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Fabrazyme[®] (agalsidase beta)

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2 For intravenous infusion

3 **DESCRIPTION**

4 Fabrazyme[®] (agalsidase beta) is a recombinant human α -galactosidase A enzyme with
5 the same amino acid sequence as the native enzyme. Purified agalsidase beta is a
6 homodimeric glycoprotein with a molecular weight of approximately 100 kD. The
7 mature protein is comprised of two subunits of 398 amino acids (approximately 51 kD),
8 each of which contains three N-linked glycosylation sites. α -galactosidase A catalyzes
9 the hydrolysis of globotriaosylceramide (GL-3) and other α -galactyl-terminated neutral
10 glycosphingolipids, such as galabiosylceramide and blood group B substances to
11 ceramide dihexoside and galactose. The specific activity of Fabrazyme is approximately
12 70 U/mg (one unit is defined as the amount of activity that results in the hydrolysis of 1
13 μ mole of a synthetic substrate, p-nitrophenyl- α -D-galactopyranoside, per minute under
14 the assay conditions).

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

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

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

27 **CLINICAL PHARMACOLOGY**

28 **Mechanism of Action**

29 Fabry disease is an X-linked genetic disorder of glycosphingolipid metabolism.
30 Deficiency of the lysosomal enzyme α -galactosidase A leads to progressive accumulation
31 of glycosphingolipids, predominantly GL-3, in many body tissues, starting early in life
32 and continuing over decades. Clinical manifestations of Fabry disease include renal
33 failure, cardiomyopathy, and cerebrovascular accidents. Accumulation of GL-3 in renal
34 endothelial cells may play a role in renal failure.

35 Fabrazyme is intended to provide an exogenous source of α -galactosidase A in Fabry

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36 disease patients. Preclinical and clinical studies evaluating a limited number of cell types
37 indicate that Fabrazyme will catalyze the hydrolysis of glycosphingolipids including GL-
38 3.

39 **Pharmacokinetics**

40 Plasma pharmacokinetic profiles of Fabrazyme were characterized at 0.3, 1.0 and 3.0
41 mg/kg in adult patients with Fabry disease. The area under the plasma concentration-
42 time curve (AUC_{∞}) and the clearance (CL) did not increase proportionately with
43 increasing doses, demonstrating that the enzyme follows non-linear pharmacokinetics
44 (**Table 1**). Plasma pharmacokinetic profiles were also characterized in adult patients
45 with Fabry disease given 1.0 mg/kg Fabrazyme every 14 days for a total of 11 infusions.
46 Refer to **Table 1** below for more details.

47 In 15 pediatric Fabry patients (ranging in age from 8 to 16 years old and weighing
48 between 27.1 to 64.9 kg) who were dosed with 1.0 mg/kg every 14 days, Fabrazyme
49 pharmacokinetics were not weight-dependent (**Table 1**). Fabrazyme concentrations were
50 about 5-times higher after IgG seroconversion, without any detectable impact on GL-3
51 clearance.

52 IgG seroconversion in pediatric patients was associated with prolonged half-life and
53 plasma concentrations of Fabrazyme, a phenomenon rarely observed in adult patients. A
54 possible cause for this prolongation likely pertains to the ability of antibodies to
55 potentially act as “carriers” for their antigens. (see **ADVERSE REACTIONS:**
56 **Immunogenicity and PRECAUTIONS: Pediatric Use**).

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Table 1: Fabrazyme Pharmacokinetic Summary								
Dose	Regimen	Mean Infusion Length (min)	Infusion number (n= patients)	AUC(0-∞) µg min/mL	Cmax µg/mL	Half-life min	CL mL/min/kg	Vss* 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
1.0 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
3.0 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								
1.0 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								
1.0 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								

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59 **CLINICAL STUDIES**

60 The safety and efficacy of Fabrazyme were assessed in a randomized, double-blind,
61 placebo-controlled, multinational, multicenter study of 58 Fabry patients (56 males and 2
62 females), ages 16 to 61 years, all naïve to enzyme replacement therapy. Patients received
63 either 1.0 mg/kg of Fabrazyme or placebo every two weeks for five months (20 weeks)
64 for a total of 11 infusions. All patients were pretreated with acetaminophen and an
65 antihistamine to decrease or prevent infusion associated reactions. Oral steroids were an
66 additional option to the pretreatment regimen for patients who exhibited severe or
67 recurrent infusion reactions. The primary efficacy endpoint of GL-3 inclusions in renal
68 interstitial capillary endothelial cells, was assessed by light microscopy and was graded
69 on an inclusion severity score ranging from 0 (normal or near normal) to 3 (severe
70 inclusions).

71 A GL-3 inclusion score of 0 was achieved in 20 of 29 (69%) patients treated with
72 Fabrazyme compared to 0 of 29 treated with placebo ($p < 0.001$). Similar reductions in
73 GL-3 inclusions were observed in the capillary endothelium of the heart and skin (**Table**
74 **2**). No differences between groups in symptoms or renal function were observed during
75 this five month study.

76 **Table 2**
77 **Reduction of GL-3 Inclusions to Normal or Near Normal Levels (0 Score) in the**
78 **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

79 * Results reported where biopsies were available

80
81 All 58 patients in the randomized study participated in an open-label extension study of
82 Fabrazyme at 1.0 mg/kg every two weeks, which continued for an additional 54 months.
83 At the end of six months of open-label treatment, most patients achieved a GL-3
84 inclusion score of 0 in capillary endothelium (**Table 2**). GL-3 was decreased to normal
85 or near normal levels in mesangial cells, glomerular capillary endothelium, interstitial
86 cells, and non-capillary endothelium. GL-3 deposition was still present in vascular
87 smooth muscle cells, tubular epithelium and podocytes, at variably reduced levels.
88 Forty-four of the 58 patients completed 54 months of the open-label extension study.

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89 Thirty-six of these 44 patients underwent follow-up skin biopsy, and 31 of these patients
90 showed sustained GL-3 clearance in the capillary endothelium of the skin. Follow-up
91 heart and kidney biopsies were assessed in only 8 of the 44 patients, which showed
92 sustained GL-3 clearance in the capillary endothelium of the kidney in 8 patients, and
93 sustained GL-3 clearance in the capillary endothelium of the heart in 6 patients. Plasma
94 GL-3 levels were reduced to normal levels ($\leq 7.03 \mu\text{g/mL}$) and remained at normal levels
95 after up to 60 months of treatment. The reduction of GL-3 inclusions suggests that
96 Fabrazyme may ameliorate disease expression; however, the relationship of GL-3
97 inclusion reduction to specific clinical manifestations of Fabry disease has not been
98 established.

99 The safety and efficacy of Fabrazyme were assessed in a multinational, multicenter,
100 uncontrolled, open-label study in 16 pediatric patients with Fabry disease (see
101 **PRECAUTIONS: Pediatric Use**).

102 The safety of Fabrazyme was evaluated in an open-label, rechallenge study in patients
103 who had a positive skin test to Fabrazyme or who had tested positive for Fabrazyme-
104 specific IgE antibodies. In this study, 6 adult male patients, who had experienced
105 multiple or recurrent infusion reactions during previous clinical trials with Fabrazyme,
106 were rechallenged with Fabrazyme administered as a graded infusion, for up to 52 weeks
107 of treatment (see **ADVERSE REACTIONS: Immunogenicity and Rechallenge**). The
108 initial two rechallenge doses of Fabrazyme were administered as a 0.5 mg/kg dose per
109 week at an initial infusion rate of 0.01 mg/min for the first 30 minutes ($1/25^{\text{th}}$ the usually
110 recommended maximum infusion rate). The infusion rate was doubled every 30 minutes
111 thereafter, as tolerated, for the remainder of the infusion up to a maximum rate of 0.25
112 mg/min. If the patient tolerated the infusion, the dose was increased to 1.0 mg/kg every
113 two weeks (usually recommended dose), and the infusion rate was increased by slow
114 titration upwards (see **DOSAGE and ADMINISTRATION**).

115 Four of the six patients treated in this study received at least 26 weeks of study
116 medication, and two patients discontinued prematurely due to recurrent infusion reactions
117 (see **PRECAUTIONS: Immunogenicity and Rechallenge**).

118 **INDICATIONS AND USAGE**

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

122 **CONTRAINDICATIONS**

123 No known contraindications.

124 **WARNINGS**

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125 **Infusion Reactions**

126 Infusion reactions have been observed in many patients during Fabrazyme infusions (see
127 **ADVERSE REACTIONS**). Some of the reactions were severe. Severe infusion
128 reactions experienced by more than one patient in clinical studies with Fabrazyme
129 included chills, vomiting, hypotension, and paresthesia. Other infusion reactions
130 included pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, fatigue,
131 pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain,
132 dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, urticaria,
133 bradycardia, and somnolence. All patients were pretreated with acetaminophen. Infusion
134 reactions occurred in some patients after receiving pretreatment with antipyretics,
135 antihistamines, and oral steroids. Infusion reactions declined in frequency with
136 continued use of Fabrazyme. However, infusion reactions may still occur despite
137 extended duration of Fabrazyme treatment.

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

144 **PRECAUTIONS**

145 **General**

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

150 **Immunogenicity and Rechallenge**

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

156 Patients who have had a positive skin test to Fabrazyme or who have tested positive for
157 Fabrazyme-specific IgE antibody have been rechallenged with Fabrazyme using a
158 rechallenge protocol (see **CLINICAL STUDIES**). Two of six patients in the rechallenge
159 study discontinued treatment with Fabrazyme prematurely due to recurrent infusion
160 reactions. Four serious infusion reactions occurred in three patients during Fabrazyme
161 infusions, including bronchospasm, urticaria, hypotension, and development of

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162 Fabrazyme-specific antibodies. Other infusion-related reactions occurring in more than
163 one patient during the study included rigors, hypertension, nausea, vomiting, and
164 pruritus. Rechallenge of these patients should only occur under the direct supervision of
165 qualified personnel, with appropriate medical support measures readily available.

166 **Information for Patients**

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

175 **Laboratory Tests**

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

178 **Drug Interactions**

179 No drug interaction studies were performed.

180 No *in vitro* metabolism studies were performed.

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181 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

185 **Pregnancy: Category B**

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

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

194 **Nursing Mothers**

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

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

200 **Responses in Women**

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

204 A total of twelve adult female patients with Fabry disease were enrolled in two separate
205 randomized, double-blind, placebo-controlled clinical studies with Fabrazyme, and two
206 female pediatric patients with Fabry disease, ages 11 years, were evaluated in an open-
207 label, uncontrolled pediatric study (see **PRECAUTIONS: Pediatric Use**). Although the
208 safety and efficacy data available in female patients in these clinical studies are limited,
209 there is no indication that female patients respond differently to Fabrazyme than do
210 males.

211 **Pediatric Use**

212 The safety and efficacy of Fabrazyme were assessed in a multinational, multicenter,
213 uncontrolled, open-label study to evaluate safety, pharmacokinetics, and
214 pharmacodynamics in 16 pediatric patients with Fabry disease (14 males, 2 females) who

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215 were ages 8 to 16 years at first treatment. All patients received Fabrazyme 1 mg/kg every
216 2 weeks for up to 48 weeks. At Baseline, all 14 males had elevated plasma GL-3 levels
217 (i.e., >7.03 µg/mL), whereas the two female patients had normal plasma GL-3 levels.
218 Twelve of the 14 male patients, and no female patients, had GL-3 inclusions observed in
219 the capillary endothelium on skin biopsies at Baseline. At Weeks 24 and 48 of treatment,
220 all 14 males had plasma GL-3 within the normal range. The 12 male patients with GL-3
221 inclusions in capillary endothelium at Baseline achieved GL-3 inclusion scores of 0 at
222 Weeks 24 and 48 of treatment. The two female patients' plasma GL-3 levels remained
223 normal through study Week 48. No new safety concerns were identified in pediatric
224 patients in this study, and the overall safety and efficacy profile of Fabrazyme treatment
225 in pediatric patients was found to be consistent with that seen in adults. Immunologic
226 responses in pediatric patients may differ from those in adults, as IgG seroconversion in
227 pediatric patients was associated with prolonged half-life concentrations of Fabrazyme, a
228 phenomenon rarely observed in adult patients (see **CLINICAL PHARMACOLOGY:**
229 **Pharmacokinetics**, and **ADVERSE REACTIONS: Immunogenicity**).

230 Patients younger than 8 years of age were not included in clinical studies. The safety and
231 efficacy in patients younger than 8 years of age have not been evaluated.

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232 **Geriatric Use**

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

235 **ADVERSE REACTIONS**

236 The most serious and most common adverse reactions reported with Fabrazyme are
237 infusion reactions (see **WARNINGS: Infusion Reactions**). Serious and/or frequently
238 occurring ($\geq 5\%$ incidence) related adverse reactions, including infusion reactions,
239 consisted of one or more of the following events: chills, pyrexia, feeling hot or cold,
240 dyspnea, nausea, flushing, headache, vomiting, paresthesia, fatigue, pruritus, pain in
241 extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness,
242 tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, pallor,
243 bradycardia, urticaria, hypotension, face edema, rash, and somnolence. The occurrence of
244 somnolence can be attributed to clinical trial specified pre-treatment with antihistamines.

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

250 The data described below reflect exposure of 80 patients, ages 16 to 61 years, to 1.0
251 mg/kg Fabrazyme every two weeks in two separate double-blind, placebo-controlled
252 clinical trials, for periods ranging from 1 to 35 months (mean 15.5 months). All 58
253 patients enrolled in one of the two studies continued into an open-label extension study of
254 Fabrazyme treatment for up to 54 additional months. Patients were treated with
255 antipyretics and antihistamines prior to the infusions.

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

259 **Table 3** enumerates treatment-emergent adverse events (regardless of relationship) that
260 occurred during the double-blind treatment periods of the two placebo-controlled trials.
261 Reported adverse events have been classified by Medical Dictionary for Regulatory
262 Activities (MedDRA) terminology System Organ Class and Preferred Term.

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Table 3
Summary of Adverse Events Occurring in at least 5% of Patients treated with Fabrazyme in Placebo-Controlled Studies

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

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Table 3
Summary of Adverse Events Occurring in at least 5% of Patients treated with Fabrazyme
in Placebo-Controlled Studies (continued)

MedDRA System Organ Class/ Preferred Term	Fabrazyme n = 80 (%)	Placebo n = 60 (%)
Musculoskeletal and Connective Tissue Disorders		
Back pain	13 (16)	6 (10)
Muscle spasms	4 (5)	1 (2)
Myalgia	6 (8)	2 (3)
Neck pain	4 (5)	1 (2)
Pain in extremity	15 (19)	5 (8)
Nervous System Disorders		
Burning sensation	5 (6)	0
Dizziness	17 (21)	6 (10)
Headache	31 (39)	17 (28)
Hypoaesthesia	7 (9)	5 (8)
Paraesthesia	25 (31)	11 (18)
Psychiatric Disorders		
Anxiety	6 (8)	3 (5)
Depression	5 (6)	1 (2)
Insomnia	7 (9)	4 (7)
Renal and Urinary Disorders		
Proteinuria	4 (5)	2 (3)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	26 (33)	15 (25)
Dyspnoea	6 (8)	1 (2)
Nasal congestion	15 (19)	9 (15)
Pharyngolaryngeal pain	13 (16)	9 (15)
Respiratory tract congestion	6 (8)	1 (2)
Wheezing	5 (6)	0
Skin and Subcutaneous Tissue Disorders		
Dermatitis contact	4 (5)	1 (2)
Pruritus	6 (8)	3 (5)
Rash	8 (10)	5 (8)
Vascular Disorders		
Hypertension	4 (5)	2 (3)

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272 Observed adverse events in the Phase 1/2 study and the open-label treatment period for
273 the extension study following the controlled study were not different in nature or
274 intensity.

275 The safety profile of Fabrazyme in pediatric Fabry disease patients, ages 8 to 16 years,
276 was found to be consistent with that seen in adults (see **PRECAUTIONS: Pediatric**
277 **Use**). The safety of Fabrazyme in patients younger than 8 years of age has not been
278 evaluated.

279 **Immunogenicity**

280 Ninety-five of 121 (79%) adult patients and 11 of 16 (69%) pediatric patients (106 of
281 137, 74% of all patients) treated with Fabrazyme in clinical studies have developed IgG
282 antibodies to Fabrazyme. Most patients who develop IgG antibodies do so within the
283 first 3 months of exposure. IgG seroconversion in pediatric patients was associated with
284 prolonged half-life of Fabrazyme, a phenomenon rarely observed in adult patients (see
285 **CLINICAL PHARMACOLOGY: Pharmacokinetics** and **PRECAUTIONS:**
286 **Pediatric Use**). A possible cause for this prolongation likely pertains to the ability of
287 antibodies to act as “carriers” for their antigens. Among the 14 female patients exposed
288 to Fabrazyme in clinical studies, four (two adult and two pediatric patients) developed
289 IgG antibodies to Fabrazyme.

290 IgG antibodies to Fabrazyme were purified from 15 patients with high antibody titers (\geq
291 12,800) and studied for inhibition of *in vitro* enzyme activity. Under the conditions of
292 this assay, most of these 15 patients had inhibition of *in vitro* enzyme activity ranging
293 between 21-74% at one or more timepoints during the study. Assessment of inhibition of
294 enzyme uptake in cells has not been performed. No general pattern was seen in
295 individual patient reactivity over time. The clinical significance of binding and/or
296 inhibitory antibodies to Fabrazyme is not known. In patients followed in the open-label
297 extension study, reduction of GL-3 in plasma and GL-3 inclusions in superficial skin
298 capillaries was maintained after antibody formation.

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

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

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310 or had a positive skin test to Fabrazyme. Patients who have had a positive skin test to
311 Fabrazyme, or who have tested positive for Fabrazyme-specific IgE antibodies in clinical
312 trials with Fabrazyme have been rechallenged (see **CLINICAL STUDIES,**
313 **PRECAUTIONS: Immunogenicity and Rechallenge** and **DOSAGE AND**
314 **ADMINISTRATION**).

315 **OVERDOSAGE**

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

318 **DOSAGE AND ADMINISTRATION**

319 The recommended dosage of Fabrazyme is 1.0 mg/kg body weight infused every 2 weeks
320 as an IV infusion. Patients should receive antipyretics prior to infusion (see
321 **WARNINGS: Infusion Reactions**).

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

329 Patients who have had a positive skin test to Fabrazyme or who have tested positive for
330 anti-Fabrazyme IgE may be successfully re-challenged with Fabrazyme. The initial re-
331 challenge administration should be a low dose at a lower infusion rate e.g., 1/2 the
332 therapeutic dose (0.5 mg/kg) at 1/25 the initial standard recommended rate (0.01
333 mg/min) Once a patient tolerates the infusion, the dose may be increased to reach the
334 approved dose of 1.0 mg/kg and the infusion rate may be increased by slowly titrating
335 upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/min), as tolerated.

336 **Instructions for Use**

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

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

341 Reconstitution and Dilution (using Aseptic Technique)

342 1. Fabrazyme vials and diluent should be allowed to reach room temperature prior to
343 reconstitution (approximately 30 minutes). The number of 35 mg and 5 mg vials
344 needed is based on the patient's body weight (kg) and the recommended dose of 1.0

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- 345 mg/kg.
- 346 Select a combination of 35 mg and 5 mg vials so that the total number of mg is equal
347 to or greater than the patient's number of kg of body weight.
- 348 2. Reconstitute each 35 mg vial of Fabrazyme by slowly injecting 7.2 mL of Sterile
349 Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial
350 gently. Each vial will yield a 5.0 mg/mL clear, colorless solution (total extractable
351 amount per vial is 35 mg, 7.0 mL).
- 352 Reconstitute each 5 mg vial of Fabrazyme by slowly injecting 1.1 mL of Sterile
353 Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial
354 gently. Each vial will yield a 5.0 mg/mL clear, colorless solution (total extractable
355 amount per vial is 5 mg, 1.0 mL).
- 356 3. Visually inspect the reconstituted vials for particulate matter and discoloration. Do
357 not use the reconstituted solution if there is particulate matter or if it is discolored.
- 358 4. The reconstituted solution should be further diluted with 0.9% Sodium Chloride
359 Injection, USP to total volume based on patient weight specified in **Table 4** below.
360 Prior to adding the volume of reconstituted Fabrazyme required for the patient dose,
361 remove an equal volume of 0.9% Sodium Chloride for Injection, USP from the
362 infusion bag.

363

Table 4

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

364

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

367 Example: Patient dose = 80 mg

368 80 mg ÷ 5 mg/mL = 16 mL of Fabrazyme

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

373 5. Gently invert infusion bag to mix the solution, avoiding vigorous shaking and

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374 agitation.

375 6. Fabrazyme should not be infused in the same intravenous line with other products.

376 7. The diluted solution may be filtered through an in-line low protein-binding 0.2 µm
377 filter during administration.

378 **Storage**

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

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

384 **HOW SUPPLIED**

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

391

392 35 mg vial: NDC 58468-0040-1

393 5 mg vial: NDC 58468-0041-1

394

395 **Rx Only**

396 U.S. Patent Number: 5,356,804

397

398 Fabrazyme is manufactured and distributed by:

399 Genzyme Corporation

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401 Cambridge, MA 02142

402 1-800-745-4447 (phone)

403 U.S. License Number: 1596

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405 Issued: TBD