%$ compared to placebo are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness and rash.

Table 2: Summary of Common Adverse Reactions* in Clinical Trials (Study 1 and 2) of Patients with Fabry Disease

Adverse Reaction	FABRAZYME (n=80) %	Placebo (n=60) %
Upper respiratory tract infection [†]	53	42
Chills [‡]	49	13
Pyrexia	39	22
Headache	39	28
Cough	33	25
Paresthesia	31	18
Fatigue	24	17
Peripheral edema	21	7
Dizziness	21	8
Rash	20	10
Pain in extremity	19	8
Myalgia [§]	18	7
Lower respiratory tract infection	18	7
Pain	16	13
Back pain	16	10
Hypertension	14	5
Pruritus	10	3
Tachycardia	9	3
Excoriation	9	2
Increased blood creatinine	9	5
Tinnitus	8	3
Dyspnea	8	2
Fall	6	3
Burning sensation	6	0
Anxiety	6	3
Depression	6	2
Wheezing	6	0
Hypoacusis	5	0
Chest discomfort	5	2
Fungal infection	5	0
Viral infection	5	0
Hot flush	5	0

* Reported at rate of at least 5% in FABRAZYME-treated patients and greater than 2.5% compared to placebo-treated patients.

† Includes reports of upper respiratory infection, nasal congestion, sinusitis, respiratory tract congestion, and pharyngitis.

‡ Includes reports of chills and feeling cold.

§ Includes reports of myalgia and muscle spasms.

Most infusion-associated reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administration of antipyretics, antihistamines, or steroids.

Adverse Reactions in Pediatric Patients

In Study 3, the safety profile of FABRAZYME in pediatric Fabry disease patients, ages 8 to 16 years, was similar to that seen in adults. The most common adverse reactions (>20%) were headache, abdominal pain, pharyngitis, fever, nausea, vomiting, rhinitis, diarrhea, arthralgia, and dizziness [see *Use in Specific Populations (8.4)* and *Clinical Studies (14)*].

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to FABRAZYME in the studies described below with the incidence of antibodies in other studies or to other agalsidase beta products may be misleading.

Patients with classic Fabry disease in Study 1, Study 2, and extension studies were tested at multiple time points for antibodies to agalsidase beta during the 55 to 58-month period. Approximately 83% (110 of 133) of adult patients receiving agalsidase beta developed antibodies; 77% (102/133) of patients developed neutralizing antibody (NAb) that inhibited *in vitro* agalsidase beta catalytic activity, which declined over time, and 6% (8/133) of patients developed NAb that inhibited cellular uptake. In pediatric patients with Fabry disease in Study 3 receiving the recommended dose who were 8 to <16 years of age, antibodies to agalsidase beta were detected in approximately 69% (11/16) of patients. Most patients who developed antibodies did so within the first 3 months of treatment. Antibody titers generally declined over time. Approximately 18% of adult patients who developed antibodies became antibody negative by 74 weeks (median time) from the time of seroconversion; however, none of the pediatric patients became antibody negative. Female patients generally had lower incidence of antibodies and lower antibody titers compared to male patients. In Study 5, patients with truncating *GLA* mutations had higher incidence of antibodies and higher antibody titers compared to patients with nontruncating *GLA* mutations. Patients with plasma α -galactosidase A activity ≤ 1.5 nmol/hr/mL had higher incidence of antibodies and higher antibody titers compared to patients with plasma α -galactosidase A activity > 1.5 nmol/hr/mL.

In general, over 90% of adult and pediatric patients treated with agalsidase beta achieved and maintained normalization of plasma globotriaosylceramide (GL-3) levels irrespective of developing antibodies to agalsidase beta.

Study 4 was an open-label, rechallenge study to evaluate the safety of FABRAZYME treatment in patients who had a positive skin test to FABRAZYME or who had tested positive for FABRAZYME-specific IgE antibodies. In this study, six adult male patients, who had experienced multiple or recurrent infusion-associated reactions during previous clinical trials of FABRAZYME, were rechallenged with FABRAZYME administered as a graded infusion for up to 52 weeks of treatment. 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 mg/kg every two weeks and the infusion rate was increased by slow upwards titration [see *Dosage and Administration*

(2.1)]. Pretreatment was not permitted for at least the first 4 infusions in order to allow early recognition of acute systemic hypersensitivity reactions. Four of the six patients treated in this study received at least 26 weeks of FABRAZYME (2 patients received 26 weeks and 2 patients received 52 weeks), and two patients discontinued prematurely due to recurrent infusion-associated reactions [see *Warnings and Precautions* (5.1, 5.2)].

Testing for IgE antibodies was performed in approximately 60 patients in clinical trials who experienced moderate to severe infusion-associated reactions or in whom mast cell activation was suspected. Seven of these patients tested positive for FABRAZYME-specific IgE antibodies or had a positive skin test to FABRAZYME. Patients who have had a positive skin test to FABRAZYME, or who have tested positive for FABRAZYME-specific IgE antibodies in clinical trials with FABRAZYME have been rechallenged [see *Dosage and Administration* (2.1) and *Warnings and Precautions* (5.1, 5.2)].

The incidences of hypersensitivity reactions were 51% (41/80) and 60% (25/42) in adult patients with persistent anti-FABRAZYME antibodies and in adult patients with high antibody titer, respectively, compared to 30% (7/23) in antibody-negative adult patients [see *Warnings and Precautions* (5.1)].

The incidence of infusion-associated reactions was 76% (84/110) in antibody-positive adult patients compared to 30% (7/23) in antibody-negative adult patients. The incidence of infusion-associated reactions was 46% (5/11) in antibody positive pediatric patients compared to 20% (1/5) in antibody negative pediatric patients [see *Warnings and Precautions* (5.2)].

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of FABRAZYME. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Cardiovascular*: cardiorespiratory arrest, cardiac failure, myocardial infarction, palpitations
- *Hypersensitivity reactions*: anaphylaxis [see *Warnings and Precautions* (5.1)], localized angioedema (including auricular swelling, eye swelling, dysphagia, lip swelling, edema, pharyngeal edema, face swelling, and swollen tongue), and bronchospasm
- *General*: hyperhidrosis, asthenia, infusion site reaction
- *Lymphatic*: lymphadenopathy
- *Musculoskeletal*: arthralgia
- *Neurologic*: cerebrovascular accident, hypoesthesia, oral hypoesthesia
- *Pulmonary*: respiratory failure, hypoxia
- *Renal*: renal failure
- *Vascular*: leukocytoclastic vasculitis

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from a pregnancy sub-study within the Fabry Disease registry, post-

marketing case reports, and case series with FABRAZYME use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes (*see Data*). Reproduction studies performed in rats at doses up to 68 times the human dose have revealed no evidence of effects on embryo-fetal development (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Available data from a pregnancy sub-study within the Fabry Disease registry, post-marketing case reports, and case series with FABRAZYME use during pregnancy have not identified a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. In the Fabry Disease registry pregnancy sub-study, 33 pregnancies exposed to FABRAZYME prior to or during pregnancy had a known outcome; 5 were reported as exposed in the first trimester.

Animal Data

The effects of agalsidase beta on embryo-fetal development in rats were evaluated at doses of 3, 10, and 30 mg/kg/day (up to 68 times the human dose of 1 mg/kg every 2 weeks on a body surface area basis) during gestation days 7 to 17. Hepatocellular necrosis consistent with accumulation of test article was evident in maternal livers in the 10 and 30 mg/kg/day groups (23 and 68 times the human dose on a body surface area basis). There were no adverse effects of agalsidase beta on embryo-fetal development in rats.

8.2 Lactation

Risk Summary

The available human data detected small amounts of agalsidase beta in human milk. Available data from the clinical study, global pharmacovigilance database, and published scientific literature are insufficient to determine the effects of FABRAZYME on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for FABRAZYME and any potential adverse effects on the breastfed child from FABRAZYME or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of FABRAZYME have been established in pediatric patients based on adequate and well-controlled studies in adults, a single-arm, open-label study in 16 pediatric patients with Fabry disease aged 8 to 16 years, and additional data in 24 patients with Fabry disease aged 2 to 7 years [*see Clinical Pharmacology (12.2) and Clinical Studies (14)*].

The overall safety profile of FABRAZYME was similar between the pediatric and the adult population [*see Adverse Reactions (6.1) and Clinical Studies (14)*].

8.5 Geriatric Use

Clinical studies of FABRAZYME did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects.

11 DESCRIPTION

Agalsidase beta is a recombinant human α -galactosidase A enzyme with the same amino acid sequence as the native enzyme. 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. The enzyme α -galactosidase A catalyzes the hydrolysis of GL-3 and other α -galactyl-terminated neutral glycosphingolipids, such as galabiosylceramide and blood group B substances to ceramide dihexoside and galactose. The specific activity of agalsidase beta is approximately 70 U/mg (one unit is defined as the amount of activity that results in the hydrolysis of 1 μ mole of a synthetic substrate, p-nitrophenyl- α -D-galactopyranoside, per minute under the assay conditions).

Agalsidase beta is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system.

FABRAZYME (agalsidase beta) for injection is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, preservative-free, white to off-white, lyophilized cake or powder for reconstitution with Sterile Water for Injection, USP.

Each 35 mg vial contains 37 mg of agalsidase beta, as well as 222 mg mannitol, 20.4 mg sodium phosphate monobasic monohydrate, and 59.2 mg sodium phosphate dibasic heptahydrate. Following reconstitution as directed, 35 mg of agalsidase beta (7 mL) may be extracted from each 35 mg vial.

Each 5 mg vial contains 5.5 mg of agalsidase beta, as well as 33.0 mg mannitol, 3.0 mg sodium phosphate monobasic monohydrate, and 8.8 mg sodium phosphate dibasic heptahydrate. Following reconstitution as directed, 5 mg of agalsidase beta (1 mL) may be extracted from each 5 mg vial.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

FABRAZYME (agalsidase beta) provides an exogenous source of α -galactosidase A in Fabry disease patients. Agalsidase beta is internalized and transported into lysosomes where it exerts enzymatic activity and reduces accumulated GL-3.

12.2 Pharmacodynamics

In Study 1, baseline mean values for plasma GL-3 were similar in the FABRAZYME (14.4 μ g/mL) and the placebo (14.7 μ g/mL) treatment groups. In the FABRAZYME treatment group, all 29 patients experienced normalization of plasma GL-3 levels (≤ 7.03 μ g/mL) and they maintained normal plasma GL-3 levels for up to 60 months of treatment. Follow-up heart and kidney biopsies were assessed at month 54 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. The reduction in tissue GL-3 is summarized in the clinical studies section (Table 4) [see *Clinical Studies (14)*].

In Study 2, patients in the FABRAZYME treatment group had mean plasma GL-3 levels that decreased from 9.0 µg/mL at baseline (N=49) to 4.8 µg/mL at one year (N=37) and 4.8 µg/mL at two years (N=18). In the placebo group, the mean plasma GL-3 was 9.1 µg/mL at baseline (N=31), 8.8 µg/mL at one year (N=21), and 9.4 µg/mL at two years (N=7).

In Study 3, 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. At weeks 24 and 48 of treatment, all 14 males had plasma GL-3 within the normal range. The two female patients' plasma GL-3 levels remained normal through study week 48. Histological evaluation of the capillary endothelium (vasculature), deep vessel endothelium, deep vessel smooth muscle cells, and perineurium of biopsied skin was conducted using histochemistry with light microscopy. Scoring was on a scale of 0 to 3 (0 defined as none; 1 as mild, 2 as moderate, and 3 as severe). At baseline, 12 of the 14 males had GL-3 inclusions present on skin biopsy (scores 1, 2, or 3) and all 12 achieved GL-3 inclusion scores of 0 at weeks 24 and 48 of treatment. The two females had no GL-3 inclusions in skin at baseline.

In Study 5, in an analysis of 24 FABRAZYME-treated pediatric patients with Fabry disease aged 2 to <8 years at FABRAZYME initiation and with elevated plasma GL-3 levels (i.e., >7.03 µg/mL) at baseline, plasma GL-3 levels fell within the normal range (i.e., ≤7.03 µg/mL) in 91% (20/22), 95% (18/19), and 92% (12/13) of patients at 6, 12, and 24 months, respectively.

12.3 Pharmacokinetics

The pharmacokinetics of FABRAZYME in clinical studies with adult and pediatric patients with Fabry disease is summarized in Table 3.

FABRAZYME exhibited nonlinear pharmacokinetics following intravenous infusions at 0.3 (30% of the approved recommended dosage), 1 mg/kg, and 3 mg/kg (3 times the approved recommended dosage) in adult patients. The area under the plasma concentration-time curve (AUC_{inf}) and the maximum plasma concentration (C_{max}) increased greater than dose proportional with increasing doses. The AUC_{inf} and C_{max} following multiple dose administrations were comparable to their values at the first dose.

In pediatric patients 8 to 16 years of age with body weight ranging from 27 to 65 kg, the AUC_{inf} and C_{max} following multiple dose administrations were higher compared to their values at the first dose. The increased plasma concentrations following multiple dose administration in pediatric patients could be due to formation of antidrug antibodies; however, such impact was not observed in adult patients [see *Adverse Reactions (6.2)* and *Use in Specific Populations (8.4)*].

Table 3: FABRAZYME Pharmacokinetic Summary

Dose	Regimen	Mean Infusion Length	Infusion number	AUC_{inf} µg	C_{max} µg/mL	Half-life	CL mL/min/kg	Vss* mL/kg
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		Length (min)	(n=patients)	min/mL	µg/mL	min	mL/min/kg	mL/kg
Study FB9702-01: Phase 1/2 Study in Adult Patients with Fabry Disease								
0.3 mg/kg	q14 days × 5	132	1 (n=3)	79 ± 24	0.6 ± 0.2	92 ± 27	4.1 ± 1.2	225 ± 62
		128	5 (n=3)	74 ± 30	0.6 ± 0.2	78 ± 67	4.6 ± 2.2	330 ± 231
1 mg/kg	q14 days × 5	115	1 (n=3)	496 ± 137	5.0 ± 1.1	67 ± 12	2.1 ± 0.7	112 ± 13
		120	5 (n=2)	466 ± 382	4.74 ± 4.3	45 ± 3	3.2 ± 2.6	243 ± 236
3 mg/kg	q14 days × 5	129	1 (n=2)	4168 ± 1401	29.7 ± 14.6	102 ± 4	0.8 ± 0.3	81 ± 45
		300	5 (n=2)	4327 ± 2074	19.8 ± 5.8	87 ± 21	0.8 ± 0.4	165 ± 80
Study 1: Phase 3 Study in Adult Patients with Fabry Disease								
1 mg/kg	q14 days × 11	280	1-3 (n=11)	649 ± 226	3.5 ± 1.6	89 ± 20	1.8 ± 0.8	120 ± 80
		280	7 (n=11)	372 ± 223	2.1 ± 1.14	82 ± 25	4.9 ± 5.6	570 ± 710
		300	11 (n=11)	784 ± 521	3.5 ± 2.2	119 ± 49	2.3 ± 2.2	280 ± 230
Study 3: Phase 2 Study in Pediatric Patients with Fabry Disease								
1 mg/kg	q14 days × 24	208	1 (n=8-9)	344 ± 307	2.2 ± 1.9	86 ± 27	5.8 ± 4.6	1097 ± 912
		111	12 (n=15)	1007 ± 688	4.9 ± 2.4	130 ± 41	1.6 ± 1.2	292 ± 185
		108	24 (n=9-10)	1238 ± 547	7.1 ± 4.4	151 ± 59	1.1 ± 0.8	247 ± 146

All data reported as the mean ± standard deviation.

* Vss = volume of distribution at steady state.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies to assess the carcinogenic or mutagenic potential of FABRAZYME. A study to evaluate the effects of agalsidase beta on fertility and general reproduction was performed in male and female rats at doses up to 10 mg/kg/day (23 times the human dose, on a body surface area basis). There were no adverse effects of agalsidase beta on fertility and early embryonic development in rats.

14 CLINICAL STUDIES

The safety and efficacy of FABRAZYME were assessed in four clinical studies in patients with Fabry disease and one matched analysis based on data from observational studies.

Study 1 was a randomized, double-blind, placebo-controlled, multinational, multicenter study of 58 patients with Fabry disease (56 males and 2 females), ages 16 to 61 years,

all naïve to enzyme replacement therapy [see *Clinical Pharmacology* (12.2)]. Patients were randomized 1:1 to receive either FABRAZYME 1 mg/kg every 2 weeks or placebo for 20 weeks. Patients had a median age of 24 years in the placebo group and 33 years in the FABRAZYME group at baseline. At baseline, all patients had plasma α GAL activity below the detection limit and 79% had leukocyte α GAL activity below the detection limit. The median plasma GL-3 at baseline was 14.4 ng/uL in the placebo group and 14.7 ng/uL in the FABRAZYME group with the overall range of <1.2 to 36 ng/uL. The median eGFR at baseline was 98.5 mL/hr in the placebo group and 83.0 mL/hr in the FABRAZYME group (overall range 24 to 153 mL/hr). All patients were pretreated with acetaminophen and an antihistamine. Oral steroids were an additional option to the pretreatment regimen for patients who exhibited severe or recurrent infusion-associated reactions.

Tissue biopsy specimens (kidney, heart, skin) were evaluated at baseline and at week 20 by light microscopy for the presence and number of GL-3 inclusions using a semi-quantitative methodology. Renal interstitial capillaries were scored based on the number of GL-3 inclusions on a scale of 0 to 3 (0 defined as "nearly none" or "trace," 1 defined as "mild," 2 defined as "moderate," and 3 defined as "severe"). The primary endpoint was the proportion of patients in either group with a renal capillary GL-3 inclusion score of zero at week 20. In the FABRAZYME group, 20 of 29 (69%) patients achieved a score of zero while 0 of 29 placebo-treated patients achieved a score of zero ($p < 0.001$). Similar reductions in GL-3 inclusions were observed in the capillary endothelium of the heart and skin (Table 4). All 58 patients who completed Study 1 were subsequently treated with FABRAZYME 1 mg/kg every two weeks in an open-label extension study. After six months of open-label treatment, most patients with available biopsy data achieved a GL-3 inclusion score of 0 in capillary endothelium (Table 4).

Table 4: Proportion of Patients with Tissue GL-3 Inclusion Score of Zero (Study 1 and open-label treatment)

	20 weeks of randomized treatment in Study 1		6 months of FABRAZYME open-label treatment	
	Placebo (n=29)	FABRAZYME (n=29)	Placebo/FABRAZYME (n=29)*	FABRAZYME/FABRAZYME (n=29)*
Kidney	0/29	20/29	24/24	23/25
Heart	1/29	21/29	13/18	19/22
Skin	1/29	29/29	25/26	26/27

* Results reported where biopsies were available.

Study 2 was a randomized (2:1 FABRAZYME to placebo), double-blind, placebo-controlled, multinational, multicenter study of 82 patients (72 males and 10 females) with Fabry disease, all naïve to enzyme replacement therapy [see *Clinical Pharmacology* (12.2)]. Of the 82 enrolled patients, 51 and 31 patients were randomized to the FABRAZYME and placebo groups, respectively. Patients were 20 to 72 years of age with a median age of 45 years at baseline, a median age of 36 years at Fabry disease diagnosis, and at a median of 10 years at symptom onset. The median plasma GL-3 at baseline was 9.3 ug/mL in the placebo group and 8.9 ug/mL in the FABRAZYME group with the overall range of 2.8 to 18.9 ug/mL. At baseline, patients had median plasma α GAL activity 1.5 nmol/hour/mL (range: 0 to 1.5), leukocyte α GAL activity 1.8 nmol/hour/mL (range: 0 to 4.0), eGFR 52 mL/min/1.73 m² (range: 25 to 113), and

protein to creatinine ratio 0.9 mg/mg (range: 0 to 7.3). Patients received either 1 mg/kg FABRAZYME IV or placebo every two weeks for up to 35 months (median follow-up 18.5 months). The primary efficacy endpoint was the time to first occurrence of a clinically significant event (renal, cardiac, or cerebrovascular event, or death). A total of 14 of 51 (28%) FABRAZYME-treated patients and 13 of 31 (42%) placebo-treated patients experienced a clinically significant event (HR 0.57, 95% CI: 0.27, 1.22).

Study 3 (Pediatric Study) was an open-label, single-arm, multinational, multicenter study in 16 pediatric patients with Fabry disease (14 males, 2 females), aged 8 to 16 years (median 12 years) [see *Clinical Pharmacology* (12.2)]. At baseline, patients had median plasma α GAL activity 0.2 nmol/hour/mL (range: 0.0, 2.0) and median leukocyte α GAL activity 0.5 nmol/hour/mg (range: 0.0, 12.5). All 14 males had elevated plasma GL-3 levels (i.e., >7.03 μ g/mL) at baseline, whereas the two females had normal plasma GL-3 levels. Median eGFR was normal (112.1 mL/min/1.73 m²) at baseline and did not change during treatment, and median urinary protein was 151.0 mg/24 hr (range: 70.0, 431.0). All patients received FABRAZYME 1 mg/kg every two weeks for up to 48 weeks.

Study 5 was a long-term, observational study assessing the rate of decline in renal function (eGFR slope) in 122 patients with Fabry disease aged 16 years and older treated with FABRAZYME. Treated patients were matched 1:1 based on age (at FABRAZYME initiation), sex, Fabry disease subtype (classic or non-classic), and baseline eGFR to a historical cohort of untreated patients with Fabry disease. The median follow-up time was 3 years in the untreated group and 4.5 years in the treated group (maximum follow-up time 5 years in both groups). In the matched cohort, the median age (at FABRAZYME initiation) was 35 years, 72% of patients were male, 84% of patients had the classic Fabry disease subtype, and the median baseline eGFR was 93 mL/min/1.73 m². The estimated mean eGFR slope was -1.5 mL/min/1.73 m²/year in the FABRAZYME-treated group and -3.2 mL/min/1.73 m²/year in the untreated group (eGFR slope difference: 1.7 mL/min/1.73 m²/year; 95% CI: 0.5, 3.0).

16 HOW SUPPLIED/STORAGE AND HANDLING

FABRAZYME (agalsidase beta) for injection is supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder in single-dose vials.

35 mg vial: NDC 58468-0040-1

5 mg vial: NDC 58468-0041-1

Refrigerate vials of FABRAZYME at 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 preservatives. Reconstituted and diluted solutions of FABRAZYME should be used immediately. If immediate use is not possible, the reconstituted and diluted solution may be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F) [see *Dosage and Administration* (2.2)].

17 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions Including Anaphylaxis and Infusion-Associated Reactions (IARs)

Advise the patient and caregiver that life-threatening hypersensitivity reactions, including

anaphylaxis, and IARs may occur with FABRAZYME treatment.

Advise the patient or caregiver that anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy.

Inform the patient and caregiver of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis, and IARs and to seek immediate medical care should symptoms occur [see *Warnings and Precautions* (5.1, 5.2)].

FABRAZYME Exposure During Pregnancy or Lactation

Advise a pregnant or lactating woman exposed to FABRAZYME to report FABRAZYME exposure to her healthcare provider and by calling 1-800-633-1610, option 1 [see *Use in Specific Populations* (8.1., 8.2)].

Patient Registry

Inform the patient and/or caregiver that a registry has been established for Fabry patients in order to better understand the variability and progression of Fabry disease in the population as a whole, and in women along with monitoring and evaluating long-term treatment effects of FABRAZYME. Additionally, the registry also monitors the effect of FABRAZYME on pregnant women and their offspring. Encourage the patient and/or caregiver to contact the registry program by visiting [www. registrynxt.com](http://www.registrynxt.com) or by calling 1-800-745-4447, extension 15500.

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PRINCIPAL DISPLAY PANEL - 5 mg Vial Carton

NDC 58468-0041-1

Rx only

Fabrazyme®
agalsidase beta

5 mg per vial

for Injection

For Intravenous
Infusion after Dilution

One single-dose vial
Discard unused portion

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PRINCIPAL DISPLAY PANEL - 35 mg Vial Carton

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Fabrazyme®
agalsidase beta

35 mg per vial

for Injection

For Intravenous
Infusion after Dilution

One single-dose vial
Discard unused portion

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For questions, Call
800-745-4447

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Infusion after Dilution

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887903

Each vial contains
agalsidase beta 37 mg,
Mannitol 222 mg,
Sodium Phosphate Monobasic,
Monohydrate 20.4 mg,
Sodium Phosphate Dibasic,
Heptahydrate 59.2 mg.

Following reconstitution with
7.2 mL Sterile Water for Injection,
USP, each vial contains
7.4 mL reconstituted solution
and a total extractable volume
of 7.0 mL at 5.0 mg/mL.

Contains No Preservatives

No U.S. Standard of Potency

sanofi

Dosage and Administration:
See prescribing information.

**Store refrigerated at
2°C-8°C (36°F-46°F).**

Do not freeze or shake.

See prescribing information
for storage of reconstituted
and diluted product.

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887903

FABRAZYME

agalsidase beta injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:58468-0041
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AGALSIDASE BETA (UNII: RZD65TSM9U) (AGALSIDASE BETA - UNII:RZD65TSM9U)	AGALSIDASE BETA	5 mg in 1 mL

Inactive Ingredients

Ingredient Name	Strength
MANNITOL (UNII: 3OWL53L36A)	33 mg in 1 mL
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE (UNII: 593YOG76RN)	3 mg in 1 mL
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE (UNII: 70WT22SF4B)	8.8 mg in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:58468-0041-1	1 in 1 CARTON	12/17/2008	
1		1 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103979	12/17/2008	

FABRAZYME

agalsidase beta injection, powder, lyophilized, for solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:58468-0040
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AGALSIDASE BETA (UNII: RZD65TSM9U) (AGALSIDASE BETA - UNII:RZD65TSM9U)	AGALSIDASE BETA	5 mg in 1 mL

Inactive Ingredients				
Ingredient Name			Strength	
MANNITOL (UNII: 3OWL53L36A)			30 mg in 1 mL	
SODIUM PHOSPHATE, MONOBASIC, MONOHYDRATE (UNII: 593YOG76RN)			2.75 mg in 1 mL	
SODIUM PHOSPHATE, DIBASIC, HEPTAHYDRATE (UNII: 70WT22SF4B)			8 mg in 1 mL	
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:58468-0040-1	1 in 1 CARTON	12/17/2008	
1		7 mL in 1 VIAL, GLASS; Type 0: Not a Combination Product		
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA		BLA103979	12/17/2008	

Labeler - Genzyme Corporation (025322157)

Establishment			
Name	Address	ID/FEI	Business Operations
Genzyme Corporation		968278916	ANALYSIS(58468-0040, 58468-0041) , API MANUFACTURE(58468-0040, 58468-0041)

Establishment			
Name	Address	ID/FEI	Business Operations
Genzyme Corporation		050424395	PACK(58468-0040, 58468-0041) , LABEL(58468-0040, 58468-0041)

Establishment			
Name	Address	ID/FEI	Business Operations
Genzyme Corporation		968278932	API MANUFACTURE(58468-0040, 58468-0041)

Establishment			
Name	Address	ID/FEI	Business Operations
Genzyme Corporation		943130096	ANALYSIS(58468-0040, 58468-0041) , API MANUFACTURE(58468-0040, 58468-0041)

Establishment			
Name	Address	ID/FEI	Business Operations
Genzyme Corporation		968302658	ANALYSIS(58468-0040, 58468-0041)

Establishment			
Name	Address	ID/FEI	Business Operations

Name	Address	ID/FEI	Business Operations
Genzyme Ireland Limited		985127419	ANALYSIS(58468-0040, 58468-0041) , MANUFACTURE(58468-0040, 58468-0041) , PACK(58468-0040, 58468-0041) , LABEL(58468-0040, 58468-0041)

Establishment			
Name	Address	ID/FEI	Business Operations
Genzyme Corporation		117450412	ANALYSIS(58468-0040, 58468-0041) , API MANUFACTURE(58468-0040, 58468-0041)

Establishment			
Name	Address	ID/FEI	Business Operations
Resilience US, Inc		118999964	ANALYSIS(58468-0040, 58468-0041)