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MYOZYME[®] (alglucosidase alfa)

TEXT OF THE LABELING OF THE DRUG

1 MYOZYME[®] (alglucosidase alfa)

2 For intravenous infusion only

3 **WARNING**

4 **RISK OF HYPERSENSITIVITY REACTIONS**

5 **LIFE-THREATENING ANAPHYLACTIC REACTIONS,**
6 **INCLUDING ANAPHYLACTIC SHOCK, HAVE BEEN**
7 **OBSERVED IN PATIENTS DURING MYOZYME INFUSION.**

8 **BECAUSE OF THE POTENTIAL FOR SEVERE INFUSION**
9 **REACTIONS, APPROPRIATE MEDICAL SUPPORT MEASURES**
10 **SHOULD BE READILY AVAILABLE WHEN MYOZYME IS**
11 **ADMINISTERED.**

12 **DESCRIPTION**

13 MYOZYME[®] (alglucosidase alfa) consists of the
14 human enzyme acid α -glucosidase (GAA),
15 encoded by the most predominant of nine
16 observed haplotypes of this gene. MYOZYME is
17 produced by recombinant DNA technology in a
18 Chinese hamster ovary cell line. Alglucosidase
19 alfa degrades glycogen by catalyzing the
20 hydrolysis of α -1,4- and α -1,6- glycosidic linkages
of lysosomal glycogen.

21 Alglucosidase alfa is a glycoprotein with a
22 calculated mass of 99,377 daltons for the
23 polypeptide chain, and a total mass of
24 approximately 109,000 daltons, including
25 carbohydrates. Alglucosidase alfa has a specific
26 activity of 3 to 5 U/mg (one unit is defined as that
27 amount of activity that results in the hydrolysis of 1
28 μ mole of synthetic substrate per minute under the
29 specified assay conditions). MYOZYME is
30 intended for intravenous infusion. It is supplied as
31 a sterile, nonpyrogenic, white to off-white,
32 lyophilized cake or powder for reconstitution with
33 10.3 mL Sterile Water for Injection, USP. Each 50
34 mg vial contains 52.5 mg alglucosidase alfa, 210

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35 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg
36 sodium phosphate dibasic heptahydrate, 31.2 mg
37 sodium phosphate monobasic monohydrate.
38 Following reconstitution as directed, each vial
39 contains 10.5 mL reconstituted solution and a total
40 extractable volume of 10 mL at 5.0 mg/mL
41 alglucosidase alfa. MYOZYME does not contain
42 preservatives; each vial is for single use only.

43 **CLINICAL PHARMACOLOGY**

44 **Mechanism of Action**

45 Pompe disease (glycogen storage disease type II,
46 GSD II, glycogenosis type II, acid maltase
47 deficiency) is an inherited disorder of glycogen
48 metabolism caused by the absence or marked
49 deficiency of the lysosomal enzyme GAA.

50 In the infantile-onset form, Pompe disease results
51 in intralysosomal accumulation of glycogen in
52 various tissues, particularly cardiac and skeletal
53 muscles, and hepatic tissues, leading to the
54 development of cardiomyopathy, progressive
55 muscle weakness, and impairment of respiratory
56 function.

57 In the juvenile- and adult-onset forms,
58 intralysosomal accumulation of glycogen is limited
59 primarily to skeletal muscle, resulting in
60 progressive muscle weakness. Death in all forms
61 is usually related to respiratory failure.

62 MYOZYME provides an exogenous source of
63 GAA. Binding to mannose-6-phosphate receptors
64 on the cell surface has been shown to occur via
65 carbohydrate groups on the GAA molecule, after
66 which it is internalized and transported into
67 lysosomes, where it undergoes proteolytic
68 cleavage that results in increased enzymatic
69 activity. It then exerts enzymatic activity in
70 cleaving glycogen.

71 **Pharmacokinetics**

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72 The pharmacokinetics of alglucosidase alfa were
73 evaluated in 13 patients of age ranging from 1
74 month to 7 months with infantile-onset Pompe
75 disease who received 20 mg/kg (as an
76 approximate 4-hour infusion) or 40 mg/kg (as an
77 approximate 6.5-hour infusion) of MYOZYME
78 every 2 weeks. The measurement of
79 alglucosidase alfa plasma concentration was
80 based on an activity assay using an artificial
81 substrate. Systemic exposure was approximately
82 dose proportional between the 20 and 40 mg/kg
83 doses (see Table 1).

84 Table 1. Pharmacokinetic Parameters (Mean ± SD)
85 After Single Intravenous Infusion of MYOZYME

| Pharmacokinetic Parameter | 20 mg/kg (n=5) | 40 mg/kg (n=8) |
|------------------------------|----------------|----------------|
| C _{max} (mcg/mL) | 162 ± 31 | 276 ± 64 |
| AUC _∞ (mcg-hr/mL) | 811 ± 141 | 1781 ± 520 |
| CL (mL/hr/kg) | 25 ± 4 | 24 ± 7 |
| V _{ss} (mL/kg) | 96 ± 16 | 119 ± 28 |
| t _{1/2} (hr) | 2.3 ± 0.4 | 2.9 ± 0.5 |

86

87 The pharmacokinetics of alglucosidase alfa were
88 also evaluated in a separate trial in 14 patients of
89 age ranging from 6 months to 3.5 years with
90 Pompe disease who received 20 mg/kg of
91 MYOZYME as an approximate 4-hour infusion
92 every 2 weeks. The pharmacokinetic parameters
93 were similar to those observed for the 20 mg/kg
94 dose group in the trial of patients of age ranging
95 from 1 month to 7 months.

96 Nineteen of 21 patients who received treatment
97 with MYOZYME and had pharmacokinetics and
98 antibody titer data available at Week 12 developed
99 antibodies to alglucosidase alfa. Five patients with
100 antibody titers ≥ 12,800 at Week 12 had an
101 average increase in clearance of 50% (range 5%
102 to 90%) from Week 1 to Week 12. The other 14
103 patients with antibody titers < 12,800 at Week 12
104 had similar average clearance values at Week 1
105 and Week 12.

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106 **CLINICAL STUDIES**

107 The safety and efficacy of MYOZYME were
108 assessed in 2 separate clinical trials in 39 Pompe
109 disease patients, who ranged in age from 1 month
110 to 3.5 years at the time of first infusion.

111 Study 1 was an international, multicenter, open-
112 label, clinical trial of 18 infantile-onset Pompe
113 disease patients. This study was conducted
114 between 2003 and 2005. Patients were
115 randomized equally to either 20 mg/kg or 40
116 mg/kg MYOZYME every two weeks, with length of
117 treatment ranging from 52 to 106 weeks.
118 Enrollment was restricted to patients ages 7
119 months or less at first infusion with clinical signs of
120 Pompe disease, with cardiac hypertrophy, and
121 who did not require ventilatory support at study
122 entry.

123 Efficacy was assessed by comparing the
124 proportions of Myozyme-treated patients who died
125 or needed invasive ventilator support with the
126 mortality experience of an historical cohort of
127 untreated infantile-onset Pompe patients with
128 similar age and disease severity. In the historical
129 cohort, 61 untreated patients with infantile-onset
130 Pompe disease diagnosed by age 6 months, born
131 between 1982 and 2002, were identified by a
132 retrospective review of medical charts. By the age
133 of 18 months, only one of the 61 historical control
134 patients was alive (98% mortality), indicating the
135 poor outcome of patients who are left untreated.

136 Within the first 12 months of treatment, 3 of 18
137 MYOZYME-treated patients required invasive
138 ventilatory support (17%, with 95% confidence
139 interval 4% to 41%); there were no deaths. With
140 continued treatment beyond 12 months, 4
141 additional patients required invasive ventilatory
142 support, after receiving between 13 and 18
143 months of MYOZYME treatment; 2 of these 4
144 patients died after receiving 14 and 25 months of

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145 treatment, and after receiving 11 days and 7.5
146 months of invasive ventilatory support,
147 respectively. No other deaths have been reported
148 through a median follow-up of 20 months, and all
149 16 surviving patients continue to be followed.
150 Survival without invasive ventilatory support was
151 substantially greater in the MYOZYME-treated
152 patients in this study than would be expected
153 compared to the poor survival of the historical
154 control patients. No differences in outcome were
155 observed between patients who received 20
156 mg/kg versus 40 mg/kg.

157 Other outcome measures in this study included
158 unblinded assessments of motor function by the
159 Alberta Infant Motor Scale (AIMS). The AIMS is a
160 measure of infant motor performance that
161 assesses motor maturation of the infant through
162 age 18 months and is validated for comparison to
163 normal, healthy infants. AIMS-assessed gains in
164 motor function occurred in 13 patients. In the
165 majority of patients, motor function was
166 substantially delayed compared to normal infants
167 of comparable age. The continued effect of
168 MYOZYME treatment over time on motor function
169 is unknown. Two of 9 patients who had
170 demonstrated gains in motor function after 12
171 months of MYOZYME treatment and continued to
172 be followed regressed despite ongoing treatment.

173 Changes from baseline to Month 12 in left
174 ventricular mass index (LVMI), an evaluation of
175 bioactivity, were measured by echocardiography.
176 For the 15 patients with both baseline and Month
177 12 echocardiograms, all had decreases from
178 baseline in LVMI (mean decrease 118 g/m², range
179 45 to 193 g/m²). The magnitude of the decrease in
180 LVMI did not correlate with the clinical outcome
181 measure of ventilator-free survival.

182 Study 2 is an ongoing, international, multicenter,
183 non-randomized, open-label clinical trial that
184 enrolled 21 patients who were ages 3 months to

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185 3.5 years at first treatment. All patients received 20
186 mg/kg MYOZYME every other week for up to 104
187 weeks. Five of 21 patients were receiving invasive
188 ventilatory support at the time of first infusion.

189 The primary outcome measure was the proportion
190 of patients alive at the conclusion of treatment. At
191 the 52-week interim analysis, 16 of 21 patients
192 were alive. Sixteen patients were free of invasive
193 ventilatory support at the time of first infusion: of
194 these, 4 died, 2 required invasive ventilatory
195 support, and 10 were free of invasive ventilatory
196 support after 52 weeks of treatment. For the 5
197 patients who were receiving invasive ventilatory
198 support at baseline, 1 died, and 4 remained on
199 invasive ventilatory support at Week 52. The
200 status of patients at Week 52 overlapped with that
201 of an untreated historical group of patients, and no
202 effect of MYOZYME treatment could be
203 determined.

204 **INDICATIONS AND USAGE**

205 MYOZYME (alglucosidase alfa) is indicated for
206 use in patients with Pompe disease (GAA
207 deficiency). MYOZYME has been shown to
208 improve ventilator-free survival in patients with
209 infantile-onset Pompe disease as compared to an
210 untreated historical control, whereas use of
211 MYOZYME in patients with other forms of Pompe
212 disease has not been adequately studied to
213 assure safety and efficacy (see **CLINICAL**
214 **STUDIES**).

215 **CONTRAINDICATIONS**

216 None known.

217 **WARNINGS**

218

219 **RISK OF HYPERSENSITIVITY REACTIONS**

220 (see boxed **WARNING**)

221 **Serious hypersensitivity reactions, including**

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222 **anaphylactic reactions, have been reported**
223 **during MYOZYME infusion. Some reactions**
224 **were life-threatening. One patient developed**
225 **anaphylactic shock during MYOZYME infusion**
226 **that required life-support measures (see**
227 **ADVERSE REACTIONS).**

228 **In clinical trials and expanded access**
229 **programs with MYOZYME, 38 of 280**
230 **(approximately 14%) patients treated with**
231 **MYOZYME have developed infusion reactions**
232 **that involved at least 2 of 3 body systems,**
233 **cutaneous, respiratory or cardiovascular**
234 **systems. These events included:**
235 **Cardiovascular: hypotension, cyanosis,**
236 **hypertension, tachycardia, ventricular**
237 **extrasystoles, bradycardia, pallor, flushing,**
238 **nodal rhythm, peripheral coldness;**
239 **Respiratory: tachypnea,**
240 **wheezing/bronchospasm, rales, throat**
241 **tightness, hypoxia, dyspnea, cough,**
242 **respiratory tract irritation, oxygen saturation**
243 **decreased; Cutaneous: angioneurotic edema,**
244 **urticaria, rash, erythema, periorbital edema,**
245 **pruritus, hyperhidrosis, cold sweat, livedo**
246 **reticularis (see ADVERSE REACTIONS). Of**
247 **these cases, 8 patients experienced severe or**
248 **significant hypersensitivity reactions.**

249 **If severe hypersensitivity or anaphylactic**
250 **reactions occur, immediate discontinuation of**
251 **the administration of MYOZYME should be**
252 **considered, and appropriate medical treatment**
253 **should be initiated. Because of the potential**
254 **for severe infusion reactions, appropriate**
255 **medical support measures should be readily**
256 **available when MYOZYME is administered.**

257 **RISK OF CARDIAC ARRHYTHMIA AND**
258 **SUDDEN CARDIAC DEATH DURING GENERAL**
259 **ANESTHESIA FOR CENTRAL VENOUS**
260 **CATHETER PLACEMENT**

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262 **Cardiac arrhythmia, including ventricular**
263 **fibrillation, ventricular tachycardia and**
264 **bradycardia, resulting in cardiac arrest or**
265 **death, or requiring cardiac resuscitation or**
266 **defibrillation have been observed in infantile-**
267 **onset Pompe disease patients with cardiac**
268 **hypertrophy, associated with the use of**
269 **general anesthesia for the placement of a**
270 **central venous catheter intended for**
271 **MYOZYME infusion.**

272
273 **Caution should be used when administering**
274 **general anesthesia for the placement of a**
275 **central venous catheter in infantile-onset**
276 **Pompe disease patients with cardiac**
277 **hypertrophy.**

278
279 **RISK OF ACUTE CARDIORESPIRATORY FAILURE**
280

281 **Acute cardiorespiratory failure requiring**
282 **intubation and inotropic support has been**
283 **observed after infusion with MYOZYME in 1**
284 **infantile-onset Pompe disease patient with**
285 **underlying cardiac hypertrophy, possibly**
286 **associated with fluid overload with**
287 **intravenous administration of MYOZYME. (See**
288 **Instructions for Use: Reconstitution, dilution**
289 **and administration for information on**
290 **appropriate infusion volumes.)**

291 **Infusion Reactions**

292 Infusion reactions occurred in 20 of 39 (51%) of
293 patients treated with MYOZYME in clinical studies
294 (see **ADVERSE REACTIONS**). Some reactions
295 were severe. Severe infusion reactions reported
296 in more than 1 patient in clinical studies and the
297 expanded access program included pyrexia,
298 decreased oxygen saturation, tachycardia,
299 cyanosis and hypotension. Other infusion
300 reactions reported in more than 1 patient in clinical
301 studies and the expanded access program
302 included rash, flushing, urticaria, pyrexia, cough,
303 tachycardia, decreased oxygen saturation,

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304 vomiting, tachypnea, agitation, increased blood
305 pressure, cyanosis, hypertension, irritability, pallor,
306 pruritus, retching, rigors, tremor, hypotension,
307 bronchospasm, erythema, face edema, feeling
308 hot, headache, hyperhidrosis, lacrimation
309 increased, livedo reticularis, nausea, periorbital
310 edema, restlessness and wheezing. Some
311 patients were pre-treated with antihistamines,
312 antipyretics and/or steroids. Infusion reactions
313 occurred in some patients after receiving
314 antipyretics, antihistamines, or steroids. Infusion
315 reactions may occur at any time during, or up to 2
316 hours after, the infusion of MYOZYME, and are
317 more likely with higher infusion rates.

318 Patients with advanced Pompe disease may have
319 compromised cardiac and respiratory function,
320 which may predispose them to a higher risk of
321 severe complications from infusion reactions.
322 Therefore, these patients should be monitored
323 more closely during administration of MYOZYME.

324 If an infusion reaction occurs, regardless of pre-
325 treatment, decreasing the infusion rate,
326 temporarily stopping the infusion, and/or
327 administration of antihistamines and/or antipyretics
328 may ameliorate the symptoms. If severe infusion
329 reactions occur, immediate discontinuation of the
330 administration of MYOZYME should be
331 considered, and appropriate medical treatment
332 should be initiated. Because of the potential for
333 severe infusion reactions, appropriate medical
334 support measures should be readily available
335 when MYOZYME is administered. Patients who
336 have experienced infusion reactions should be
337 treated with caution when readministered
338 MYOZYME.

339 **PRECAUTIONS**

340 **General**

341 Patients with an acute underlying illness at the
342 time of MYOZYME infusion appear to be at

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343 greater risk for infusion reactions. Careful
344 consideration should be given to the patient's
345 clinical status prior to administration of
346 MYOZYME.

347 **Information for Patients**

348 Patients and their caregivers should be informed
349 that a registry for patients with Pompe disease has
350 been established in order to better understand the
351 variability and progression of Pompe disease and
352 to continue to monitor and evaluate treatments.
353 Patients and their caregivers are encouraged to
354 participate and should be advised that their
355 participation may involve long-term follow-up.
356 Information regarding the registry program may be
357 found at www.pompergistry.com or by calling 1-
358 800-745-4447.

359 **Laboratory Tests**

360 There are no marketed tests for antibodies against
361 alglucosidase alfa. If testing is warranted, contact
362 your local Genzyme representative or Genzyme
363 Corporation at 1-800-745-4447.

364 Results from 2 intravenous repeated-dose animal
365 toxicology studies using doses of 100 or 200
366 mg/kg MYOZYME (about 1.6 to 3.2 times the
367 recommended human dose based on body
368 surface area) in Cynomolgus monkeys to evaluate
369 the possibility of liver accumulation over time
370 showed GAA levels above background in liver
371 tissue several days following the last dose;
372 however, no concurrent changes in liver enzymes
373 or histopathology were observed. It is suggested
374 that liver enzymes be evaluated prior to the
375 initiation of MYOZYME treatment and periodically
376 thereafter. Care should be exercised in
377 interpreting these tests since aspartate
378 aminotransferase and alanine aminotransferase
379 levels may also be raised as a result of the muscle
380 pathology in patients with Pompe disease.

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381 **Drug Interactions**

382 No drug interaction studies have been performed.

383 **Carcinogenesis, Mutagenesis, Impairment of**
384 **Fertility**

385 Long-term studies in animals to evaluate
386 carcinogenic potential or studies to evaluate
387 mutagenic potential have not been performed with
388 MYOZYME.

389 MYOZYME at intravenous doses up to 40 mg/kg,
390 administered every other day (about 0.2 times the
391 recommended human bi-weekly dose based on
392 body surface area) had no effect on fertility and
393 reproductive performance in mice.

394 **Pregnancy: Teratogenic Effects: Pregnancy Category B.**

395 A reproduction study has been performed in
396 pregnant mice at doses up to 40 mg/kg/day (about
397 0.2 times the recommended human bi-weekly dose
398 based on body surface area) and has revealed no
399 evidence of impaired fertility or harm to the fetus
400 due to MYOZYME. There are, however, no
401 adequate and well-controlled studies in pregnant
402 women. Because animal reproduction studies are
403 not always predictive of human response, this drug
404 should be used during pregnancy only if clearly
405 needed.

406 Women of childbearing potential are encouraged to
407 enroll in the Pompe patient registry (see
408 **PRECAUTIONS: Information for Patients**).

409 **Nursing Mothers**

410 It is not known whether MYOZYME is excreted in
411 human milk. Because many drugs are excreted in
412 human milk, caution should be exercised when
413 MYOZYME is administered to a nursing woman
414 (See **PRECAUTIONS: Information for Patients**
415 regarding a registry program. Nursing women are
416 encouraged to participate in the registry program).

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417 **Pediatric Use**

418 Pediatric patients aged 1 month to 3.5 years at
419 time of first infusion have been treated with
420 MYOZYME in clinical trials (see **CLINICAL**
421 **STUDIES**). Other open-label clinical trials of
422 MYOZYME have been performed in older pediatric
423 patients ranging from 2 to 16 years at the initiation
424 of treatment (juvenile-onset Pompe disease);
425 however the risks and benefits of MYOZYME
426 treatment have not been established in the
427 juvenile-onset Pompe disease population.

428 **Geriatric Use**

429 Clinical studies did not include any subjects aged
430 65 years and older. It is not known whether they
431 respond differently than younger subjects.

432 **ADVERSE REACTIONS**

433 The most serious adverse reactions reported with
434 MYOZYME were cardiorespiratory failure and
435 anaphylactic reactions. Cardiorespiratory failure,
436 possibly associated with fluid overload, was
437 reported in one infantile-onset Pompe disease
438 patient, and pre-existing cardiac hypertrophy likely
439 contributed to the severity of the reaction (see
440 **WARNINGS: Risk of Acute Cardiorespiratory**
441 **Failure**). Anaphylactic reactions have been
442 reported during MYOZYME infusion (see boxed
443 **WARNING: Risk of Hypersensitivity Reactions,**
444 **and WARNINGS: Hypersensitivity Reactions**).

445 The most common serious treatment-emergent
446 adverse events (regardless of relationship)
447 observed in clinical studies with MYOZYME were
448 pneumonia, respiratory failure, respiratory distress,
449 catheter-related infection, respiratory syncytial virus
450 infection, gastroenteritis and fever.

451 The most common treatment-emergent adverse
452 events (regardless of relationship) were fever,
453 diarrhea, rash, vomiting, cough, pneumonia, otitis

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454 media, upper respiratory tract infection,
455 gastroenteritis and decreased oxygen saturation.

456 The most common adverse reactions requiring
457 intervention were infusion-related reactions (see
458 **WARNINGS: Infusion Reactions**). Twenty of 39
459 patients (51%) treated with MYOZYME in clinical
460 studies developed infusion reactions during the
461 infusion or during the 2 hours following infusion.
462 The majority of these reactions were mild to
463 moderate. Infusion reactions reported in more than
464 1 patient in clinical studies and the expanded
465 access program included rash, flushing, urticaria,
466 pyrexia, cough, tachycardia, decreased oxygen
467 saturations, vomiting, tachypnea, agitation,
468 increased blood pressure, cyanosis, hypertension,
469 irritability, pallor, pruritus, retching, rigors, tremor,
470 hypotension, bronchospasm, erythema, face
471 edema, feeling hot, headache, hyperhidrosis,
472 lacrimation increased, livedo reticularis, nausea,
473 periorbital edema, restlessness and wheezing.
474 Most infusion-related reactions requiring
475 intervention were ameliorated with slowing of the
476 infusion rate, temporarily stopping the infusion,
477 and/or administration of antipyretics,
478 antihistamines, or steroids.

479 The data described below reflect exposure of 39
480 Pompe disease patients to 20 or 40 mg/kg of
481 MYOZYME administered every other week in 2
482 separate clinical trials for periods ranging from 1 to
483 106 weeks (mean 61 weeks). Patients were ages
484 1 month to 3.5 years at first treatment. The
485 population was nearly evenly distributed in gender
486 (18 females and 21 males).

487 Because clinical trials are conducted under more
488 controlled conditions, the observed adverse
489 reaction rates may not predict the rates observed in
490 patients in clinical practice.

491 Table 2 enumerates treatment-emergent adverse
492 events (regardless of relationship) that occurred in

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493 at least 20% of patients treated with MYOZYME in
494 clinical trials described above. Reported
495 frequencies of adverse events have been classified
496 by MedDRA terms.

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497 **Table 2: Summary of Adverse Events by**
498 **System Organ Class and Preferred Term**
499 **Occurring in at Least 20% of Patients Treated**
500 **with MYOZYME in Clinical Trials**

| System Organ Class Preferred Term | Number of Patients (N=39) n (%) | Number of Adverse Events n |
|---|---------------------------------------|----------------------------------|
| Any Adverse Events = | 39 (100) | 1859 |
| General disorders and administration site conditions | 38 (97) | |
| Pyrexia | 36 (92) | 169 |
| Respiratory, thoracic and mediastinal disorders | 38 (97) | |
| Cough | 18 (46) | 69 |
| Respiratory distress | 13 (33) | 18 |
| Respiratory failure | 12 (31) | 24 |
| Rhinorrhea | 11 (28) | 16 |
| Tachypnea | 9 (23) | 15 |
| Infections and infestations | 37 (95) | |
| Pneumonia | 18 (46) | 43 |
| Otitis media | 17 (44) | 35 |
| Upper respiratory tract infection | 17 (44) | 39 |
| Gastroenteritis | 16 (41) | 17 |
| Pharyngitis | 14 (36) | 26 |
| Ear Infection | 13 (33) | 23 |
| Oral candidiasis | 12 (31) | 20 |
| Catheter related infection | 11 (28) | 15 |
| Bronchiolitis | 9 (23) | 10 |
| Nasopharyngitis | 9 (23) | 25 |
| Gastrointestinal disorders | 32 (82) | |
| Diarrhea | 24 (62) | 62 |
| Vomiting | 19 (49) | 62 |
| Gastroesophageal reflux disease | 10 (26) | 13 |
| Constipation | 9 (23) | 14 |
| Skin and subcutaneous tissue disorders | 32 (82) | |
| Rash | 21 (54) | 72 |
| Diaper dermatitis | 14 (36) | 34 |
| Urticaria | 8 (21) | 25 |
| Investigations | 28 (72) | |
| Oxygen saturation decreased | 16 (41) | 44 |
| Cardiac disorders | 24 (62) | |
| Tachycardia | 9 (23) | 31 |
| Bradycardia | 8 (21) | 18 |
| Injury, poisoning and procedural complications | 22 (56) | |
| Post procedural pain | 10 (26) | 20 |
| Blood and lymphatic system disorders | 17 (44) | |
| Anemia | 12 (31) | 23 |
| Vascular disorders | 14 (36) | |
| Flushing | 8 (21) | 15 |

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502 Five additional juvenile-onset Pompe disease
503 patients were evaluated in a single-center, open-
504 label, non-randomized, uncontrolled clinical trial.
505 Patients were ages 5 to 15 years, ambulatory (able
506 to walk at least 10 meters in 6 minutes), and not
507 receiving invasive ventilatory support at study
508 entry. All 5 patients received treatment with 20
509 mg/kg MYOZYME for 26 weeks. The most
510 common treatment-emergent adverse events
511 (regardless of causality) observed with MYOZYME
512 treatment in this study were headache, pharyngitis,
513 upper abdominal pain, malaise and rhinitis.

514 **Immunogenicity**

515 The majority of patients (34 of 38; 89%) in the two
516 clinical trials tested positive for IgG antibodies to
517 alglucosidase alfa. The data reflect the percentage
518 of patients whose test results were considered
519 positive for antibodies to alglucosidase alfa using
520 an enzyme-linked immunosorbent assay (ELISA)
521 and radioimmunoprecipitation (RIP) assay for
522 alglucosidase alfa-specific IgG antibodies. Most
523 patients who develop antibodies do so within the
524 first 3 months of exposure. There is evidence to
525 suggest that patients developing sustained titers
526 $\geq 12,800$ of anti-alglucosidase alfa antibodies may
527 have a poorer clinical response to treatment, or
528 may lose motor function as antibody titers increase.
529 Treated patients who experience a decrease in
530 motor function should be tested for neutralization of
531 enzyme uptake or activity. Five patients with
532 antibody titers $\geq 12,800$ at Week 12 had an
533 average increase in clearance of 50% from Week 1
534 to Week 12 (see **CLINICAL PHARMACOLOGY:**
535 **Pharmacokinetics**).

536 Infusion reactions were reported in 20 of 39
537 patients (51%) treated with MYOZYME in clinical
538 studies and appear to be more common in
539 antibody-positive patients: 8 of 15 patients with
540 high antibody titers experienced infusion reactions
541 whereas none of 3 antibody-negative patients

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542 experienced infusion reactions.

543 Approximately 40 patients in clinical trials and
544 expanded access programs have undergone
545 testing for MYOZYME-specific IgE antibodies.
546 Testing was performed for infusion reactions,
547 especially moderate to severe or recurrent
548 reactions, for which mast-cell activation was
549 suspected. Three of these patients tested positive
550 for MYOZYME specific IgE binding antibodies, 1 of
551 whom experienced an anaphylactic reaction (see
552 **WARNINGS: Hypersensitivity Reactions**).

553 **OVERDOSAGE**

554 There have been no reports of overdose with
555 MYOZYME. In clinical trials, patients received
556 doses up to 40 mg/kg of body weight.

557 **DOSAGE AND ADMINISTRATION**

558 The recommended dosage regimen of MYOZYME
559 is 20 mg/kg body weight administered every 2
560 weeks as an intravenous infusion. The total
561 volume of infusion is determined by the patient's
562 body weight and should be administered over
563 approximately 4 hours.

564 Infusions should be administered in a step-wise
565 manner using an infusion pump. The initial
566 infusion rate should be no more than 1 mg/kg/hr.
567 The infusion rate may be increased by 2 mg/kg/hr
568 every 30 minutes, after patient tolerance to the
569 infusion rate is established, until a maximum rate
570 of 7 mg/kg/hr is reached. Vital signs should be
571 obtained at the end of each step. If the patient is
572 stable, MYOZYME may be administered at the
573 maximum rate of 7 mg/kg/hr until the infusion is
574 completed. The infusion rate may be slowed
575 and/or temporarily stopped in the event of infusion
576 reactions. See Table 3 below for the rate of
577 infusion at each step, expressed as mL/hr based
578 on the recommended infusion volume by patient
579 weight.

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580 Table 3. Recommended infusion volumes and
581 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) |
|---------------------------|----------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| 1.25 - 10 | 50 | 3 | 8 | 13 | 18 |
| 10.1 - 20 | 100 | 5 | 15 | 25 | 35 |
| 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 |

582

583 **Instructions for Use**

584 MYOZYME does not contain any preservatives.
585 Vials are single-use only. Any unused product
586 should be discarded.

587 **Reconstitution, dilution and administration**

588 MYOZYME should be reconstituted, diluted and
589 administered by a health care professional.

590 Use aseptic technique during preparation. Do not
591 use filter needles during preparation.

- 592 1. Determine the number of vials to be
593 reconstituted based on the individual patient's
594 weight and the recommended dose of 20
595 mg/kg.

596
597 Patient weight (kg) x dose (mg/kg) = patient
598 dose (in mg)

599
600 Patient dose (in mg) divided by 50 mg/vial =
601 number of vials to reconstitute. If the number
602 of vials includes a fraction, round up to the
603 next whole number.

604
605 Example: Patient weight (16 kg) x dose (20

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- 606 mg/kg) = patient dose (320 mg)
607
608 320 mg divided by 50 mg/vial = 6.4 vials;
609 therefore, 7 vials should be reconstituted
610
611 Remove the required number of vials from the
612 refrigerator and allow them to reach room
613 temperature prior to reconstitution
614 (approximately 30 minutes).
- 615 2. Reconstitute each MYOZYME vial by **slowly**
616 injecting 10.3 mL of Sterile Water for Injection,
617 USP to the inside wall of each vial. Each vial
618 will yield 5 mg/mL. The total extractable dose
619 per vial is 50 mg per 10 mL. Avoid forceful
620 impact of the water for injection on the powder
621 and avoid foaming. This is done by slow drop-
622 wise addition of the water for injection down
623 the inside of the vial and not directly onto the
624 lyophilized cake. Tilt and roll each vial gently.
625 Do not invert, swirl, or shake.
- 626 3. The reconstituted MYOZYME solution should
627 be protected from light.
- 628 4. Perform an immediate visual inspection on the
629 reconstituted vials for particulate matter and
630 discoloration. If upon immediate inspection
631 opaque particles are observed or if the
632 solution is discolored do not use. The
633 reconstituted solution may occasionally
634 contain some alglucosidase alfa particles
635 (typically less than 10 in a vial) in the form of
636 thin white strands or translucent fibers
637 subsequent to the initial inspection. This may
638 also happen following dilution for infusion.
639 These particles have been shown to contain
640 alglucosidase alfa and may appear after the
641 initial reconstitution step and increase over
642 time. Studies have shown that these particles
643 are removed via in-line filtration without having
644 a detectable effect on the purity or strength.

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- 645 5. MYOZYME should be diluted in 0.9% Sodium
646 Chloride for Injection, USP, immediately after
647 reconstitution, to a final MYOZYME
648 concentration of 0.5 to 4 mg/mL. See Table 3
649 for the recommended total infusion volume
650 based on patient weight.
- 651 6. Slowly withdraw the reconstituted solution
652 from each vial. Avoid foaming in the syringe.
- 653 7. Remove airspace from the infusion bag to
654 minimize particle formation due to the
655 sensitivity of MYOZYME to air-liquid
656 interfaces.
- 657 8. Add the reconstituted MYOZYME solution
658 slowly and directly into the sodium chloride
659 solution. Do not add directly into airspace that
660 may remain within the infusion bag. Avoid
661 foaming in the infusion bag.
- 662 9. Gently invert or massage the infusion bag to
663 mix. Do not shake.

664
665 The diluted solution should be filtered through a
666 0.2 µm, low protein-binding, in-line filter during
667 administration to remove any visible particles.

668
669 MYOZYME should not be infused in the same
670 intravenous line with other products.

671 **Storage**

672 Store MYOZYME under refrigeration between
673 2° to 8°C (36° to 46°F). Do not use MYOZYME
674 after the expiration date on the vial.

675 The reconstituted and diluted solution should be
676 administered without delay. If immediate use is
677 not possible, the reconstituted and diluted solution
678 is stable for up to 24 hours at 2° to 8°C (36° to
679 46°F). Storage of the reconstituted solution at
680 room temperature is not recommended. The
681 reconstituted and diluted MYOZYME solution

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682 should be protected from light. DO NOT FREEZE
683 OR SHAKE.

684 **HOW SUPPLIED**

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

691 NDC 58468-0150-1

692 **Rx Only**

693

694 MYOZYME is manufactured and distributed by:

695 Genzyme Corporation

696 500 Kendall Street

697 Cambridge, MA 02142

698 1-800-745-4447

699 US License Number: 1596

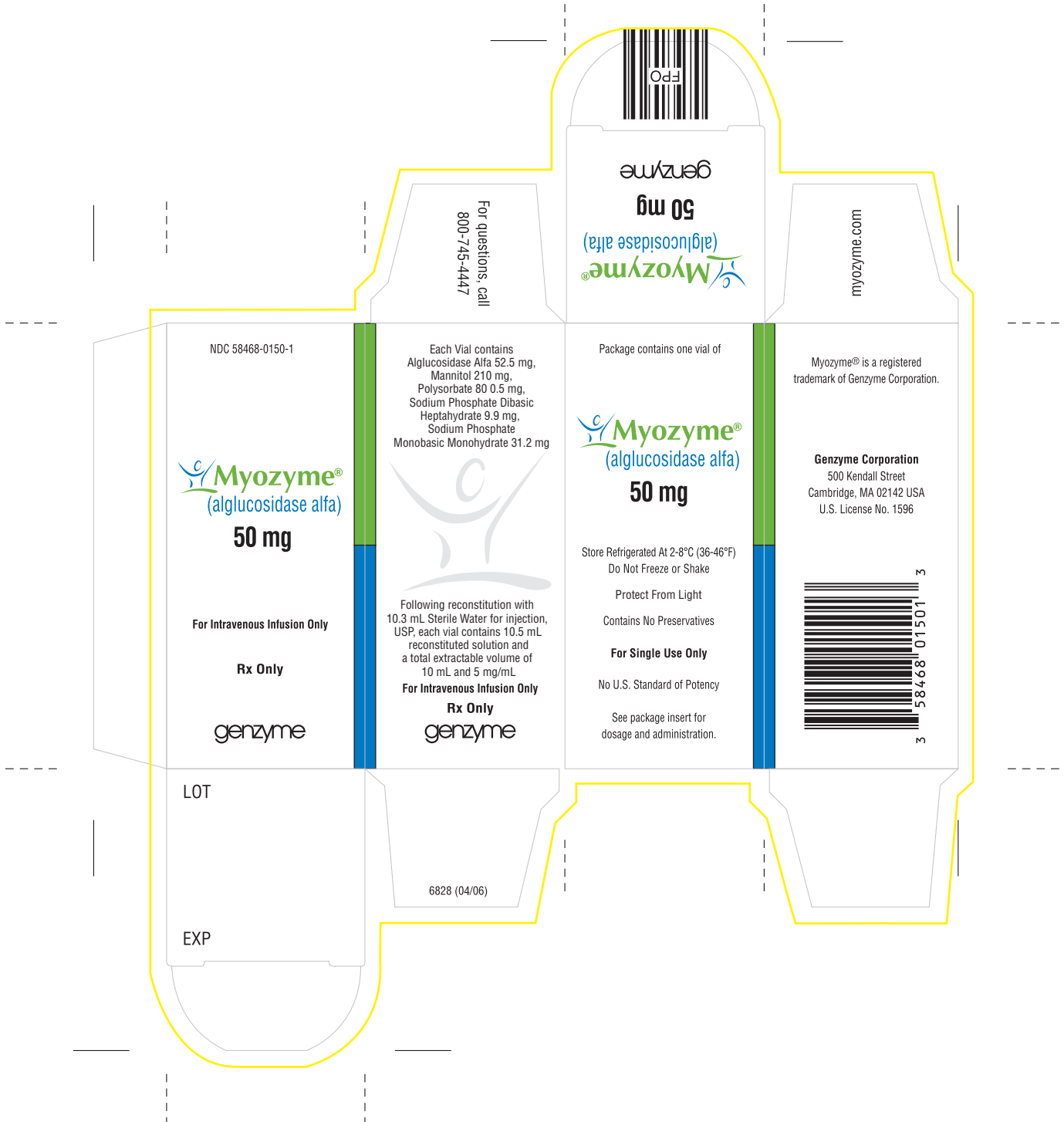
700 MYOZYME and Genzyme are registered

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Graphic Support: George Dias @ 22618

04.14.06
 USA Myozyme Carton
 Size: 1.343" x 1.343" x 3"
 6828 (04/06) r12

- PMS 369
- PMS 300
- Black
- Die Line
- Varnish



r10 04.05.06 Graphic Support: Donna DiGiacomo @ X 21651

Myozyme 50 mg label
3³/₈" x 1¹/₄" 6827 (04/06)

- PMS 369
- PMS 300
- Black
- Varnish
- Dieline/FPO Area (Do not print)

