Fabrazyme® (agalsidase beta)

For intravenous infusion

DESCRIPTION

Fabrazyme® is a recombinant human a-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. α-galactosidase A catalyzes the hydrolysis of globotriaosylceramide (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 Fabrazyme® is approximately 70 U/mg (one unit is defined as the amount of activity that results in the hydrolysis of 1 µmole of a synthetic substrate, p-nitrophenyl-α-D-galactopyranoside, per minute under the assay conditions).

Fabrazyme® is produced by recombinant DNA technology in a Chinese Hamster Ovary mammalian cell expression system.

Fabrazyme® is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with Sterile Water for Injection, USP. Each 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 vial.

CLINICAL PHARMACOLOGY

Mechanism of Action

Fabry disease is an X-linked genetic disorder of glycosphingolipid metabolism. Deficiency of the lysosomal enzyme α-galactosidase A leads to progressive accumulation of glycosphingolipids, predominantly GL-3, in many body tissues, occurring over a period of years or decades. Clinical manifestations of Fabry disease include renal failure, cardiomyopathy, and cerebrovascular accidents. Accumulation of GL-3 in renal endothelial cells may play a role in renal failure.

Fabrazyme® is intended to provide an exogenous source of α-galactosidase A in Fabry disease patients. Preclinical and clinical studies evaluating a limited number of cell types indicate that Fabrazyme® will catalyze the hydrolysis of glycosphingolipids including GL-3.

Pharmacokinetics

Plasma profiles of Fabrazyme® were studied at 0.3, 1.0 and 3.0 mg/kg in 15 patients with Fabry disease. The area under the plasma concentration-time curve (AUC_{∞}) and the clearance did not increase proportionately with increasing doses, demonstrating that the enzyme follows non-linear pharmacokinetics. Terminal half-life was dose independent with a range of 45 - 102 minutes.

In 11 patients with Fabry disease given 1.0 mg/kg Fabrazyme® every 14 days for a total of 11 infusions, the pharmacokinetic responses following repeated dosing fell into three categories. In some patients, pharmacokinetic responses were maintained with repeated dosing, whereas in other patients, pharmacokinetic values decreased at infusion seven relative to baseline and returned to baseline values by infusion 11. In the remaining patients, AUC declined and failed to return to baseline by infusion 11. In these patients, the average AUC was 25% of its initial level. Some patients with elevated titers of antibody to agalsidase were among those with decreased AUC. The development of antibodies to agalsidase did not influence half-life, but reduced both apparent Cmax and AUC. The long-term consequence of antibody development to the pharmacokinetics of agalsidase has not been established.

CLINICAL STUDIES

The safety and efficacy of Fabrazyme® were assessed in a randomized, double-blind, placebo-controlled, multinational, multicenter study of 58 Fabry patients (56 males and two 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. All patients were pretreated with acetaminophen and an antihistamine to decrease or prevent infusion associated reactions. Oral steroids were an additional option to the pretreatment regimen for patients who exhibited severe or recurrent infusion reactions. The primary efficacy endpoint of GL-3 inclusions in renal interstitial capillary endothelial cells, was assessed by light microscopy and was graded on an inclusion severity score ranging from 0 (normal or near normal) to 3 (severe inclusions).

A GL-3 inclusion score of 0 was achieved in 20 of 29 (69%) patients treated with Fabrazyme® compared to 0 of 29 treated with placebo ($p<0.001$). Similar reductions in GL-3 inclusions were observed in the capillary endothelium of the heart and skin (Table 1). No differences between groups in symptoms or renal function were observed during this five month study.

Table 1
Reduction of GL-3 Inclusions to Normal or Near Normal Levels (0 Score) in the Capillary Endothelium of the Kidney, Heart and Skin

	5 Months of the Controlled Study		6 Months of the Open-label Extension Study	
	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

All 58 patients in the randomized study participated in an open-label extension study of Fabrazyme® at 1.0 mg/kg every two weeks indefinitely. At the end of six months of open-label treatment, most patients achieved a GL-3 inclusion score of 0 in capillary endothelium (Table 1). GL-3 was decreased to normal or near normal levels in mesangial cells, glomerular capillary endothelium, interstitial cells and non-capillary endothelium. GL-3 deposition was still present in vascular smooth muscle cells, tubular epithelium and podocytes, at variably reduced levels. Plasma GL-3 levels were reduced to levels below the limit of detection and remained so up to 18 months of treatment.

The reduction of GL-3 inclusions suggests that Fabrazyme® may ameliorate disease expression; however, the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established.

INDICATIONS AND USAGE

Fabrazyme® (agalsidase beta) is indicated for use in patients with Fabry disease. Fabrazyme® reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types (**see CLINICAL STUDIES**).

CONTRAINDICATIONS

No known contraindications.

WARNINGS

Infusion Reactions

Infusion reactions occurred in many patients treated with Fabrazyme® (**see ADVERSE**

REACTIONS). Some of the reactions were severe. Infusion reactions included fever, rigors, chest tightness, hypertension, hypotension, pruritis, myalgia, dyspnea, urticaria, abdominal pain, and headache. All patients were pretreated with acetaminophen and an antihistamine. Infusion reactions occurred in some patients after receiving antipyretics, antihistamines and oral steroids.

Patients should be given antipyretics prior to infusion. If an infusion reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of additional antipyretics, antihistamines and/or steroids may ameliorate the symptoms. Because of the potential for severe infusion reactions, appropriate medical support measures should be readily available when Fabrazyme® is administered.

PRECAUTIONS

General

Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions (**see WARNINGS**). Patients with compromised cardiac function should be monitored closely if the decision is made to administer Fabrazyme®.

Most patients develop IgG antibodies to Fabrazyme® (**see ADVERSE REACTIONS: Immunogenicity**). Some patients developed IgE or skin test reactivity specific to Fabrazyme®. Physicians should consider testing for IgE (**see Laboratory Tests**) in patients who experienced suspected allergic reactions and consider the risks and benefits of continued treatment in patients with anti- Fabrazyme® IgE.

Information for Patients

Patients should be informed that a Registry has been established in order to better understand the variability and progression of Fabry disease in the population as a whole and in women (see **Responses in Women**), and to monitor and evaluate long-term treatment effects of Fabrazyme®. The Registry will also monitor the effect of Fabrazyme® on pregnant women and their offspring, and determine if Fabrazyme® is excreted in breast milk. Patients should be encouraged to participate and advised that their participation is voluntary and may involve long-term follow-up. For more information visit www.fabryregistry.com or call (800) 745-4447.

Laboratory Tests

There are no marketed tests for antibodies against Fabrazyme®. If testing is warranted, contact your local Genzyme representative or Genzyme Corporation at 800-745-4447.

Drug Interactions

No drug interaction studies were performed.

No *in vitro* metabolism studies were performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies to assess the carcinogenic or mutagenic potential of Fabrazyme®. There are no studies assessing the potential effect of Fabrazyme® on fertility in humans.

Pregnancy: Category B

Reproduction studies have been performed in rats at doses up to 30 times the human dose and have revealed no evidence of impaired fertility or negative effects on embryo fetal development due to Fabrazyme®. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Women of childbearing potential should be encouraged to enroll in the Fabry patient registry (see **PRECAUTIONS: Information for Patients**).

Nursing Mothers

It is not known whether Fabrazyme® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Fabrazyme® is administered to a nursing woman.

Nursing mothers should be encouraged to enroll in the Fabry registry (see **PRECAUTIONS: Information for Patients**).

Responses in Women

Fabry disease is an X-linked genetic disorder. However, some heterozygous women will develop signs and symptoms of Fabry disease due to the variability of the X chromosome inactivation within cells. Generally, the rates of progression of organ impairment are slower than in male Fabry disease patients and severity of signs and symptoms is variable.

Two women were enrolled in the clinical studies with Fabrazyme®. Therefore, no determination can be made whether symptomatic women respond to Fabrazyme® differently than men. There is also insufficient information to determine whether the relationship between cellular histologic evaluations of biopsies and clinical manifestations differ between women and men.

Pediatric Use

The safety and effectiveness of Fabrazyme® in pediatric patients have not been established.

Geriatric Use

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

ADVERSE REACTIONS

The most serious and most common adverse reactions reported with Fabrazyme® are infusion reactions. Serious and/or frequently occurring infusion reactions consisted of one or more of the following: tachycardia, hypertension, throat tightness, chest pain/tightness, dyspnea, fever, chills/rigors, abdominal pain, pruritus, urticaria, nausea, vomiting, lip or ear edema, and rash (**see WARNINGS: Infusion reactions.**) Infusion reactions declined in frequency with continued use of Fabrazyme®. However, serious infusion reactions may occur after extended durations of Fabrazyme® treatment.

Other reported serious adverse events included stroke, pain, ataxia, bradycardia, cardiac arrhythmia, cardiac arrest, decreased cardiac output, vertigo, hypoacousia, and nephrotic syndrome. These adverse events also occur as manifestations of Fabry disease; an alteration in frequency or severity cannot be determined from the small numbers of patients studied.

The data described below reflect exposure of 29 patients to 1.0 mg/kg Fabrazyme® every two weeks for 5 months in a placebo-controlled study. All 58 patients continued into an open-label extension study of Fabrazyme® treatment for up to 30 additional months. An additional 28 patients received open-label treatment. All patients were treated with antipyretics and antihistamines prior to the infusions.

Because clinical trials are conducted under widely varying and controlled conditions, the observed adverse reaction rates may not predict the rates observed in patients in clinical practice.

Table 2 enumerates adverse events and selected laboratory abnormalities that occurred during the placebo-controlled trial in at least 2 patients more in the Fabrazyme® group than was observed in the placebo group. Reported adverse events have been classified by organ system. Observed adverse events in the Phase 1/2 study and the open-label treatment period following the controlled study were not different in nature or severity.

Table 2
Incidence (%) Of Adverse Events Occurring In The Placebo-Controlled Study

Adverse Event	Placebo (N = 29)	Fabrazyme® (N = 29)
Body as a Whole		
Chest pain	3 (10)	5 (17)
Fever	5 (17)	14 (48)
Pain	3 (10)	6 (21)
Pallor	1 (3)	4 (14)
Rigors	4 (14)	15 (52)
Temperature changed sensation	1 (3)	5 (17)
Cardiovascular		
Cardiomegaly	1 (3)	3 (10)
Hypertension	0	3 (10)
Hypotension	2 (7)	4 (14)
Edema dependent	1 (3)	6 (21)
Central and Peripheral Nervous System		
Dizziness	2 (7)	4 (14)
Headache	11 (38)	13 (45)
Paraesthesia	2 (7)	4 (14)
Gastro-Intestinal System		
Dyspepsia	1 (3)	3 (10)
Nausea	4 (14)	8 (28)
Musculo-Skeletal System		
Arthrosis	0	3 (10)
Skeletal pain	0	6 (21)
Psychiatric		
Anxiety	5 (17)	8 (28)
Depression	1 (3)	3 (10)
Reproductive, Male		
Testicular pain	0	2 (7)
Respiratory System		
Bronchitis	1 (3)	3 (10)
Bronchospasm	0	2 (7)
Laryngitis	0	2 (7)
Pharyngitis	2 (7)	8 (28)
Rhinitis	7 (24)	11 (38)
Sinusitis	0	2 (7)

Immunogenicity

Sixty-three of 71 (89%) patients in the clinical studies treated with Fabrazyme® have developed antibodies to Fabrazyme®. Most patients who develop antibodies do so within the first 3 months of exposure. Antibodies to Fabrazyme® were purified from 15 patients with high antibody titers (= 12,800) and studied for inhibition of *in vitro* enzyme activity. Under the conditions of this assay, most of these 15 patients had inhibition of *in vitro* enzyme activity ranging between 14-74% at one or more timepoints during the study. No general pattern was seen in individual patient reactivity over time. The clinical significance of binding and/or inhibitory antibodies to Fabrazyme® is not known. In patients followed in the open-label study, reduction of GL-3 in plasma and GL-3 inclusions in superficial skin capillaries was maintained after antibody formation.

The data reflect the percentage of patients whose test results were considered positive for antibodies to Fabrazyme® using an ELISA and radioimmunoprecipitation (RIP) assay for antibodies. These results are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibodies in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to Fabrazyme® with the incidence of antibodies to other products may be misleading.

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

The recommended dosage of Fabrazyme® 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 in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hr) each subsequent infusion. Thirty-one of 58 (53%) patients have received infusions at rates = 33 mg/hr.

Patients should receive antipyretics prior to infusion (**see WARNINGS**).

Instructions for Use

Fabrazyme® does not contain any preservatives. Vials are for single-use only. Any unused product should be discarded.

Shaking or agitation of this product should be avoided. Do not use filter needles during the preparation of the infusion.

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.

   Patient weight (in kg) = Patient dose (in mg)

   Patient dose (in mg) ÷ 35 mg/vial = Number of vials to reconstitute (if the number of vials includes a fraction, round up to the next whole number)

   Example: Patient weight (80 kg) = Patient dose (80 mg)

   80 mg ÷ 35 mg/vial = 2.29 vials, therefore, 3 vials should be reconstituted.

2. Reconstitute each vial of Fabrazyme® by slowly injecting 7.2 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5.0 mg/mL clear, colorless solution (total extractable amount per vial is 35 mg, 7.0 mL).

3. Visually inspect the reconstituted vials for particulate matter and discoloration. Do not use the reconstituted solution if there is particulate matter or if it is discolored.

4. The reconstituted solution should be further diluted with 0.9% Sodium Chloride Injection, USP to a final total volume of 500 mL. Prior to adding the volume of reconstituted Fabrazyme® required for the patient dose, remove an equal volume of 0.9% Sodium Chloride for Injection, USP from the 500 mL infusion bag.

   Patient dose (in mg) ÷ 5 mg/mL = Number of mL of reconstituted Fabrazyme® required for patient dose.

   Example: Patient dose = 80 mg

   80 mg ÷ 5 mg/mL = 16 mL of Fabrazyme®

   Slowly withdraw the reconstituted solution from each vial up to the total volume required for the patient dose. Inject the reconstituted Fabrazyme® solution directly into the Sodium Chloride solution. Do not inject in the airspace within the infusion bag. Discard any vial with unused reconstituted solution.

5. Gently invert infusion bag to mix the solution, avoiding vigorous shaking and agitation.
6. Fabrazyme® should not be infused in the same intravenous line with other products.
7. The diluted solution may be filtered through an in-line low protein-binding 0.2 µm filter during administration.

Storage

Store Fabrazyme® 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).

HOW SUPPLIED

Fabrazyme® is supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder. Fabrazyme® is 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. NDC 58468-0040-1

Rx Only
U.S. Patent Number: 5,356,804

Fabrazyme® is manufactured and distributed by:
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US License Number: 1596

Issued: 24 April 2003