

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LUMIZYME® (alglucosidase alfa)
Inje ctable for intravenous infusion
Initial U.S. Approval: 2010

WARNING: ANAPHYLAXIS and RESTRICTED DISTRIBUTION PROGRAM

- Life-threatening anaphylactic reactions, severe allergic reactions and immune mediated reactions have been observed in some patients during LUMIZYME® infusions. Therefore, appropriate medical support should be readily available when LUMIZYME is administered (5.1, 5.2).
- Because of the potential risk of rapid disease progression in Pompe disease patients less than 8 years of age, LUMIZYME is available only through a restricted distribution program called the LUMIZYME ACE Program®. Only prescribers and healthcare facilities enrolled in the program may prescribe, dispense or administer LUMIZYME. LUMIZYME may be administered only to patients who are enrolled in and meet all the conditions of the LUMIZYME ACE Program. To enroll in the LUMIZYME ACE Program call 1-800-745-4447 (5.3).

INDICATIONS AND USAGE

LUMIZYME® (alglucosidase alfa) is a lysosomal glycogen-specific enzyme indicated for patients 8 years and older with late (non-infantile) onset Pompe disease (GAA deficiency) who do not have evidence of cardiac hypertrophy. The safety and efficacy of LUMIZYME have not been evaluated in controlled clinical trials in infantile-onset patients, or in late (non-infantile) onset patients less than 8 years of age (1).

DOSAGE AND ADMINISTRATION

- The recommended dosage of LUMIZYME is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion (2).

DOSAGE FORMS AND STRENGTHS

- Dosage form: Lyophilized powder for solution for intravenous infusion (3).
- Dosage strength: 5 mg/mL (3).

CONTRAINDICATIONS

- None (4).

WARNINGS AND PRECAUTIONS

- Life-threatening anaphylactic reactions: Ensure that appropriate medical support measures, including cardiopulmonary resuscitation equipment are readily available (5.1).
- Severe allergic or anaphylactic reactions: If severe allergic or anaphylactic reactions occur, consider immediate discontinuation of LUMIZYME and initiate appropriate medical treatment (5.1).
- Severe cutaneous and systemic immune mediated reactions: Monitor patients for the development of systemic immune mediated reactions involving skin and other organs (5.2).
- Acute cardiorespiratory failure: Patients with compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Appropriate medical support and monitoring measures should be readily available (5.4).
- General anesthesia: Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for LUMIZYME infusion (5.5).

ADVERSE REACTIONS

- The most frequently reported adverse reactions (≥5%) in clinical studies were infusion reactions and included: anaphylaxis, urticaria, diarrhea, vomiting, dyspnea, pruritus, rash/erythema, pharyngolaryngeal pain, neck pain, hypoacusis, flushing/feeling hot, pain in extremity, fall, and chest discomfort (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

USE IN SPECIFIC POPULATIONS

- Pregnancy: Physicians are encouraged to enroll pregnant patients in the Pompe Registry (8.1).
- Nursing Mothers: Physicians are encouraged to enroll nursing patients in the Pompe Registry (8.3).
- Pediatrics: LUMIZYME is not for use in patients with infantile-onset Pompe disease or late (non-infantile) onset Pompe disease who are less than 8 years of age. The safety and efficacy of LUMIZYME have not been evaluated in controlled clinical trials in these patients (8.4).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 11/2013

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1 **FULL PRESCRIBING INFORMATION**

2 **WARNING: ANAPHYLAXIS and RESTRICTED DISTRIBUTION**
3 **PROGRAM**

4 **Life-threatening anaphylactic reactions, severe allergic reactions and**
5 **immune mediated reactions have been observed in some patients**
6 **during LUMIZYME[®] infusions. Therefore, appropriate medical**
7 **support should be readily available when LUMIZYME is**
8 **administered [see *Warnings and Precautions (5.1, 5.2)*].**

9 **Because of the potential risk of rapid disease progression in Pompe**
10 **disease patients less than 8 years of age, LUMIZYME is available**
11 **only through a restricted distribution program called the**
12 **LUMIZYME ACE Program[®]. Only prescribers and healthcare**
13 **facilities enrolled in the program may prescribe, dispense or**
14 **administer LUMIZYME. LUMIZYME may be administered only to**
15 **patients who are enrolled in and meet all the conditions of the**
16 **LUMIZYME ACE Program. To enroll in the LUMIZYME ACE**
17 **Program call 1-800-745-4447 [see *Warnings and Precautions (5.3)*].**

16 **1 INDICATIONS AND USAGE**

17 LUMIZYME (alglucosidase alfa) [see *Description (11)*] is a
18 lysosomal glycogen-specific enzyme indicated for patients 8
19 years and older with late (non-infantile) onset Pompe disease
20 (acid α -glucosidase (GAA) deficiency) who do not have evidence
21 of cardiac hypertrophy. The safety and efficacy of LUMIZYME
22 have not been evaluated in controlled clinical trials in infantile-
23 onset patients, or in late (non-infantile) onset patients less than 8
24 years of age [see *Use in Specific Populations (8.4)*].

25 **2 DOSAGE AND ADMINISTRATION**

26 **2.1 Recommended Dose**

27
28 The recommended dosage of LUMIZYME is 20 mg/kg body
29 weight administered every 2 weeks as an intravenous infusion.

30
31 **2.2 Instructions for Use**

32 LUMIZYME does not contain any preservatives. Vials are
33 single-use only. Discard any unused product.

34 The total volume of infusion is determined by the patient's body
35 weight and should be administered over approximately 4 hours.
36 Infusions should be administered in a step-wise manner using an
37 infusion pump. The initial infusion rate should be no more than 1
38 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr

39 every 30 minutes, after patient tolerance to the infusion rate is
40 established, until a maximum rate of 7 mg/kg/hr is reached. Vital
41 signs should be obtained at the end of each step. If the patient is
42 stable, LUMIZYME may be administered at the maximum rate of
43 7 mg/kg/hr until the infusion is completed. The infusion rate may
44 be slowed or temporarily stopped in the event of infusion
45 reactions. See *Table 1* below for the rate of infusion at each step,
46 expressed as mL/hr based on the recommended infusion volume
47 by patient weight.

48
49 **Table 1: Recommended Infusion Volumes and Rates**

Patient Weight Range (kg)	Total infusion volume (mL)	Step 1 1 mg/kg/hr (mL/hr)	Step 2 3 mg/kg/hr (mL/hr)	Step 3 5 mg/kg/hr (mL/hr)	Step 4 7 mg/kg/hr (mL/hr)
20.1 – 30	150	8	23	38	53
30.1 – 35	200	10	30	50	70
35.1 – 50	250	13	38	63	88
50.1 – 60	300	15	45	75	105
60.1 – 100	500	25	75	125	175
100.1 – 120	600	30	90	150	210
120.1 – 140	700	35	105	175	245
140.1 – 160	800	40	120	200	280
160.1 – 180	900	45	135	225	315
180.1 – 200	1,000	50	150	250	350

50

51 **2.3 Reconstitution, Dilution, and Administration**

52 LUMIZYME should be reconstituted, diluted and administered
53 by a healthcare professional.

54 Use aseptic technique during preparation. Do not use filter
55 needles during preparation.

- 56 a. Determine the number of vials to be reconstituted based on
57 the individual patient's weight and the recommended dose of
58 20 mg/kg.

59

60 Patient weight (kg) x dose (mg/kg) = patient
61 dose (in mg)

62

63 Patient dose (in mg) divided by 50 mg/vial = number of vials
64 to reconstitute. If the number of vials includes a fraction,
65 round up to the next whole number.

66

67 Example: Patient weight (68 kg) x dose (20
68 mg/kg) = patient dose (1,360 mg)

69

70 1,360 mg divided by 50 mg/vial = 27.2 vials; therefore, 28
71 vials should be reconstituted

- 72
73 Remove the required number of vials from the refrigerator
74 and allow them to reach room temperature prior to
75 reconstitution (approximately 30 minutes).
- 76 b. Reconstitute each LUMIZYME vial by slowly injecting 10.3
77 mL of Sterile Water for Injection, USP to the inside wall of
78 each vial. Each vial will yield a concentration of 5 mg/mL.
79 The total extractable dose per vial is 50 mg per 10 mL.
80 Avoid forceful impact of the water for injection on the
81 powder and avoid foaming. This is done by slow drop-wise
82 addition of the water for injection down the inside of the vial
83 and not directly onto the lyophilized cake. Tilt and roll each
84 vial gently. Do not invert, swirl, or shake.
- 85 c. The reconstituted LUMIZYME solution should be protected
86 from light.
- 87 d. Perform an immediate visual inspection on the reconstituted
88 vials for particulate matter and discoloration. If upon
89 immediate inspection opaque particles are observed or if the
90 solution is discolored do not use. The reconstituted solution
91 may occasionally contain some alglucosidase alfa particles
92 (typically less than 10 in a vial) in the form of thin white
93 strands or translucent fibers subsequent to the initial
94 inspection. This may also happen following dilution for
95 infusion. These particles have been shown to contain
96 alglucosidase alfa and may appear after the initial
97 reconstitution step and increase over time. Studies have
98 shown that these particles are removed via in-line filtration
99 without having a detectable effect on the purity or strength.
- 100 e. LUMIZYME should be diluted in 0.9% Sodium Chloride for
101 Injection, USP, immediately after reconstitution, to a final
102 LUMIZYME concentration of 0.5 to 4 mg/mL. See [Table 1](#)
103 for the recommended total infusion volume based on patient
104 weight.
- 105 f. Slowly withdraw the reconstituted solution from each vial.
106 Avoid foaming in the syringe.
- 107 g. Remove airspace from the infusion bag to minimize particle
108 formation due to the sensitivity of LUMIZYME to air-liquid
109 interfaces.
- 110 h. Add the reconstituted LUMIZYME solution slowly and

- 111 directly into the sodium chloride solution. Do not add
112 directly into airspace that may remain within the infusion
113 bag. Avoid foaming in the infusion bag.
- 114 i. Gently invert or massage the infusion bag to mix. Do not
115 shake.
- 116 j. Administer LUMIZYME using an in-line low protein
117 binding 0.2 µm filter.
- 118 k. Do not infuse LUMIZYME in the same intravenous line with
119 other products.
- 120 LUMIZYME does not contain any preservatives. Vials are
121 single-use only. Discard any unused product.

122

123 **3 DOSAGE FORMS AND STRENGTHS**

124 LUMIZYME is supplied as a sterile, nonpyrogenic, white to off-
125 white, lyophilized cake or powder for reconstitution with Sterile
126 Water for Injection, USP to yield a concentration of 5 mg/mL;
127 and then further diluted with 0.9% Sodium Chloride for Injection,
128 USP for intravenous infusion.

129 Single-use vials are available in 50 mg dosage only.

130

131 **4 CONTRAINDICATIONS**

132 None.

133

134 **5 WARNINGS AND PRECAUTIONS**

135 **5.1 Anaphylaxis and Allergic Reactions**

136 (*see Boxed Warning*)

137 Anaphylaxis and severe allergic reactions have been observed in
138 patients during and up to 3 hours after LUMIZYME infusion.
139 Some of the reactions were life-threatening and included
140 anaphylactic shock, respiratory arrest, apnea, dyspnea,
141 bradycardia, tachycardia, and hypotension. Other accompanying
142 reactions included chest discomfort/pain, throat tightness,
143 bronchospasm, wheezing, tachypnea, cyanosis, decreased oxygen
144 saturation/hypoxia, convulsions, angioedema (including tongue or
145 lip swelling, periorbital edema, and face edema), pruritus, rash,
146 urticaria, hyperhidrosis, nausea, dizziness, hypertension,
147 flushing/erythema, fever, pallor, peripheral coldness, feeling hot,
148 restlessness, nervousness, headache, back pain, and paraesthesia.

149 Some of these reactions were IgE-mediated [see *Adverse*
150 *Reactions (6.2)*].

151 If anaphylaxis or other severe allergic reactions occur, immediate
152 discontinuation of the administration of LUMIZYME should be
153 considered, and appropriate medical treatment should be initiated.
154 Severe reactions are generally managed with infusion
155 interruption, administration of antihistamines, corticosteroids,
156 intravenous fluids, and/or oxygen, when clinically indicated. In
157 some cases of anaphylaxis, epinephrine has been administered.
158 Because of the potential for severe allergic reactions, appropriate
159 medical support, including cardiopulmonary resuscitation
160 equipment, should be readily available when LUMIZYME is
161 administered.

162 The risks and benefits of re-administering LUMIZYME
163 following an anaphylactic or severe allergic reaction should be
164 considered. Some patients have been rechallenged and have
165 continued to receive LUMIZYME under close clinical
166 supervision. Extreme care should be exercised, with appropriate
167 resuscitation measures available, if the decision is made to re-
168 administer the product [see *Adverse Reactions (6.2)*].

169 **5.2 Immune Mediated Reactions**

170 (*see Boxed Warning*)

171 Severe cutaneous reactions have been reported with alglucosidase
172 alfa including necrotizing skin lesions [see *Adverse Reactions*
173 *(6.3)*]. Systemic immune mediated reactions, including possible
174 type III immune mediated reactions have been observed with
175 alglucosidase alfa. These reactions occurred several weeks to 3
176 years after initiation of alglucosidase alfa infusions. Skin biopsy
177 in one patient demonstrated deposition of anti-rhGAA antibodies
178 in the lesion. Another patient developed severe inflammatory
179 arthropathy in association with fever and elevated erythrocyte
180 sedimentation rate. Nephrotic syndrome secondary to
181 membranous glomerulonephritis was observed in a few Pompe
182 patients treated with alglucosidase alfa who had persistently
183 positive anti-rhGAA IgG antibody titers. In these patients renal
184 biopsy was consistent with immune complex deposition. Patients
185 improved following treatment interruption. It is therefore
186 recommended to perform periodic urinalysis [see *Adverse*
187 *Reactions (6.3)*].

188 Patients should be monitored for the development of systemic
189 immune mediated reactions involving skin and other organs while
190 receiving LUMIZYME. If immune mediated reactions occur,
191 discontinuation of the administration of LUMIZYME should be

192 considered, and appropriate medical treatment initiated. The risks
193 and benefits of re-administering alglucosidase alfa following an
194 immune mediated reaction should be considered. Some patients
195 have successfully been rechallenged and have continued to
196 receive alglucosidase alfa under close clinical supervision.

197 **5.3 Distribution Program for LUMIZYME®**

198 (*see Boxed Warning*)

199 LUMIZYME is available only under a restricted distribution
200 program called the LUMIZYME ACE (Alglucosidase Alfa
201 Control and Education) Program.

202 The purpose of the program is to ensure that the known risks of
203 anaphylaxis and severe allergic reactions and the potential risks
204 of severe cutaneous and systemic immune mediated reactions
205 associated with the use of LUMIZYME are communicated to
206 patients, caregivers, and prescribers. In addition, the purpose of
207 the program is to mitigate the potential risk of rapid disease
208 progression in infantile-onset Pompe disease patients and late
209 (non-infantile) onset Pompe disease patients less than 8 years of
210 age for whom the safety and effectiveness of LUMIZYME have
211 not been evaluated.

212 Under this program, only trained and certified prescribers, and
213 healthcare facilities enrolled in the program are able to prescribe,
214 dispense or administer LUMIZYME, and only patients who are
215 enrolled in and meet all the conditions of the LUMIZYME ACE
216 Program may receive LUMIZYME.

217 For information about the ACE Program call 1-800-745-4447.
218

219 **5.4 Risk of Acute Cardiorespiratory Failure**

220 Patients with acute underlying respiratory illness or compromised
221 cardiac and/or respiratory function may be at risk of serious
222 exacerbation of their cardiac or respiratory compromise during
223 infusions. Appropriate medical support and monitoring measures
224 should be readily available during LUMIZYME infusion, and
225 some patients may require prolonged observation times that
226 should be based on the individual needs of the patient. Acute
227 cardiorespiratory failure has been observed in a few infantile-
228 onset Pompe disease patients with underlying cardiac
229 hypertrophy, possibly associated with fluid overload with
230 intravenous administration of alglucosidase alfa [*see Dosage and*
231 *Administration (2.2)*].
232

233 **5.5 Precautions for General/Regional Anesthesia**

234 Administration of general anesthesia can be complicated by the
235 presence of severe cardiac and skeletal (including respiratory)
236 muscle weakness. Therefore, caution should be used when
237 administering general anesthesia.

238

239 **5.6 Monitoring: Laboratory Tests**

240 Patients should be monitored for IgG antibody formation every 3
241 months for 2 years and then annually thereafter. Testing for IgG
242 titers may also be considered if patients develop allergic or other
243 immune mediated reactions. Patients who experience
244 anaphylactic or allergic reactions may also be tested for IgE
245 antibodies to alglucosidase alfa and other mediators of
246 anaphylaxis [see *Adverse Reactions (6.2)*].

247

248 There are currently no marketed tests for antibodies against
249 alglucosidase alfa, however a testing service is provided by
250 Genzyme. Contact your local Genzyme representative or
251 Genzyme Corporation at 1-800-745-4447 for information on
252 testing and to obtain a sample collection box.

253

254 **6 ADVERSE REACTIONS**

255 **6.1 Clinical Trials Experience**

256 Because clinical trials are conducted under widely varying
257 conditions, adverse reaction rates observed in the clinical trials of
258 a drug cannot be directly compared to rates in the clinical trials of
259 another drug and may not reflect the rates observed in clinical
260 practice. Assessment of adverse reactions is based on the
261 exposure of 90 patients (45 male, 45 female) with late-onset
262 Pompe disease, ages 10 to 70 years, to 20 mg/kg LUMIZYME or
263 placebo in a randomized, double-blind, placebo-controlled study
264 designed to enroll patients age 8-70 years. The youngest
265 LUMIZYME-treated patient was 16 years of age, and the
266 youngest placebo-treated patient was 10 years of age. All
267 patients were naïve to enzyme replacement therapy. Patients
268 were randomized in a 2:1 ratio and received LUMIZYME or
269 placebo every other week for 78 weeks (18 months). The study
270 population included 34 males and 26 females (N=60) in the
271 LUMIZYME group and 11 males and 19 females (N=30) in the
272 placebo group. Two patients receiving LUMIZYME discontinued
273 the study due to anaphylactic reactions. A third patient in the
274 LUMIZYME group died during the study due to brain stem
275 ischemia secondary to thrombosis of a basilar aneurysm, which
276 was considered unrelated to treatment.

277

278 Serious adverse reactions reported with LUMIZYME in the
279 randomized, double-blind, placebo-controlled study included
280 anaphylaxis [see *Boxed Warning and Warnings and Precautions*
281 (5.1)]. Anaphylactic reactions included: angioedema, throat
282 tightness and chest pain/discomfort. One patient with a history of
283 Wolff-Parkinson-White syndrome experienced a serious adverse
284 reaction of supraventricular tachycardia. Other serious adverse
285 events that occurred in a higher incidence in LUMIZYME-treated
286 patients compared to placebo included coronary artery disease,
287 intervertebral disc protrusion, pneumonia, gastroenteritis, and
288 dehydration.

289 The most common adverse reactions observed were infusion
290 reactions. Infusion reactions, defined as an adverse reaction
291 occurring during the infusion or within 2 hours after completion
292 of the infusion, that occurred in LUMIZYME-treated patients at
293 an incidence of $\geq 5\%$ compared to placebo in the controlled study
294 included anaphylaxis, urticaria, diarrhea, vomiting, dyspnea,
295 pruritus, rash/erythema, pharyngolaryngeal pain, neck pain,
296 hypoacusis, flushing/feeling hot, pain in extremity, fall, and chest
297 discomfort. Additional infusion reactions observed in other
298 clinical trials and expanded access programs with LUMIZYME
299 included respiratory distress, cough, livedo reticularis, agitation,
300 irritability, retching, rigors, tremor and increased lacrimation.

301
302 If an infusion reaction occurs, decreasing the infusion rate,
303 temporarily stopping the infusion, and/or administration of
304 antihistamines and/or antipyretics may ameliorate the symptoms.
305 If severe infusion or allergic reactions occur, immediate
306 discontinuation of the administration of LUMIZYME should be
307 considered, and appropriate medical treatment should be initiated
308 [see *Warnings and Precautions (5.1)*]. Severe infusion reactions
309 are generally managed with infusion interruption, administration
310 of antihistamines, corticosteroids, intravenous fluids, and/or
311 oxygen, when clinically indicated. In some cases of anaphylactic
312 reactions, epinephrine was administered. Patients who have
313 experienced infusion reactions should be treated with caution
314 when they are re-administered LUMIZYME.

315
316 Delayed onset infusion reactions have also been observed with
317 LUMIZYME infusion. Delayed onset infusion reactions, defined
318 as adverse reactions that occurred within 48 hours after
319 completion of LUMIZYME infusion, occurred in LUMIZYME-
320 treated patients at an incidence of $\geq 3\%$ compared to placebo-
321 treated patients in a controlled trial. Symptoms included
322 urticaria, dizziness, procedural pain, pharyngolaryngeal pain,
323 malaise, muscle spasms, musculoskeletal pain, musculoskeletal

324 weakness, musculoskeletal stiffness, neck pain, insomnia, and
325 epistaxis. Patients should be counseled about the possibility of
326 delayed onset infusion reactions and given proper follow up
327 instructions.

328
329 *Table 2* enumerates adverse reactions that occurred in
330 LUMIZYME-treated patients at an incidence of $\geq 5\%$ compared
331 to placebo-treated patients during the randomized, double-blind,
332 placebo-controlled study. Reported adverse reactions have been
333 classified by Medical Dictionary for Regulatory Activities
334 (MedDRA) terminology System Organ Class and Preferred Term.
335

336 **Table 2: Summary of Adverse Reactions Occurring in LUMIZYME[®]-Treated Patients at an**
337 **Incidence $\geq 5\%$ Compared to Placebo-Treated Patients**

System Organ Class	Preferred Term	LUMIZYME [®] n=60 N (%)	Placebo n=30 N (%)
Blood and lymphatic system disorders	Lymphadenopathy	5 (8.3)	0 (0)
Ear and labyrinth disorders	Hypoacusis	20 (33.3)	7 (23.3)
	Vertigo	4 (6.7)	0 (0)
	Ear discomfort or pain	7 (11.7)	2 (6.7)
Eye disorders	Vision blurred	3 (5)	0 (0)
Gastrointestinal disorders	Constipation	6 (10)	0 (0)
	Dyspepsia	5 (8.3)	0 (0)
	Vomiting	13 (21.7)	3 (10)
General disorders and administration site conditions	Chest discomfort or pain	10 (16.7)	2 (6.7)
	Infusion site reactions	8 (13.3)	0 (0)
	Malaise	3 (5)	0 (0)
	Edema, peripheral	10 (16.7)	3 (10)
	Pain	5 (8.3)	1 (3.3)
Immune system disorders	Anaphylaxis	4 (6.7)	0 (0)
Infections and infestations	Gastroenteritis	6 (10)	1 (3.3)
	Respiratory tract infection	3 (5)	0 (0)
	Upper respiratory tract infection	11 (18.3)	3 (10)
Injury, poisoning and procedural complications	Procedural pain	9 (15)	3 (10)
Metabolism and nutrition disorders	Hypokalemia	3 (5)	0 (0)
Musculoskeletal and connective tissue disorders	Muscle twitching	5 (8.3)	1 (3.3)
	Musculoskeletal pain	22 (36.7)	9 (30)
	Musculoskeletal stiffness or tightness	9 (15)	2 (6.7)
Nervous system disorders	Somnolence	3 (5)	0 (0)
	Tremor	4 (6.7)	0 (0)
Renal and urinary disorders	Nephrolithiasis	3 (5)	0 (0)
Respiratory, thoracic and mediastinal disorders	Dyspnea, exertional	4 (6.7)	0 (0)
	Epistaxis	3 (5)	0 (0)
Skin and subcutaneous tissue disorders	Hyperhidrosis	5 (8.3)	0 (0)
	Pruritis	6 (10)	1 (3.3)
	Urticaria	6 (10)	0 (0)

338

339 **6.2 Immunogenicity**

340 As with all therapeutic proteins, there is potential for
341 immunogenicity. The data reflect the percentage of patients
342 whose tests results were considered positive for antibodies to
343 alglucosidase alfa using an enzyme-linked immunosorbent assay
344 (ELISA) and confirmed by a radioimmunoprecipitation (RIP)
345 assay for alglucosidase alfa-specific IgG antibodies. The
346 detection of antibody formation is highly dependent on the
347 sensitivity and specificity of the assay. Additionally, the
348 observed incidence of antibody (including neutralizing antibody)
349 positivity in an assay may be influenced by several factors
350 including assay methodology, sample handling, timing of sample
351 collection, concomitant medications, and underlying disease. For
352 these reasons, comparison of the incidence of antibodies to
353 alglucosidase alfa with the incidence of antibodies to other
354 products may be misleading.

355
356 In the randomized, double-blind, placebo-controlled study, all
357 patients with available samples treated with LUMIZYME (N=59,
358 100%) developed IgG antibodies to alglucosidase alfa. All
359 patients who developed IgG antibodies did so within the first 3
360 months of exposure (median time to seroconversion was 4
361 weeks). There was no apparent association between mean or
362 peak IgG antibody titers and the occurrence of adverse reactions.

363
364 Patients who developed IgG antibodies to alglucosidase alfa were
365 also evaluated for inhibition of enzyme activity or cellular uptake
366 of enzyme in *in vitro* assays. None of the 59 evaluable patients
367 tested positive for inhibition of enzyme activity. Antibody titers
368 for cellular uptake inhibition were present in 18 of 59 patients
369 (31%) by Week 78. All other patients tested negative for
370 inhibition of cellular uptake. Patients who were positive for
371 uptake inhibition tended to have higher IgG titers than patients
372 who tested negative for uptake inhibition. Among the 32 patients
373 with evaluable pharmacokinetic (PK) samples, 5 patients tested
374 positive for uptake inhibition at times corresponding to PK
375 sampling times as compared to other patients. The clearance
376 values for 4 of these 5 patients were approximately 1.2- to 1.8-
377 fold greater in the presence (Week 52) as compared to in the
378 absence of inhibitory antibodies (Week 0) [see *Clinical*
379 *Pharmacology (12.3)*].

380
381 Patients in the clinical studies or in the postmarketing setting have
382 undergone testing for alglucosidase alfa-specific IgE antibodies.
383 Testing was performed in patients who experienced moderate to

384 severe or recurrent infusion reactions, for which mast-cell
385 activation was suspected.

386
387 Ten patients in the randomized, double-blind, placebo-controlled
388 study underwent testing for alglucosidase alfa-specific IgE
389 antibodies. Two of 10 patients evaluated tested positive for
390 alglucosidase alfa-specific IgE-binding antibodies, both of whom
391 experienced anaphylactic reactions [see *Boxed Warning and*
392 *Warnings and Precautions (5.1)*]. One patient who developed
393 IgE antibodies discontinued the study following anaphylaxis.

394
395 A small number of LUMIZYME-treated patients in the
396 postmarketing setting who were evaluated tested positive for
397 presence of alglucosidase alfa-specific IgE antibodies. Some of
398 these patients experienced anaphylaxis [see *Boxed Warning and*
399 *Warnings and Precautions (5.1)*].

400
401 Some patients who tested positive for alglucosidase alfa-specific
402 IgE antibodies were successfully rechallenged with LUMIZYME
403 using a slower infusion rate at lower initial doses and have
404 continued to receive treatment under close clinical supervision
405 [see *Warnings and Precautions (5.1)*].

406
407 Patients who develop IgE antibodies to alglucosidase alfa appear
408 to be at a higher risk for the occurrence of anaphylaxis and severe
409 allergic reactions [see *Warnings and Precautions (5.1)*].
410 Therefore, these patients should be monitored more closely
411 during administration of LUMIZYME.

412

413 **6.3 Postmarketing Experience**

414 The following adverse reactions have been identified during post
415 approval use of LUMIZYME. Because these reactions are
416 reported voluntarily from a population of uncertain size, it is not
417 always possible to reliably estimate their frequency or establish a
418 causal relationship to drug exposure. In postmarketing
419 experience with LUMIZYME, deaths, and serious adverse
420 reactions have been reported, including anaphylaxis [see *Boxed*
421 *Warning and Warnings and Precautions (5.1)*]. Adverse events
422 resulting in death reported in the postmarketing setting with
423 LUMIZYME treatment included cardiorespiratory arrest,
424 respiratory failure, hemothorax, pneumothorax, cardiac failure,
425 sepsis, aortic dissection, cerebrovascular accident, and skin
426 necrosis. The most frequently reported serious adverse reactions
427 were infusion reactions. Recurrent reactions consisting of flu-like
428 illness or a combination of events such as fever, chills, myalgia,

429 arthralgia, pain, or fatigue occurring after completion of infusions
430 and lasting for 1 - 3 days have been observed in some patients
431 treated with alglucosidase alfa. The majority of patients were
432 successfully rechallenged with alglucosidase alfa using lower
433 doses and/or pretreatment with anti-inflammatory drugs and/or
434 corticosteroids and were able to continue to receive treatment
435 under close clinical supervision.

436
437 In addition to the infusion reactions reported in clinical trials [*see*
438 *Adverse Reactions (6.1)*], the following serious adverse events
439 have been reported in at least 2 patients: dyspnea, respiratory
440 failure, bronchospasm, stridor, decreased oxygen
441 saturation/hypoxia, pharyngeal edema, chest discomfort, chest
442 pain, hypotension, hypertension, erythema, flushing, lung
443 infection, tachycardia, cyanosis, hypersensitivity, and abdominal
444 pain. One case of hyperparathyroidism has been reported.
445 Additional adverse drug reactions included proteinuria and
446 nephrotic syndrome [*see Warnings and Precautions (5.2)*].

447
448 Systemic and cutaneous immune mediated reactions, including
449 nephrotic syndrome secondary to membranous
450 glomerulonephritis and necrotizing skin lesions have been
451 reported in postmarketing safety experience with alglucosidase
452 alfa [*see Warnings and Precautions (5.2)*].

453

454 **7 DRUG INTERACTIONS**

455 **7.1 Interference with Other Drugs**

456 No drug interaction or *in vitro* metabolism studies were
457 performed.

458

459 **8 USE IN SPECIFIC POPULATIONS**

460 **8.1 Pregnancy**

461 Teratogenic Effects

462 Pregnancy Category B. Reproduction studies have been
463 performed in pregnant mice at intravenous doses up to 40
464 mg/kg/day (plasma AUC of 64.6 mg•min/mL, 0.4 times the
465 human steady-state exposure at the recommended bi-weekly
466 dose) and pregnant rabbits at intravenous doses up to 40
467 mg/kg/day (plasma AUC of 85 mg•min/mL, 0.5 times the human
468 steady-state exposure at the recommended bi-weekly dose) and
469 have revealed no evidence of impaired fertility or harm to the
470 fetus due to alglucosidase alfa. There are, however, no adequate
471 and well-controlled studies in pregnant women. Because animal

472 reproduction studies are not always predictive of human response,
473 this drug should be used during pregnancy only if clearly needed.

474

475 Women of childbearing potential are encouraged to enroll in the
476 Pompe Registry [see *Patient Counseling Information (17)*].

477 **8.2 Labor and Delivery**

478 Information on the effect of LUMIZYME on labor and delivery is
479 unknown. Pregnant women are encouraged to enroll in the
480 Pompe Registry [see *Patient Counseling Information (17)*].

481 **8.3 Nursing Mothers**

482 It is not known whether LUMIZYME is excreted in human milk.
483 Because many drugs are excreted in human milk, caution should
484 be exercised when LUMIZYME is administered to a nursing
485 woman. Nursing women are encouraged to enroll in the Pompe
486 Registry [see *Patient Counseling Information (17)*].

487 **8.4 Pediatric Use**

488 LUMIZYME is not for use in patients with infantile-onset Pompe
489 disease or late (non-infantile) onset Pompe disease who are less
490 than 8 years of age. The safety and effectiveness of LUMIZYME
491 in these patients have not been evaluated in clinical trials.

492

493 The safety and effectiveness of LUMIZYME was assessed in a
494 randomized, double-blind, placebo-controlled study of 90 patients
495 with late (non-infantile) onset Pompe disease. Patients age 8 to
496 70 years were eligible for enrollment. The study included 2
497 patients 16 years of age or less (n=1, age 16 years, LUMIZYME
498 treatment group, n=1, age 10 years, placebo group) [see *Clinical
499 Studies (14.1)*].

500

501 **8.5 Geriatric Use**

502 The randomized, double-blind, placebo-controlled study of
503 LUMIZYME did not include sufficient numbers (n=4) of patients
504 aged 65 years and over to determine whether they respond
505 differently from younger patients [see *Clinical Studies (14.1)*].

506

507 **10 OVERDOSAGE**

508 There have been no reports of overdose with LUMIZYME. In
509 the placebo-controlled study, patients received doses up to 20
510 mg/kg body weight every other week.

511

512 **11 DESCRIPTION**

513 LUMIZYME (alglucosidase alfa) consists of the human enzyme
514 acid α -glucosidase (GAA), encoded by the most predominant of
515 nine observed haplotypes of this gene. LUMIZYME is produced
516 by recombinant DNA technology in a Chinese hamster ovary cell
517 line. The LUMIZYME manufacturing process differs from that
518 for MYOZYME[®], resulting in differences in some product
519 attributes. Alglucosidase alfa degrades glycogen by catalyzing the
520 hydrolysis of α -1,4- and α -1,6- glycosidic linkages of lysosomal
521 glycogen.

522
523 Alglucosidase alfa is a glycoprotein with a calculated mass of
524 99,377 daltons for the polypeptide chain, and a total mass of
525 approximately 109,000 daltons, including carbohydrates.
526 Alglucosidase alfa has a specific activity of 3 to 5 Units/mg (one
527 unit is defined as that amount of activity that results in the
528 hydrolysis of 1 micromole of synthetic substrate per minute under
529 specified assay conditions). LUMIZYME is intended for
530 intravenous infusion. It is supplied as a sterile, nonpyrogenic,
531 white to off-white, lyophilized cake or powder for reconstitution
532 with 10.3 mL Sterile Water for Injection, USP. Each 50 mg vial
533 contains 52.5 mg alglucosidase alfa, 210 mg mannitol, 0.5 mg
534 polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate,
535 31.2 mg sodium phosphate monobasic monohydrate. Following
536 reconstitution as directed, each vial contains 10.5 mL
537 reconstituted solution and a total extractable volume of 10 mL at
538 5 mg/mL alglucosidase alfa. LUMIZYME does not contain
539 preservatives; each vial is for single use only.

540

541 **12 CLINICAL PHARMACOLOGY**

542 **12.1 Mechanism of Action**

543 Pompe disease (acid maltase deficiency, glycogen storage disease
544 type II, GSD II, glycogenosis type II) is an inherited disorder of
545 glycogen metabolism caused by the absence or marked deficiency
546 of the lysosomal enzyme GAA.

547

548 LUMIZYME provides an exogenous source of GAA. Binding to
549 mannose-6-phosphate receptors on the cell surface has been
550 shown to occur via carbohydrate groups on the GAA molecule,
551 after which it is internalized and transported into lysosomes,
552 where it undergoes proteolytic cleavage that results in increased
553 enzymatic activity. It then exerts enzymatic activity in cleaving
554 glycogen.

555

556 **12.2 Pharmacodynamics**

557 Clinical pharmacodynamic studies have not been conducted for
558 LUMIZYME.

559

560 **12.3 Pharmacokinetics**

561 The pharmacokinetics of alglucosidase alfa were studied in 32
562 late-onset Pompe disease patients from the randomized, double-
563 blind, placebo-controlled study ranging in age from 21 to 70
564 years old who received LUMIZYME 20 mg/kg every other week.
565 The pharmacokinetics were not time-dependent for patients who
566 did not develop high antibody titer/inhibitory antibody.
567 Parameter values did not change across visits at Weeks 0, 12, and
568 52. At Week 52 of bi-weekly administration the estimates of
569 AUC (2700 mcg•h/mL with 30.4% coefficient of variation
570 [CV],n=29), C_{max} (372 mcg /mL with 22.7% CV,n=29) and
571 clearance (601 mL/h with 28.2% CV,n=29) were determined at
572 steady-state. The declining portion of the concentration-time
573 profile of alglucosidase alfa appears biphasic within the observed
574 sampling time. The half-life for the first phase is 2.4 hours with a
575 between subject variation of 10%. Concentrations of
576 alglucosidase alfa were not sampled long enough to adequately
577 determine the half-life for the second phase.

578

579 Higher mean clearance (42%) was observed at Week 52 in 4 of
580 5 patients that tested positive for antibodies that inhibit the
581 cellular uptake of enzyme. Pharmacokinetics in 4 of these 5
582 individuals over time indicated an increase in clearance with
583 increase in IgG titer. Positive inhibitory antibody status
584 correlated with higher IgG titers in patients who received
585 LUMIZYME. The relationship between exposure and efficacy
586 has not been defined.

587

588 **13 NONCLINICAL TOXICOLOGY**

589 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

590 Long-term studies in animals to evaluate carcinogenic potential or
591 studies to evaluate mutagenic potential have not been performed
592 with alglucosidase alfa.

593

594 Alglucosidase alfa at intravenous doses up to 40 mg/kg,
595 administered every other day (plasma AUC of 64.6 mg•min/mL,
596 0.4 times the human exposure at the recommended bi-weekly
597 dose) had no effect on fertility and reproductive performance in
598 mice.

599

600 **14 CLINICAL STUDIES**

601 **14.1 Controlled Clinical Trials**

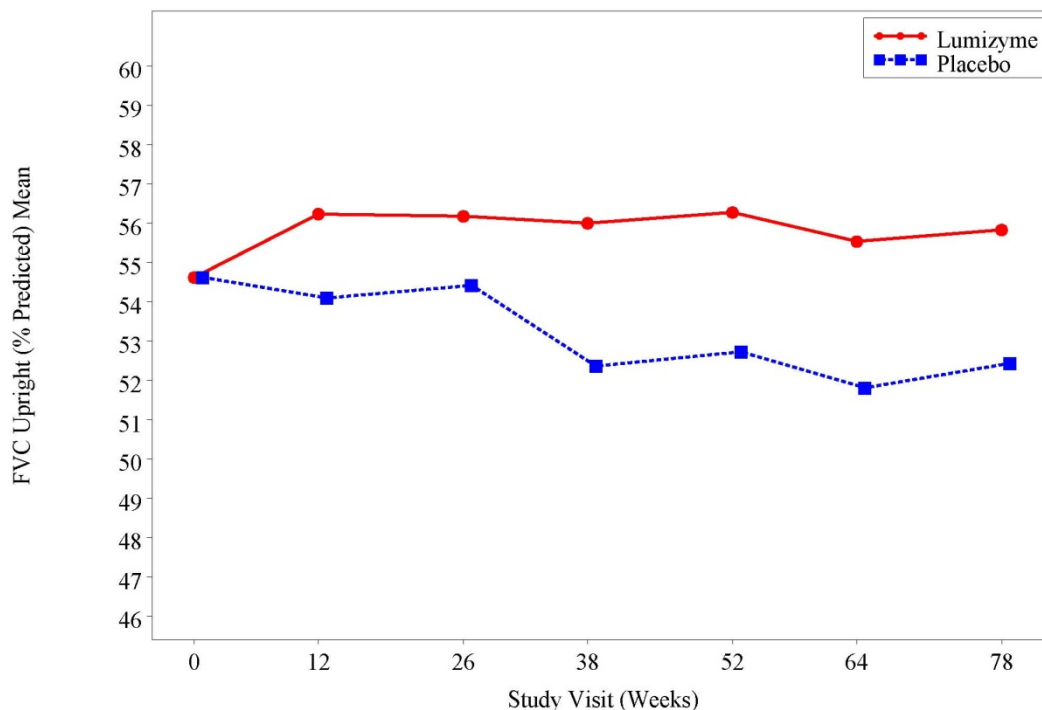
602 The safety and efficacy of LUMIZYME was assessed in 90
603 patients with late-onset Pompe disease, ages 10 to 70 years, in a
604 randomized double-blind, placebo-controlled study designed to
605 enroll patients age 8-70 years. The youngest LUMIZYME-
606 treated patient was 16 years of age, and the youngest placebo-
607 treated patient was 10 years of age. All patients were naïve to
608 enzyme replacement therapy. Patients were allocated in a 2:1
609 ratio and received 20 mg/kg LUMIZYME (n=60) or placebo
610 (n=30) every other week for 78 weeks (18 months). The study
611 population included 34 males and 26 females (N=60) in the
612 LUMIZYME group and 11 males and 19 females (N=30) in the
613 placebo group. At baseline, all patients were ambulatory (some
614 required assistive walking devices), did not require invasive
615 ventilator support or non-invasive ventilation while awake and
616 sitting upright and had a forced vital capacity (FVC) between 30
617 and 79% of predicted in the sitting position. Patients who could
618 not walk 40 meters in 6 minutes or were unable to perform
619 appropriate pulmonary and muscle function testing were excluded
620 from the study.

621
622 A total of 81 of 90 patients completed the study. Of the 9 patients
623 who discontinued, 5 were in the LUMIZYME group and 4 were
624 in the placebo group. Three patients discontinued the study due
625 to an adverse event; two patients were in the LUMIZYME
626 treatment group and one patient was in placebo group. One
627 patient in the LUMIZYME group died [see [Adverse Reactions](#)
628 [\(6.1\)](#)]. Four patients discontinued study participation to pursue
629 treatment with commercial therapy, and one patient discontinued
630 the study for personal reasons.

631
632 At study entry, the mean % predicted FVC in the sitting position
633 among all patients was about 55%. After 78 weeks, the mean %
634 predicted FVC increased to 56.2% for LUMIZYME-treated
635 patients and decreased to 52.8% for placebo-treated patients
636 indicating a LUMIZYME treatment effect of 3.4% (95%
637 confidence interval: [1.3% to 5.5%]; p=0.004). Stabilization of %
638 predicted FVC in the LUMIZYME-treated patients was observed
639 (see [Figure 1](#)).

640
641

642 **Figure 1: Mean FVC Upright (% Predicted) Over Time**



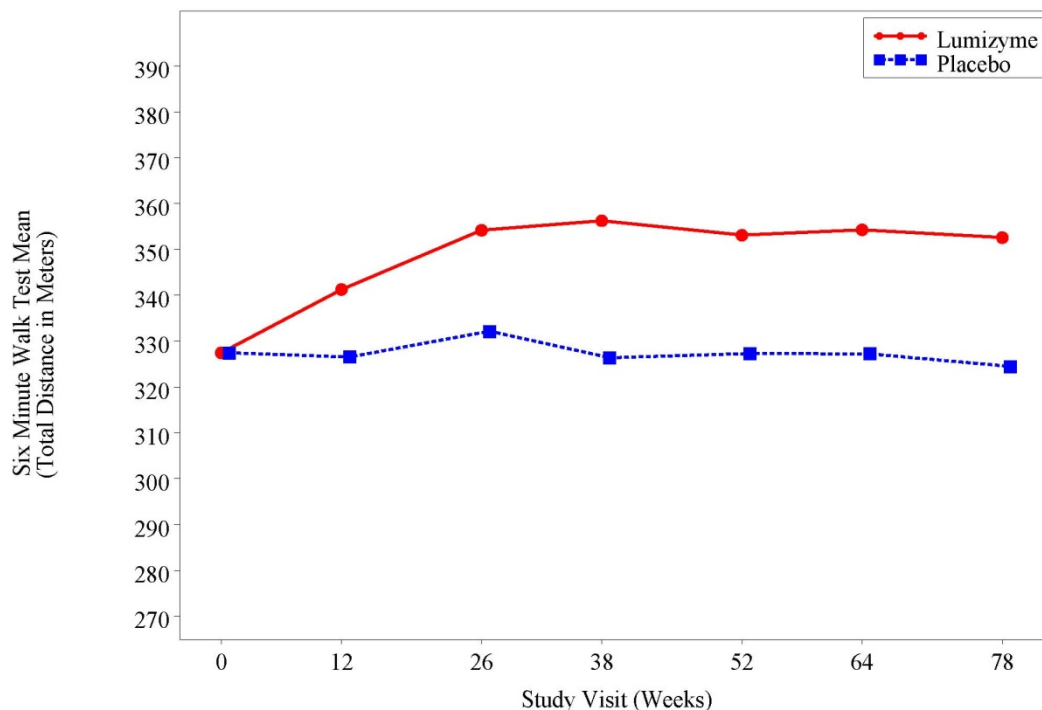
Note: ANCOVA least squares means adjusting for baseline values

643
644

645 At study entry, the mean 6 minute walk test (6MWT) among all
646 patients was about 330 meters. After 78 weeks, the mean 6MWT
647 increased by 25 meters for LUMIZYME-treated patients and
648 decreased by 3 meters for placebo-treated patients indicating a
649 LUMIZYME treatment effect of 28 meters (95% confidence
650 interval: [-1 to 52 meters]; $p=0.06$) (see [Figure 2](#)).

651
652

653 **Figure 2: Mean Six Minute Walk Test Total Distance Walked Over Time**



Note: ANCOVA least squares means adjusting for baseline values

654
655

656 **14.2 Uncontrolled Studies**

657

658 The effectiveness of LUMIZYME has not been established in
659 infantile-onset patients. Descriptive data from infantile-onset
660 patients who have received LUMIZYME commercially outside
661 the U.S. have been collected in the Pompe Registry. The Pompe
662 Registry is a multi-center, multi-national, voluntary,
663 observational disease registry. Fifteen infantile-onset patients
664 enrolled in the registry were matched to the baseline
665 characteristics of an untreated historical control cohort. These
666 patients were diagnosed with Pompe disease and received
667 treatment with LUMIZYME prior to 6 months of age (range 0.6
668 to 6 months). The median duration of treatment was 15 months
669 (range 3 to 48 months). Estimated survival in LUMIZYME-
670 treated patients was 57% at 18 months and 37% at 36 months,
671 compared to the 2% survival in the historical control group at
672 both time points. The median age of death or last follow-up was
673 19 months (range 5 to 51 months).

674

675 Descriptive clinical data from patients with infantile-onset Pompe
676 disease in the Pompe Registry were used to verify the overall

677 effectiveness of LUMIZYME for patients 8 years and older with
678 late-onset Pompe disease.

679

680 **16 HOW SUPPLIED/STORAGE AND HANDLING**

681 LUMIZYME 50 mg vials are supplied as a sterile, nonpyrogenic,
682 white to off-white lyophilized cake or powder. LUMIZYME is
683 supplied in single-use, clear Type I glass 20 mL (cc) vials. The
684 closure consists of a siliconized butyl stopper and an aluminum
685 seal with a plastic flip-off cap.

686

687 Store LUMIZYME under refrigeration between 2° to 8°C (36° to
688 46°F). Do not use LUMIZYME after the expiration date on the
689 vial.

690

691 The reconstituted and diluted solution should be administered
692 without delay. If immediate use is not possible, the reconstituted
693 and diluted solution is stable for up to 24 hours at 2° to 8°C (36°
694 to 46°F). Storage of the reconstituted solution at room
695 temperature is not recommended. The reconstituted and diluted
696 LUMIZYME solution should be protected from light. Do not
697 freeze or shake.

698 LUMIZYME does not contain any preservatives. Vials are single-
699 use only. Discard any unused product.

700

701 **NDC 58468-0160-1** (Carton of one single-use vial)

702 **NDC 58468-0160-2** (Carton of ten single-use vials)

703

704 **17 PATIENT COUNSELING INFORMATION**

705 **17.1 Distribution Program for LUMIZYME®**

706 Patients and caregivers should be informed that LUMIZYME is
707 available only under a restricted distribution program called the
708 LUMIZYME ACE (Alglucosidase Alfa Control and Education)
709 Program.

710 The purpose of the program is to ensure that the known risks of
711 anaphylaxis and severe allergic reactions and the potential risks
712 of severe cutaneous and systemic immune mediated reactions
713 associated with the use of LUMIZYME are communicated to
714 patients, caregivers, and prescribers. In addition, the purpose of
715 the program is to mitigate the potential risk of rapid disease
716 progression in infantile-onset Pompe disease patients and late
717 (non-infantile) onset Pompe disease patients less than 8 years of

718 age with for whom the safety and effectiveness of LUMIZYME
719 have not been evaluated.

720 Patients and caregivers should also be informed that only trained
721 and certified prescribers, and healthcare facilities enrolled in the
722 program are able to prescribe, dispense or administer
723 LUMIZYME, and that patients must be enrolled in and meet all
724 the conditions of the LUMIZYME ACE Program to receive
725 LUMIZYME.

726

727 **17.2 Pompe Registry**

728 Patients and their caregivers should be informed that a registry for
729 patients with Pompe disease (the Pompe Registry) has been
730 established in order to better understand the variability and
731 progression of Pompe disease, and to continue to monitor and
732 evaluate long-term treatment effects of LUMIZYME. The
733 Pompe Registry will also monitor the effect of LUMIZYME on
734 pregnant women and their offspring [*see Use in Specific*
735 *Populations (8)*]. Patients and their caregivers are encouraged to
736 participate in the Pompe Registry and advised that their
737 participation is voluntary and may involve long-term follow-up.
738 For more information regarding the registry program visit
739 www.pomperegistry.com or by calling 1-800-745-4447.

740 **17.3 Infusion Reactions**

741 Patients and caregivers should be informed that the most common
742 adverse reactions observed with LUMIZYME were infusion
743 reactions. Infusion reactions may occur during or within 2 hours
744 after completion of the infusion. Symptoms associated with
745 infusion reactions include urticaria, diarrhea, vomiting, dyspnea,
746 pruritus, rash/erythema, pharyngolaryngeal pain, neck pain,
747 hypoacusis, flushing/feeling hot, pain in extremity, fall, and chest
748 discomfort, respiratory distress, cough, livedo reticularis,
749 agitation, irritability, retching, rigors, tremor and increased
750 lacrimation.

751

752 LUMIZYME is manufactured and distributed by:
753 Genzyme Corporation
754 500 Kendall Street
755 Cambridge, MA 02142
756 1-800-745-4447 (phone)

757

758 US License Number: 1596

759

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761 trademarks of Genzyme Corporation. LUMIZYME ACE
762 Program is a registered Service Mark of Genzyme Corporation.
763