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Fabrazyme insert for India
Proof 3 r23 06.25.21 op: rs area: box language(s): English
code: GEN job: 606950 12" x 10½" 817903
Insert is 100% of actual size

For the use only of Registered Medical Practitioners or a Hospital or a Laboratory

This package insert is updated periodically. Please read carefully before using a new pack

Agalsidase beta Powder for concentrate for solution for infusion

FABRAZYME®

817903

FPO Data Matrix

FPO Data Matrix

DESCRIPTION
Proprietary Name: Fabrazyme®
Generic or official name (INN/USAN): agalsidase beta
Chemical Name: recombinant human alpha-galactosidase A, r-hαGAL

Based on the amino acid sequence, the molecular formula is:
C2029H3080N544O587S27

Fabrazyme (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. Agalsidase beta is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line, a methodology that has been used for several approved products over the past fifteen years. The protein is purified by a column chromatography process that includes measures to inactivate and remove potential viruses, resulting in a highly purified, active enzyme.

THERAPEUTIC OR PHARMACOLOGICAL CLASS
Pharmacotherapeutic group: Alimentary tract and metabolism products - enzyme
ATC code: A16AB04 agalsidase beta

PHARMACEUTICAL FORM(S)/COMPOSITION
Fabrazyme (agalsidase beta). Lyophilized powder for reconstitution with Sterile Water for Injection.

35 mg Vial
The active ingredient is agalsidase beta. Each 35mg vial contains 37mg of agalsidase beta with an extractable dose of 35mg after reconstitution.

5 mg Vial
The active ingredient is agalsidase beta. Each 5mg vial contains 5.5 mg of agalsidase beta with an extractable dose of 5 mg after reconstitution.

Excipients:

	35 mg Vial	5 mg Vial
Mannitol	222 mg	33.0 mg
Sodium phosphate monobasic, monohydrate	20.4 mg	3.0 mg
Sodium phosphate dibasic, heptahydrate	59.2 mg	8.8 mg

NATURE AND CONTENTS OF CONTAINER
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 (35 mg) or single use clear Type I glass 5 mL (cc) vials (5 mg). The closure consists of a siliconised butyl stopper and an aluminum seal with a plastic flip-off cap.

Packaging Size : 1 vial per carton

35 mg Vial
Each 35 mg vial of Fabrazyme® 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. 35 mg (7 mL) may be extracted from the vial.

5 mg Vial
Each 5 mg vial of Fabrazyme 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. 5 mg (1 mL) may be extracted from the vial.

INDICATIONS
Fabrazyme® (agalsidase beta) is indicated for the treatment of long term enzyme replacement therapy in patients with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency)

DOSAGE AND ADMINISTRATION
GENERAL
The recommended dose of Fabrazyme® is 1.0 mg/kg body weight infused every 2 weeks as an IV infusion.

In clinical trials, the initial IV infusion rate was administered at a rate of no more than 0.25 mg/min or 15 mg/hr. The infusion rate may be slowed in the event of infusion-associated reactions. After patient tolerance has been established, the infusion rate may be increased gradually with subsequent infusions, as tolerated.

Overall, the safety and efficacy of Fabrazyme®-treatment administered at 1.0 mg/kg every 2 weeks in children between the ages of 8 and 16 years is consistent with that seen in adults. The safety and efficacy of Fabrazyme® at this dose in patients younger than 8 years of age have not been evaluated.

The safety and efficacy of Fabrazyme in patients older than 65 years have not been established.
No changes in dose are necessary for patients with renal insufficiency. Studies in patients with hepatic insufficiency have not been performed.

SPECIAL POPULATIONS
ADMINISTRATION
Intravenous (IV) infusion.

CONTRAINDICATIONS
No specified.

WARNINGS
As with any intravenously administered protein product, patients may develop antibodies to the protein and immune-mediated reactions are possible. Most patients develop IgG antibodies to Fabrazyme®. Patients with antibodies to r-hαGAL have a higher risk of infusion-associated reactions (See Adverse Reactions).

Patients treated with Fabrazyme may develop infusion-associated reactions the majority of which are mild to moderate in intensity. If an infusion-associated reaction occurs during a Fabrazyme infusion, decreasing the infusion rate, temporarily stopping the infusion and/or administration of antipyretics, antihistamines, and/or steroids may ameliorate the symptoms. If severe allergic or anaphylactoid reactions occur, immediate discontinuation of the administration of Fabrazyme and current medical standards for emergency treatment are to be provided. The risks and benefits of re-administering Fabrazyme following a severe hypersensitivity or anaphylactoid reaction should be considered.

Patients who have had a positive skin test or who have tested positive for IgE antibodies to r-hαGAL have been successfully rechallenged with Fabrazyme. The initial rechallenge administration should be at a low dose and a lower infusion rate (1/2 the therapeutic dose (0.5mg/kg) at 1/25 the initial standard recommended rate (0.01mg/min)). Once a patient tolerates the infusion, the dose may be increased to reach the therapeutic dose of 1 mg/kg and the infusion rate may be increased by slowly titrating upwards, as tolerated.

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

INTERACTIONS
Drug/Drug
No formal drug/drug interaction studies have been performed.
No in vitro metabolism studies have been performed.

Drug/Food
Interactions with food and drink are unlikely. No formal drug/food interaction studies have been conducted.

Drug/Laboratory Tests
None specified.

PREGNANCY
Reproduction studies have been performed in rats at doses up to 10mg/kg/day in the fertility study and 30 mg/kg/day in the embryo-fetal development study. These studies have revealed no evidence of impaired fertility or harm to the fetus 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.

No studies of perinatal toxicity have been performed.

Labor and Delivery: not specified.

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

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
No studies on the ability to drive or use heavy machinery have been conducted with Fabrazyme.

ADVERSE REACTIONS
Table 1 presents the incidence of adverse drug reactions, related to Fabrazyme, in a total of 168 patients treated with Fabrazyme in the Phase 1/2 Extension study, the Phase 3 Double-Blind/Open-Label Extension studies, the Phase 4 Double-Blind/Open-Label Extension studies, and the Phase 2 Pediatric study for a minimum of one infusion to a maximum of 5 years.

Adverse event terms are listed by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and frequency. The majority of these product-related adverse events were assessed to be mild or moderate in intensity.

Table 1: Incidence of Adverse Drug Reactions with Fabrazyme Treatment in the Phase 1/2 Extension, Phase 3 Double-Blind, Phase 3 Extension, Phase 4 Double-Blind, Phase 4 Extension, and Phase 2 Pediatric Studies

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

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

Table 2 presents the incidence of adverse drug reactions, related to Fabrazyme, in a total of 181 unique patients treated with Fabrazyme in the Phase 2 Japan study, the Phase 1/2 Extension study, the Phase 3 Double-Blind/Open-Label Extension studies, the Phase 4 Double-Blind/Open-Label Extension studies, and the Phase 2 Pediatric study for a minimum of one infusion to a maximum of 5 years. Adverse Event terms are listed by MedDRA System Organ Class and frequency. The majority of these product-related adverse events were assessed to be mild or moderate in intensity.

Table 2: Incidence of Adverse Drug Reactions with Fabrazyme Treatment in the Phase 2 Japan, Phase 1/2 Extension, Phase 3 Double-Blind, Phase 3 Extension, Phase 4 Double-Blind, Phase 4 Extension, and Phase 2 Pediatric Studies

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

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

The occurrence of somnolence can be attributed to clinical trial specified pre-treatment with antihistamines

The safety profile of Fabrazyme treatment in pediatric patients 8 years of age and older in a Phase 2 trial was consistent with that seen in adults. Limited information from a Phase 3b trial, suggests that the safety profile of Fabrazyme treatment in patients ages 5-7, treated with either 0.5mg/kg every 2 weeks or 1.0mg/kg every 4 weeks is similar to that of patients 8 years of age and older treated at 1.0mg/kg every 2 weeks.

Infusion-associated reactions (IARs) (defined as product-related adverse events occurring on the same day as the infusion) were the most frequently reported related adverse events in the Phase 1/2 Extension, Phase 3 Double-Blind, Phase 3 Extension, Phase 4 Double-Blind, Phase 4 Extension, and Phase 2 Pediatric studies. These IARs included events of chills, fever (pyrexia/body temperature increased/hyperthermia), temperature change sensation (feeling cold/feeling hot), nausea, vomiting, hypertension (blood pressure increased), flushing (hot flush), paraesthesia (burning sensation), fatigue (lethargy/malaise/asthenia), pain (pain in extremity), headache, pruritus (pruritus generalized), chest pain (chest discomfort), urticaria, dyspnea (dyspnea exacerbated), dizziness, pallor, somnolence, and tachycardia.

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

Currently available data demonstrate that the total number of Fabrazyme treated patients experiencing any related adverse event on the same day as the infusion has decreased over time.

The majority of these IARs are thought to be associated with the formation of IgG antibodies and/or complement activation. The majority of patients developed IgG antibodies to r-hαGAL, which is not unexpected (See Warnings, Section 5). The mean time to seroconversion was within 3 months of the first infusion with Fabrazyme. The majority of seropositive patients in clinical trials exhibited either consistently low titers or declining titers over time: low responders (highest titer value was ≤ 800), tolerized (no detectable antibody by radioimmunoprecipitation [RIP]), or downward trend (based on a ≥ 4-fold reduction in titer from peak measurement to the last measurement). There was no evidence that IgG seroconversion had any impact on the efficacy of Fabrazyme.

POST-MARKETING EXPERIENCE
During the post-marketing period, the adverse drug reaction profile was generally similar to that seen during the clinical studies. Adverse drug reactions seen during the post-marketing period included: feeling hot and cold, malaise, musculoskeletal pain, oedema, rhinitis, 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. One case of membranous glomerulonephritis has been reported.

A small number of patients have experienced anaphylactoid reactions which in some cases were considered life-threatening. Signs and symptoms of possible anaphylactoid reactions have included events of localized angioedema, generalized urticaria, bronchospasm and hypotension.
(See Warnings)

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

INTERFERENCES WITH LABORATORY AND DIAGNOSTIC TEST
None specified.

ABUSE AND DEPENDENCE
There have been no reports of patient abuse or dependence on Fabrazyme®

PHARMACODYNAMICS
MODE OF ACTION/PHARMACODYNAMIC CHARACTERISTICS

Fabry disease is characterized by the deficiency of α-galactosidase A, a lysosomal hydrolase which catalyses the hydrolysis of glycosphingolipids, in particular globotriaosylceramide (GL-3), to terminal galactose and ceramide dihexoside. Reduced or absent α-galactosidase activity results in the accumulation of GL-3 in many cell types, including the endothelial and parenchymal cells.

The rationale for enzyme replacement therapy is to restore a level of enzymatic activity sufficient to hydrolyse the accumulated substrate. After intravenous infusion, 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.

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

Pharmacokinetics of Fabrazyme was evaluated in 11 adult Fabry patients in Europe. Following an intravenous infusion of 1 mg/kg of Fabrazyme over a period averaging 280-300 minutes, mean maximum plasma concentrations (Cmax) ranged from 2.09 to 3.49 µg/mL. The mean AUC_{∞} ranged from 372 to 784 µg/mL•min. The mean volume of distribution (Vz) was 0.23-0.49 L/kg and the mean volume of distribution at steady state (Vss) was 0.12 to 0.57 L/kg. Mean plasma clearance ranged from 1.75 to 4.87 mL/min/kg and the mean elimination half-life (t1/2) ranged from 82.3 to 119 minutes.

Pharmacokinetics of Fabrazyme was also evaluated in 13 Fabry patients in Japan. The results of these evaluations show that Fabrazyme pharmacokinetics is comparable in Caucasian and Japanese Fabry patients. In a Phase 2 study, in 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, Fabrazyme pharmacokinetics were not weight-dependent. After single dose administration, baseline clearance was 77 mL/min with a volume of distribution at steady state (Vss) of 2.6L; half- life was 55 minutes. After IgG seroconversion, clearance decreased to 35 mL/min, Vss increased to 5.4L, and half-life increased to 240 minutes. The net effect of these changes after IgG seroconversion was an increase in exposure of 2 to 3-fold based on AUC and Cmax. As a result, Fabrazyme concentrations were about 5-times higher after IgG seroconversion, without any detectable impact on efficacy (GL-3 clearance). Between-subject variability was moderate: 37% for CL and 26% for Vss.

In a Phase 3b study, 30 pediatric patients with available pharmacokinetics data aged 5 to 18 years, were treated with agalsidase beta, 0.5 mg/kg every 2 weeks and 1.0 mg/kg every 4 weeks (both being lower than the recommended dose of 1.0 mg/kg/every 2 weeks). The mean CL was 4.6 and 2.3 ml/min/kg, mean Vss was 0.27 and 0.22 l/kg, and mean elimination half-life was 88 and 107 minutes respectively. After IgG seroconversion, there was no apparent change in CL, while Vss was 1.8 to 2.2 fold higher, with the net effect being a small decrease in Cmax (up to 34%) and no change in AUC.

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

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

GENOTOXICITY
Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, single-dose toxicity, repeated-dose toxicity and reproductive toxicity. Genotoxic and carcinogenic potential are not expected.

IMPAIRMENT OF FERTILITY
There have been no studies conducted to assess the potential effect of Fabrazyme on fertility in humans.

Non-clinical data reveal no special hazard for humans based on studies of safety, pharmacology, single-dose toxicity, repeated-dose toxicity and reproductive toxicity that included evaluation of both fertility and embryo-fetal development. Genotoxic and carcinogenic potential are not expected.

INCOMPATIBILITIES / COMPATIBILITIES
In the absence of compatibility studies, Fabrazyme must not be mixed with other medicinal products in the same infusion

STORAGE CONDITIONS AND SHELF-LIFE
Store Fabrazyme under refrigeration, between 2° to 8°C (36° to 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° to 8°C (36° to 46°F).

Shelf Life
Shelf Life of Lyophilized Powder in Vials: 36 months when stored at 2-8°C.

Shelf-Life After Reconstitution
The reconstituted solution should be diluted as soon as possible after reconstitution.

Shelf-Life After Dilution
If necessary, Fabrazyme diluted for infusion in 0.9% Sodium Chloride for Injection, is stable when stored for up to 24 hours at 2° to 8°C (36° to 46°F) or at room temperature, 23° to 27°C (73° to 81°F).

PREPARATION AND HANDLING
Fabrazyme is supplied as a sterile, non-pyrogenic, white to off-white, lyophilized cake or powder for reconstitution with Sterile (Purified) Water for Injection,

The powder concentrate for solution for infusion must be reconstituted with sterile water for injection, diluted with 0.9% sodium chloride intravenous solution and then administered by intravenous infusion.

Prolonged exposure of Fabrazyme to the air/liquid interface, either through time or by agitation, may cause the formation of protein particles. Stress handling and forced particle formation studies have been performed to assess the impact of an in-line filter on drug product and dose in the presence of these particles. Following the admixture of Fabrazyme into 0.9% sodium chloride infusion bags, and induction of particles, the use of an in-line low protein binding 0.2µm filter led to the removal of the visible particles with no detectible loss of protein or activity.

Each vial of Fabrazyme is intended for single use only.

Reconstitution and Dilution (Using Aseptic Technique)

1. Fabrazyme vials and diluent should be allowed to reach room temperature (23°C to 27°C or 73°F to 81°F) prior to reconstitution (approximately 30 minutes). The number of vials is based on the patient's body weight (kg) and the recommended dose of 1.0 mg/kg.
2. Reconstitute each 35 mg Fabrazyme vial by slowly injecting 7.2 mL of Sterile Water for Injection, 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 Fabrazyme vial by slowly injecting 1.1 mL of Sterile Water for Injection, USP/EP to 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 the reconstituted solution if there is particulate matter or if it is discolored.
4. After reconstitution, it is recommended to promptly dilute the vials. Failure to promptly dilute the vials could result in particle formation.
5. Fabrazyme should be diluted in sodium chloride 9 mg/ml (0.9%) solution for infusion, immediately after reconstitution, to a final concentration between 0.05 mg/ml and 0.7 mg/ml. Determine the total volume of sodium chloride 0.9% solution for infusion (between 50 and 500 ml) based on the individual dose. For doses lower than 35 mg use a minimum of 50 ml, for doses of 35 to 70 mg use a minimum of 100 ml, for doses of 70 to 100 mg use a minimum of 250 ml and for doses greater than 100 mg use only 500 ml. 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 0.9% sodium chloride solution. Discard any vial with unused reconstituted solution.
6. Gently invert or lightly massage the infusion bag to mix the solution, avoiding vigorous shaking and agitation.
7. Fabrazyme should not be infused in the same intravenous line with other products.
8. The diluted solution may be filtered through an in-line low protein binding 0.2 µm filter during administration.

Administration:
In clinical trials, the initial IV infusion rate was administered at a rate of no more than 0.25 mg/min or 15 mg/hour. The infusion rate may be slowed in the event of infusion-associated reactions. After patient tolerance to the infusion has been established, the infusion rate may be increased gradually with subsequent infusions, as tolerated.

Manufactured by:

Genzyme Corporation
11 Forbes Road, Northborough, MA 01532, USA (labelling / packaging site and batch release site)

Genzyme Ireland Limited, IDA Industrial Park, Old Kilmeaden Road
Waterford, Ireland (Fill / Finish / packaging, testing and labelling)

Importer:
M/s Sanofi Healthcare India Private Limited, Gala No. 4, Ground Floor, Building No. B1, Citylink Warehousing Complex, S. No.121/10/A,121/10/B & 69, NH3, Vadape, Tal : Bhiwandi-16, (Thane-Z5), Pin : 421302

Source: Agalsidase beta CCDS version no 4 dated 08th December 2016

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