

## 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)

Injection, powder, lyophilized for solution for intravenous use

Initial U.S. Approval: 2003

### -----RECENT MAJOR CHANGES-----

Warnings and Precautions, Anaphylaxis and Allergic Reactions (5.1)  
12/2008

### -----INDICATIONS AND USAGE-----

Fabrazyme 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 (1).

### -----DOSAGE AND ADMINISTRATION-----

1 mg/kg body weight given every two weeks as an IV infusion. Patients should receive antipyretics prior to infusion (2).

### -----DOSAGE FORMS AND STRENGTHS-----

- Lyophilized powder for reconstitution with sterile Water for Injection, USP to yield 5 mg/ml (3).
- Available as 35 mg or 5 mg single use vials (3).

### -----CONTRAINDICATIONS-----

- None (4).

### -----WARNINGS AND PRECAUTIONS-----

- Life-threatening anaphylactic and severe allergic reactions have been observed in some patients during Fabrazyme infusions. If severe allergic or anaphylactic reactions occur, immediately discontinue administration of Fabrazyme and provide necessary emergency treatment. Appropriate medical support measures should be readily available when Fabrazyme is administered because of the potential for severe infusion reactions (5.1).
- Infusion reactions occurred in approximately 50 to 55% of patients during Fabrazyme administration in clinical trials. Some reactions were severe. In patients experiencing infusion reactions, pretreatment with an antipyretic and antihistamine is recommended. If an infusion reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administering additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms (5.2).

- If severe infusion reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered, and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, IV fluids and/or oxygen as clinically indicated (5.2).
- Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion reactions, and these patients should be monitored closely during Fabrazyme administration (5.3).
- Re-administration of Fabrazyme to patients who have previously experienced severe or serious allergic reactions to Fabrazyme should be done only after careful consideration of the risks and benefits of continued treatment, and only under the direct supervision of qualified personnel and with appropriate medical support measures readily available (5.4).

### -----ADVERSE REACTIONS-----

- The most common adverse reactions reported are infusion reactions. Serious and/or frequently occurring ( $\geq 5\%$  incidence) related adverse reactions, including infusion reactions, consisted of one or more of the following: chills, fever, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, paresthesia, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, pallor, bradycardia, urticaria, hypotension, face edema, rash, and somnolence (6).

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

### -----DRUG INTERACTIONS-----

- No drug interaction studies were performed (7).
- No in vitro metabolism studies were performed (7).

### -----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Registry available (8.1).
- Nursing Mothers: Registry available (8.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: [12/2008]

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## 1 FULL PRESCRIBING INFORMATION

### 3 1 INDICATIONS AND USAGE

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

### 8 2 DOSAGE AND ADMINISTRATION

#### 9 2.1 Recommended Dose

10 The recommended dosage of Fabrazyme is 1 mg/kg body weight infused every 2 weeks  
11 as an intravenous (IV) infusion. Patients should receive antipyretics prior to infusion [*see*  
12 *Warnings and Precautions (5.2)*].

13  
14 The initial IV infusion rate should be no more than 0.25 mg/min (15 mg/hr). The  
15 infusion rate may be slowed in the event of infusion reactions. After patient tolerance to  
16 the infusion is well established, the infusion rate may be increased in increments of 0.05  
17 to 0.08 mg/min (increments of 3 to 5 mg/hr) with each subsequent infusion. For patients  
18 weighing < 30 kg, the maximum infusion rate should remain at 0.25 mg/min (15 mg/hr).  
19 For patients weighing ≥ 30 kg, the administration duration should not be less than 1.5  
20 hours (based on individual patient tolerability).

21  
22 Patients who have had a positive skin test to Fabrazyme or who have tested positive for  
23 anti-Fabrazyme IgE may be successfully re-challenged with Fabrazyme. The initial re-  
24 challenge administration should be a low dose at a lower infusion rate, e.g., 1/2 the  
25 therapeutic dose (0.5 mg/kg) at 1/25 the initial standard recommended rate (0.01  
26 mg/min). Once a patient tolerates the infusion, the dose may be increased to reach the  
27 approved dose of 1 mg/kg and the infusion rate may be increased by slowly titrating  
28 upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/min), as tolerated.

#### 30 2.2 Instructions for Use

31 Fabrazyme does not contain any preservatives. Vials are for single-use only. Discard  
32 any unused product.

33  
34 Avoid shaking or agitating this product. Do not use filter needles during the preparation  
35 of the infusion.

#### 37 Reconstitution and Dilution (using Aseptic Technique)

- 38  
39 1. Allow Fabrazyme vials and diluent to reach room temperature prior to  
40 reconstitution (approximately 30 minutes). The number of 35 mg and 5 mg vials  
41 needed is based on the patient's body weight (kg) and the recommended dose of 1  
42 mg/kg.

Select a combination of 35 mg and 5 mg vials so that the total number of mg is equal to or greater than the patient's number of kg of body weight.

2. Reconstitute each 35 mg vial of Fabrazyme by slowly injecting 7.2 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 35 mg, 7 mL).

Reconstitute each 5 mg vial of Fabrazyme by slowly injecting 1.1 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 5 mg, 1 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 total volume based on patient weight specified in **Table 1** below. 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 infusion bag.

**Table 1**

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

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. Do not infuse Fabrazyme in the same intravenous line with other products.

- 83  
84 7. The diluted solution may be filtered through an in-line low protein-binding  
85 0.2 µm filter during administration.  
86

### 87 **3 DOSAGE FORMS AND STRENGTHS**

88 Fabrazyme is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or  
89 powder for reconstitution with Sterile Water for Injection, USP to yield a concentration  
90 of 5 mg/ml; and then further diluted with 0.9% Sodium Chloride Injection, USP for  
91 intravenous infusion.

92  
93 Single use vials are available in 35 mg and 5 mg dosages.  
94

### 95 **4 CONTRAINDICATIONS**

96 None.  
97

### 98 **5 WARNINGS AND PRECAUTIONS**

#### 99 **5.1 Anaphylaxis and Allergic Reactions**

100 Life-threatening anaphylactic and severe allergic reactions have been observed in patients  
101 during Fabrazyme infusions. Reactions have included localized angioedema (including  
102 swelling of the face, mouth, and throat), bronchospasm, hypotension, generalized  
103 urticaria, dysphagia, rash, dyspnea, flushing, chest discomfort, pruritus, and nasal  
104 congestion. Interventions have included cardiopulmonary resuscitation, oxygen  
105 supplementation, IV fluids, hospitalization, and treatment with inhaled beta-adrenergic  
106 agonists, epinephrine, and IV corticosteroids.  
107

108 In clinical trials and postmarketing safety experience with Fabrazyme, approximately 1%  
109 of patients developed anaphylactic or severe allergic reactions during Fabrazyme  
110 infusion.  
111

112 If anaphylactic or severe allergic reactions occur, immediately discontinue the  
113 administration of Fabrazyme and initiate necessary emergency treatment. Because of the  
114 potential for severe allergic reactions, appropriate medical support measures should be  
115 readily available when Fabrazyme is administered.  
116

117 The risks and benefits of re-administering Fabrazyme following an anaphylactic or severe  
118 allergic reaction should be considered. Extreme care should be exercised, with  
119 appropriate medical support measures readily available, if the decision is made to re-  
120 administer the product [*see Warnings and Precautions (5.4) and Clinical Studies (14)*].  
121

#### 122 **5.2 Infusion Reactions**

123 In clinical trials with Fabrazyme, approximately 50-55% of patients experienced infusion  
124 reactions during Fabrazyme administration, some of which were severe [*see Warnings*

125 *and Precautions (5.1)*]. Severe infusion reactions experienced by more than one patient  
126 in clinical studies with Fabrazyme included chills, vomiting, hypotension, and  
127 paresthesia. Other infusion reactions included pyrexia, feeling hot or cold, dyspnea,  
128 nausea, flushing, headache, fatigue, pruritus, pain in extremity, hypertension, chest pain,  
129 throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea,  
130 edema peripheral, myalgia, urticaria, bradycardia, and somnolence.

131

132 Most patients in clinical trials were pretreated with acetaminophen. In patients  
133 experiencing infusion reactions, pretreatment with an antipyretic and antihistamine is  
134 recommended. Infusion reactions occurred in some patients after receiving pretreatment  
135 with antipyretics, antihistamines, and oral steroids. Infusion reactions tended to decline  
136 in frequency with continued use of Fabrazyme. However, infusion reactions may still  
137 occur despite extended duration of Fabrazyme treatment. If an infusion reaction occurs,  
138 decreasing the infusion rate, temporarily stopping the infusion, and/or administering  
139 additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms. If  
140 severe infusion reactions occur, immediate discontinuation of the administration of  
141 Fabrazyme should be considered, and appropriate medical treatment should be initiated.  
142 Severe reactions are generally managed with administration of antihistamines,  
143 corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. Because of  
144 the potential for severe infusion reactions, appropriate medical support measures should  
145 be readily available when Fabrazyme is administered. Patients who have experienced  
146 infusion reactions should be treated with caution when re-administering Fabrazyme.

147

### 148 **5.3 Compromised Cardiac Function**

149 Patients with advanced Fabry disease may have compromised cardiac function, which  
150 may predispose them to a higher risk of severe complications from infusion reactions  
151 [*see Warnings and Precautions (5.1) and (5.2)*]. Patients with compromised cardiac  
152 function should be monitored closely if the decision is made to administer Fabrazyme.

153

### 154 **5.4 Immunogenicity and Re-challenge**

155 In clinical trials with Fabrazyme, a few patients developed IgE antibodies or skin test  
156 reactivity specific to Fabrazyme. Two of six patients in the re-challenge study  
157 discontinued treatment with Fabrazyme prematurely due to recurrent infusion reactions.  
158 Four serious infusion reactions occurred in three patients during Fabrazyme infusions,  
159 including bronchospasm, urticaria, hypotension, and development of Fabrazyme-specific  
160 antibodies. Other infusion-related reactions occurring in more than one patient during the  
161 study included rigors, hypertension, nausea, vomiting, and pruritus. Physicians should  
162 consider testing for IgE antibodies in patients who experienced suspected allergic  
163 reactions and consider the risks and benefits of continued treatment in patients with anti-  
164 Fabrazyme IgE antibodies [*see Warnings and Precautions (5.1) and Dosage and*  
165 *Administration (2)*].

166

167 Patients who have had a positive skin test to Fabrazyme or who have tested positive for  
168 Fabrazyme-specific IgE antibody have been re-challenged with Fabrazyme using a re-  
169 challenge protocol [*see Clinical Studies (14)*]. Re-challenge of these patients should only

170 occur under the direct supervision of qualified personnel, with appropriate medical  
171 support measures readily available.

172

### 173 **5.5 Monitoring: Laboratory Tests**

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

176

## 177 **6 ADVERSE REACTIONS**

### 178 **6.1 Adverse Reactions in Clinical Studies**

179 The most serious adverse reactions reported with Fabrazyme treatment during clinical  
180 trials were anaphylactic and allergic reactions [*see Warnings and Precautions (5.1)*].

181

182 The most common adverse reactions reported with Fabrazyme are infusion reactions,  
183 some of which were severe [*see Warnings and Precautions (5.1) and (5.2)*]. Serious  
184 and/or frequently occurring ( $\geq 5\%$  incidence) related adverse reactions consisted of one or  
185 more of the following: chills, pyrexia, feeling hot or cold, dyspnea, nausea, flushing,  
186 headache, vomiting, paresthesia, fatigue, pruritus, pain in extremity, hypertension, chest  
187 pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea,  
188 edema peripheral, myalgia, back pain, pallor, bradycardia, urticaria, hypotension, face  
189 edema, rash, and somnolence. The occurrence of somnolence can be attributed to clinical  
190 trial specified pre-treatment with antihistamines. Most infusion-related reactions  
191 requiring intervention were ameliorated with slowing of the infusion rate, temporarily  
192 stopping the infusion, and/or administration of antipyretics, antihistamines, or steroids.

193

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

199

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

206

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

211

212 **Table 2** enumerates treatment-emergent adverse reactions (regardless of relationship)  
 213 that occurred during the double-blind treatment periods of the two placebo-controlled  
 214 trials (Study 1 and Study 2) [see *Clinical Studies (14)*]. Reported adverse reactions have  
 215 been classified by Medical Dictionary for Regulatory Activities (MedDRA) terminology  
 216 System Organ Class and Preferred Term.

217

**Table 2**  
**Summary of Adverse Reactions (regardless of relationship) Occurring in**  
**Fabrazyme Treated Patients at an Incidence Greater than 2.5% Compared to**  
**Placebo Treated Patients**

MedDRA System Organ Class/ Preferred Term	Fabrazyme n=80 (%)	Placebo n=60 (%)
<b>Cardiac Disorders</b>		
Tachycardia	7 (9)	2 (3)
Ventricular wall thickening	4 (5)	1 (2)
<b>Ear and Labyrinth Disorders</b>		
Tinnitus	6 (8)	2 (3)
Hypoacusis	4 (5)	0
<b>Gastrointestinal Disorders</b>		
Toothache	5 (6)	2 (3)
Dry mouth	3 (4)	0
<b>General Disorders and Administration Site Conditions</b>		
Chills	34 (43)	7 (12)
Pyrexia	31 (39)	13 (22)
Fatigue	19 (24)	10 (17)
Edema peripheral	17 (21)	4 (7)
Pain	13 (16)	8 (13)
Feeling cold	9 (11)	1 (2)
Adverse event	8 (10)	3 (5)
Chest discomfort	4 (5)	1 (2)
<b>Infections and Infestations</b>		
Upper respiratory tract infection	35 (44)	18 (30)
Lower respiratory tract infection	14 (18)	4 (7)
Sinusitis	7 (9)	2 (3)
Pharyngitis	5 (6)	1 (2)
Fungal infection	4 (5)	0
Viral infection	4 (5)	0
Localised infection	3 (4)	0
<b>Injury, Poisoning and Procedural Complications</b>		
Procedural pain	20 (25)	12 (20)
Post procedural complication	8 (10)	1 (2)
Excoriation	7 (9)	1 (2)
Fall	5 (6)	2 (3)
Contusion	3 (4)	0

**Table 2**  
**Summary of Adverse Reactions (regardless of relationship) Occurring in**  
**Fabrazyme Treated Patients at an Incidence Greater than 2.5% Compared to**  
**Placebo Treated Patients**

<b>MedDRA System Organ Class/ Preferred Term</b>	<b>Fabrazyme n=80 (%)</b>	<b>Placebo n=60 (%)</b>
Thermal burn	3 (4)	0
<b>Investigations</b>		
Blood creatinine increased	7 (9)	3 (5)
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Pain in extremity	15 (19)	5 (8)
Back pain	13 (16)	6 (10)
Myalgia	11 (14)	3 (5)
Muscle spasms	4 (5)	1 (2)
<b>Nervous System Disorders</b>		
Headache	31 (39)	17 (28)
Paresthesia	25 (31)	11 (18)
Dizziness	17 (21)	5 (8)
Burning sensation	5 (6)	0
<b>Psychiatric Disorders</b>		
Anxiety	5 (6)	2 (3)
Depression	5 (6)	1 (2)
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Cough	26 (33)	15 (25)
Nasal congestion	15 (19)	9 (15)
Dyspnea	6 (8)	1 (2)
Respiratory tract congestion	6 (8)	1 (2)
Wheezing	5 (6)	0
<b>Skin and Subcutaneous Tissue Disorders</b>		
Rash	16 (20)	6 (10)
Pruritus	8 (10)	2 (3)
<b>Vascular Disorders</b>		
Hypertension	11 (14)	3(5)
Hot flush	4 (5)	0

218  
219 Observed adverse reactions in the Phase 1/2 study and the open-label treatment period for  
220 the extension study following the controlled study were not different in nature or  
221 intensity.

222  
223 The safety profile of Fabrazyme in pediatric Fabry disease patients, ages 8 to 16 years,  
224 was found to be consistent with that seen in adults [*see Use in Specific Populations (8.4)*  
225 *and Clinical Studies (14)*]. The safety of Fabrazyme in patients younger than 8 years of  
226 age has not been evaluated.  
227

## 228 **6.2 Immunogenicity**

229 Ninety-five of 121 (79%) adult patients and 11 of 16 (69%) pediatric patients (106 of  
230 137, 74% of all patients) treated with Fabrazyme in clinical studies have developed IgG  
231 antibodies to Fabrazyme. Most patients who develop IgG antibodies do so within the  
232 first 3 months of exposure. IgG seroconversion in pediatric patients was associated with  
233 prolonged half-life of Fabrazyme, a phenomenon rarely observed in adult patients [*see*  
234 *Clinical Pharmacology (12.3) and Use in Specific Populations (8.4)*]. A possible cause  
235 for this prolongation likely pertains to the ability of antibodies to act as “carriers” for  
236 their antigens. Among the 14 female patients exposed to Fabrazyme in clinical studies,  
237 four (two adult and two pediatric patients) developed IgG antibodies to Fabrazyme.

238  
239 IgG antibodies to Fabrazyme were purified from 15 patients with high antibody titers  
240 ( $\geq 12,800$ ) and studied for inhibition of in vitro enzyme activity. Under the conditions of  
241 this assay, most of these 15 patients had inhibition of in vitro enzyme activity ranging  
242 between 21-74% at one or more timepoints during the study. Assessment of inhibition of  
243 enzyme uptake in cells has not been performed. No general pattern was seen in  
244 individual patient reactivity over time. The clinical significance of binding and/or  
245 inhibitory antibodies to Fabrazyme is not known. In patients followed in the open-label  
246 extension study, reduction of GL-3 in plasma and GL-3 inclusions in superficial skin  
247 capillaries was maintained after antibody formation.

248  
249 As with all therapeutic proteins, there is potential for immunogenicity. The data reflect  
250 the percentage of patients whose test results were considered positive for antibodies to  
251 Fabrazyme using an ELISA and radioimmunoprecipitation (RIP) assay for antibodies.  
252 The incidence of antibody formation is highly dependent on the sensitivity and specificity  
253 of the assay. Additionally, the observed incidence of antibody (including neutralizing  
254 antibody) positivity in an assay may be influenced by several factors including assay  
255 methodology, sample handling, timing of sample collection, concomitant medications,  
256 and underlying disease. For these reasons, comparison of the incidence of antibodies to  
257 Fabrazyme with the incidence of antibodies to other products may be misleading.

258  
259 Testing for IgE was performed in approximately 60 patients in clinical trials who  
260 experienced moderate to severe infusion reactions or in whom mast cell activation was  
261 suspected. Seven of these patients tested positive for Fabrazyme-specific IgE antibodies

262 or had a positive skin test to Fabrazyme. Patients who have had a positive skin test to  
263 Fabrazyme, or who have tested positive for Fabrazyme-specific IgE antibodies in clinical  
264 trials with Fabrazyme have been re-challenged [*see Clinical Studies (14), Warnings and*  
265 *Precautions (5.4) and Dosage and Administration (2)*].

266

### 267 **6.3 Postmarketing Experience**

268 In postmarketing experience with agalsidase beta, severe infusion-related reactions have  
269 been reported, some of which were life-threatening, including anaphylaxis [*see Warnings*  
270 *and Precautions (5.1)*]. Reactions have included localized angioedema (including  
271 auricular swelling, eye swelling, dysphagia, lip swelling, edema, pharyngeal edema, face  
272 swelling, and swollen tongue), generalized urticaria, bronchospasm, and hypotension.

273

274 In addition to the adverse reactions reported in **Adverse Reactions in Clinical Studies**  
275 **(6.1)**, the following adverse reactions have been reported during postmarketing use of  
276 agalsidase beta: arthralgia, asthenia, erythema, hyperhidrosis, infusion site reaction,  
277 lacrimation increased, leukocytoclastic vasculitis, lymphadenopathy, oral hypoesthesia,  
278 palpitations, and rhinorrhea. Because these reactions are reported voluntarily from a  
279 population of uncertain size, it is not always possible to reliably estimate their frequency  
280 or establish a casual relationship to drug exposure.

281

## 282 **7 DRUG INTERACTIONS**

### 283 **7.1 Interference with Other Drugs**

284 No drug interaction studies were performed.

285

286 No in vitro metabolism studies were performed.

287

### 288 **7.2 Interference with Laboratory Tests**

289 There is no known interference by Fabrazyme with laboratory tests. Antibody samples  
290 should be collected prior to Fabrazyme infusions.

291

## 292 **8 USE IN SPECIFIC POPULATIONS**

### 293 **8.1 Pregnancy**

294 Pregnancy Category B –

295

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

302

303 Women of childbearing potential should be encouraged to enroll in the Fabry patient  
304 registry. The registry will monitor the effect of Fabrazyme on pregnant women and their  
305 offspring. For more information, visit [www.fabryregistry.com](http://www.fabryregistry.com) or call (800) 745-4447  
306 [see *Patient Counseling Information (17)*].  
307

## 308 **8.2 Labor and Delivery**

309 There is no information on the effect of Fabrazyme during labor and delivery. Pregnant  
310 females are encouraged to enroll in the Fabry registry [see *Patient Counseling*  
311 *Information (17)*].

312

## 313 **8.3 Nursing Mothers**

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

317

318 Nursing mothers should be encouraged to enroll in the Fabry registry [see *Use in Specific*  
319 *Populations (8.1) and Patient Counseling Information (17)*].  
320

## 321 **8.4 Pediatric Use**

322 The safety and efficacy of Fabrazyme were assessed in a multi-national, multi-center,  
323 uncontrolled, open-label study in 16 pediatric patients with Fabry disease (14 males, 2  
324 females), ages 8 to 16 years [see *Clinical Studies (14)*]. Patients younger than 8 years of  
325 age were not included in clinical studies. The safety and efficacy in patients younger  
326 than 8 years of age have not been evaluated.  
327

## 328 **8.5 Geriatric Use**

329 Clinical studies of Fabrazyme did not include sufficient numbers of subjects aged 65 and  
330 over to determine whether they respond differently from younger subjects.  
331

## 332 **8.6 Responses in Women**

333 Fabry disease is an X-linked genetic disorder. However, some heterozygous women will  
334 develop signs and symptoms of Fabry disease due to the variability of the X-chromosome  
335 inactivation within cells.  
336

337 A total of twelve adult female patients with Fabry disease were enrolled in two separate  
338 randomized, double-blind, placebo-controlled clinical studies with Fabrazyme, and two  
339 female pediatric patients with Fabry disease, ages 11 years, were evaluated in an open-  
340 label, uncontrolled pediatric study [see *Use in Specific Populations (8.4) and Clinical*  
341 *Studies (14)*]. Although the safety and efficacy data available in female patients in these  
342 clinical studies are limited, there is no indication that female patients respond differently  
343 to Fabrazyme compared to males.  
344

**345 10 OVERDOSAGE**

346 There have been no reports of overdose with Fabrazyme. In clinical trials, patients  
347 received doses up to 3 mg/kg body weight. The adverse reactions experienced by  
348 patients who received treatment with 3 mg/kg were similar to the adverse reactions  
349 experienced by patients who received treatment with 1 mg/kg.

350

**351 11 DESCRIPTION**

352 Fabrazyme (agalsidase beta) is a recombinant human  $\alpha$ -galactosidase A enzyme with the  
353 same amino acid sequence as the native enzyme. Purified agalsidase beta is a  
354 homodimeric glycoprotein with a molecular weight of approximately 100 kD. The  
355 mature protein is comprised of two subunits of 398 amino acids (approximately 51 kD),  
356 each of which contains three N-linked glycosylation sites.  $\alpha$ -galactosidase A catalyzes  
357 the hydrolysis of globotriaosylceramide (GL-3) and other  $\alpha$ -galactyl-terminated neutral  
358 glycosphingolipids, such as galabiosylceramide and blood group B substances to  
359 ceramide dihexoside and galactose. The specific activity of Fabrazyme is approximately  
360 70 U/mg (one unit is defined as the amount of activity that results in the hydrolysis of 1  
361  $\mu$ mole of a synthetic substrate, p-nitrophenyl- $\alpha$ -D-galactopyranoside, per minute under  
362 the assay conditions).

363

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

366

367 Fabrazyme is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic,  
368 white to off-white, lyophilized cake or powder for reconstitution with Sterile Water for  
369 Injection, USP. Each 35 mg vial contains 37 mg of agalsidase beta as well as 222 mg  
370 mannitol, 20.4 mg sodium phosphate monobasic monohydrate, and 59.2 mg sodium  
371 phosphate dibasic heptahydrate. Following reconstitution as directed, 35 mg of  
372 agalsidase beta (7 mL) may be extracted from each 35 mg vial.

373

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

378

**379 12 CLINICAL PHARMACOLOGY****380 12.1 Mechanism of Action**

381 Fabry disease is an X-linked genetic disorder of glycosphingolipid metabolism.  
382 Deficiency of the lysosomal enzyme  $\alpha$ -galactosidase A leads to progressive accumulation  
383 of glycosphingolipids, predominantly GL-3, in many body tissues, starting early in life  
384 and continuing over decades. Clinical manifestations of Fabry disease include renal  
385 failure, cardiomyopathy, and cerebrovascular accidents. Accumulation of GL-3 in renal  
386 endothelial cells may play a role in renal failure.

387

388 Fabrazyme is intended to provide an exogenous source of  $\alpha$ -galactosidase A in Fabry  
389 disease patients. Nonclinical and clinical studies evaluating a limited number of cell  
390 types indicate that Fabrazyme will catalyze the hydrolysis of glycosphingolipids  
391 including GL-3.

392

## 393 **12.2 Pharmacodynamics**

394 In a placebo-controlled study conducted in patients with Fabry disease after intravenous  
395 administration of 1 mg/kg of Fabrazyme every two weeks for 20 weeks, a reduction of  
396 GL-3 was observed in the capillary endothelium (vasculature) of kidney, heart and skin  
397 as determined by histological assessment, and in plasma as determined by ELISA [*see*  
398 *Clinical Studies (14)*].

399

## 400 **12.3 Pharmacokinetics**

401 Plasma pharmacokinetic profiles of Fabrazyme were characterized at 0.3, 1, and 3 mg/kg  
402 in adult patients with Fabry disease. The area under the plasma concentration-time curve  
403 ( $AUC_{\infty}$ ) and the clearance (CL) did not increase proportionately with increasing doses,  
404 demonstrating that the enzyme follows non-linear pharmacokinetics (**Table 3**). Plasma  
405 pharmacokinetic profiles were also characterized in adult patients with Fabry disease  
406 given 1 mg/kg Fabrazyme every 14 days for a total of 11 infusions. Refer to **Table 3**  
407 below for more details.

408

409 In 15 pediatric Fabry patients (ranging in age from 8 to 16 years old and weighing  
410 between 27.1 to 64.9 kg) who were dosed with 1 mg/kg every 14 days, Fabrazyme  
411 pharmacokinetics were not weight-dependent (**Table 3**). Fabrazyme concentrations were  
412 about five times higher after IgG seroconversion, without any detectable impact on GL-3  
413 clearance.

414

415 IgG seroconversion in pediatric patients was associated with prolonged half-life and  
416 plasma concentrations of Fabrazyme, a phenomenon rarely observed in adult patients. A  
417 possible cause for this prolongation likely pertains to the ability of antibodies to  
418 potentially act as “carriers” for their antigens [*see Adverse Reactions (6.2) and Use in*  
419 *Specific Populations (8.4)*].

420  
421  
422

**Table 3**  
**Fabrazyme Pharmacokinetic Summary**

Dose	Regimen	Mean Infusion Length (min)	Infusion number (n= patients)	AUC(0-∞) µg min/mL	C <sub>max</sub> µg/mL	Half-life min	CL mL/min/kg	V <sub>ss</sub> * 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 AGAL-1-002-98: Phase 3 Study in Adult Patients with Fabry Disease								
1 mg/kg	q14 days x 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 AGAL-016-01: 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. *V <sub>ss</sub> = volume of distribution at steady state								

423

424

425 **13 NONCLINICAL TOXICOLOGY**426 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

430

431 **14 CLINICAL STUDIES**

432 The safety and efficacy of Fabrazyme were assessed in 4 clinical studies in patients with  
 433 Fabry disease.

434

435 Study 1 was a randomized, double-blind, placebo-controlled, multi-national, multi-center  
 436 study of 58 Fabry patients (56 males and 2 females), ages 16 to 61 years, all naïve to  
 437 enzyme replacement therapy. Patients received either 1 mg/kg of Fabrazyme or placebo  
 438 every two weeks for five months (20 weeks) for a total of 11 infusions. All patients were  
 439 pretreated with acetaminophen and an antihistamine to decrease or prevent infusion  
 440 associated reactions. Oral steroids were an additional option to the pretreatment regimen  
 441 for patients who exhibited severe or recurrent infusion reactions. The primary efficacy  
 442 endpoint of GL-3 inclusions in renal interstitial capillary endothelial cells, was assessed  
 443 by light microscopy and was graded on an inclusion severity score ranging from 0  
 444 (normal or near normal) to 3 (severe inclusions).

445

446 A GL-3 inclusion score of 0 was achieved in 20 of 29 (69%) patients treated with  
 447 Fabrazyme compared to 0 of 29 treated with placebo ( $p < 0.001$ ). Similar reductions in  
 448 GL-3 inclusions were observed in the capillary endothelium of the heart and skin (**Table**  
 449 **4**). No differences between groups in symptoms or renal function were observed during  
 450 this five month study.

451

452

**Table 4**

453

454

455

**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

456

\* Results reported where biopsies were available

457

458 All 58 patients in Study 1 participated in an open-label extension study of Fabrazyme at 1  
459 mg/kg every two weeks, which continued for an additional 54 months. At the end of six  
460 months of open-label treatment, most patients achieved a GL-3 inclusion score of 0 in  
461 capillary endothelium (**Table 4**). GL-3 was decreased to normal or near normal levels in  
462 mesangial cells, glomerular capillary endothelium, interstitial cells, and non-capillary  
463 endothelium. GL-3 deposition was still present in vascular smooth muscle cells, tubular  
464 epithelium and podocytes, at variably reduced levels. Forty-four of the 58 patients  
465 completed 54 months of the open-label extension study. Thirty-six of these 44 patients  
466 underwent follow-up skin biopsy, and 31 of these patients showed sustained GL-3  
467 clearance in the capillary endothelium of the skin. Follow-up heart and kidney biopsies  
468 were assessed in only 8 of the 44 patients, which showed sustained GL-3 clearance in the  
469 capillary endothelium of the kidney in 8 patients, and sustained GL-3 clearance in the  
470 capillary endothelium of the heart in 6 patients. Plasma GL-3 levels were reduced to  
471 normal levels ( $\leq 7.03 \mu\text{g/mL}$  determined by LC/MS/MS) and remained at normal levels  
472 after up to 60 months of treatment. The reduction of GL-3 inclusions suggests that  
473 Fabrazyme may ameliorate disease expression; however, the relationship of GL-3  
474 inclusion reduction to specific clinical manifestations of Fabry disease has not been  
475 established.

476

477 Study 2 was a randomized (2:1 Fabrazyme to placebo), double-blind, placebo-controlled,  
478 multi-national, and multi-center study of 82 patients (72 males and 10 females), ages 20  
479 to 72 years, all naïve to enzyme replacement therapy. Patients received either 1 mg/kg of  
480 Fabrazyme or placebo every two weeks for up to a maximum of 35 months (median 18.5  
481 months). There was significant difference in post-baseline plasma GL-3 levels in the  
482 Fabrazyme-treated patients compared to placebo. The reduction in plasma GL-3 levels in  
483 the Fabrazyme group compared to the placebo group was significant at one year  
484 ( $p < 0.0001$ ) and at two years ( $p = 0.0019$ ). Fourteen patients (8 in Fabrazyme treated and 6  
485 in placebo) had skin biopsies at first infusion and final visit. All Fabrazyme-treated  
486 patients had capillary endothelium and deep vessel endothelium scores of zero at the final  
487 visit. Four (4) of 6 placebo patients had non-zero capillary endothelium scores  
488 ( $p = 0.0150$ ), and 6 of 6 had non-zero deep vessel endothelium scores ( $p = 0.0003$ ).

489

490 Sixty-seven patients who participated in Study 2 were subsequently entered into an open-  
491 label extension study in which all patients received 1 mg/kg of Fabrazyme every two  
492 weeks for up to a maximum of 18 months. There was a statistically significant reduction  
493 in mean plasma GL-3 levels with durability in effect through the additional 18 months of  
494 treatment in the extension study from pretreatment baseline.

495

496 Study 3 (Pediatric Study) was an open-label uncontrolled, multi-national, multi-center  
497 study to evaluate safety, pharmacokinetics, and pharmacodynamics of Fabrazyme  
498 treatment in 16 pediatric patients with Fabry disease (14 males, 2 females), who were  
499 ages 8 to 16 years at first treatment. All patients received Fabrazyme 1 mg/kg every two  
500 weeks for up to 48 weeks. At Baseline, all 14 males had elevated plasma GL-3 levels  
501 (i.e.,  $> 7.03 \mu\text{g/mL}$ ), whereas the two female patients had normal plasma GL-3 levels.

502 Twelve of the 14 male patients, and no female patients, had GL-3 inclusions observed in  
503 the capillary endothelium on skin biopsies at Baseline. At Weeks 24 and 48 of treatment,  
504 all 14 males had plasma GL-3 within the normal range. The 12 male patients with GL-3  
505 inclusions in capillary endothelium at Baseline achieved GL-3 inclusion scores of 0 at  
506 Weeks 24 and 48 of treatment. The two female patients' plasma GL-3 levels remained  
507 normal through study Week 48.

508

509 No new safety concerns were identified in pediatric patients in this study, and the overall  
510 safety and efficacy profile of Fabrazyme treatment in pediatric patients was found to be  
511 consistent with that seen in adults. Immunologic responses in pediatric patients may  
512 differ from those in adults, as IgG seroconversion in pediatric patients was associated  
513 with prolonged half-life concentrations of Fabrazyme, a phenomenon rarely observed in  
514 adult patients [*see Clinical Pharmacology (12.3), Adverse Reactions (6.2), and Use in*  
515 *Specific Populations (8.4)*].

516

517 Study 4 was an open-label, re-challenge study to evaluate the safety of Fabrazyme  
518 treatment in patients who had a positive skin test to Fabrazyme or who had tested positive  
519 for Fabrazyme-specific IgE antibodies. In this study, six adult male patients, who had  
520 experienced multiple or recurrent infusion reactions during previous clinical trials with  
521 Fabrazyme, were re-challenged with Fabrazyme administered as a graded infusion, for up  
522 to 52 weeks of treatment [*see Warnings and Precautions (5.4)*]. The initial two re-  
523 challenge doses of Fabrazyme were administered as a 0.5 mg/kg dose per week at an  
524 initial infusion rate of 0.01 mg/min for the first 30 minutes (1/25<sup>th</sup> the usually  
525 recommended maximum infusion rate). The infusion rate was doubled every 30 minutes  
526 thereafter, as tolerated, for the remainder of the infusion up to a maximum rate of 0.25  
527 mg/min. If the patient tolerated the infusion, the dose was increased to 1 mg/kg every  
528 two weeks (usually recommended dose), and the infusion rate was increased by slow  
529 titration upwards [*see Dosage and Administration (2)*]. Four of the six patients treated in  
530 this study received at least 26 weeks of study medication, and two patients discontinued  
531 prematurely due to recurrent infusion reactions [*see Warnings and Precautions (5.4)*].

532

## 533 **16 HOW SUPPLIED/STORAGE AND HANDLING**

534 Fabrazyme is supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or  
535 powder. Fabrazyme 35 mg vials are supplied in single-use, clear Type I glass 20 mL (cc)  
536 vials. The closure consists of a siliconized butyl stopper and an aluminum seal with a  
537 plastic purple flip-off cap. Fabrazyme 5 mg vials are supplied in single use, clear Type I  
538 glass 5 mL (cc) vials. The closure consists of a siliconized butyl stopper and an  
539 aluminum seal with a plastic gray flip-off cap.

540

541 35 mg vial: NDC 58468-0040-1

542 5 mg vial: NDC 58468-0041-1

543

544 Refrigerate vials of Fabrazyme at 2° to 8°C (36° to 46°F). DO NOT USE Fabrazyme  
545 after the expiration date on the vial. Reconstituted and diluted solutions of Fabrazyme

546 should be used immediately. This product contains no preservatives. If immediate use is  
547 not possible, the reconstituted and diluted solution may be stored for up to 24 hours at 2°  
548 to 8°C (36° to 46°F).  
549

## 550 **17 PATIENT COUNSELING INFORMATION**

551 Patients should be informed that a Registry has been established in order to better  
552 understand the variability and progression of Fabry disease in the population as a whole  
553 and in women [*see Use in Specific Populations (8.6)*], and to monitor and evaluate long-  
554 term treatment effects of Fabrazyme. The Registry will also monitor the effect of  
555 Fabrazyme on pregnant women and their offspring. Patients should be encouraged to  
556 participate and advised that their participation is voluntary and may involve long-term  
557 follow-up. For more information visit [www.fabryregistry.com](http://www.fabryregistry.com) or call (800) 745-4447.  
558

559

560

561 Fabrazyme is manufactured and distributed by:

562 Genzyme Corporation

563 500 Kendall Street

564 Cambridge, MA 02142

565 1-800-745-4447 (phone)

566

567 U.S. License Number: 1596

568

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