MYOZYME® (alglucosidase alfa)

For intravenous infusion only

WARNING

Risk of Anaphylaxis

Life-threatening anaphylactic reactions have been observed in some patients during MYOZYME infusions. Therefore, appropriate medical support should be readily available when MYOZYME is administered.

Risk of Cardiorespiratory Failure

Patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to infusion reactions, and require additional monitoring.

DESCRIPTION

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

Alglucosidase alfa is a glycoprotein with a calculated mass of 99,377 daltons for the polypeptide chain, and a total mass of approximately 109,000 daltons, including carbohydrates. Alglucosidase alfa has a specific activity of 3 to 5 U/mg (one unit is defined as that amount of activity that results in the hydrolysis of 1 μmole of synthetic substrate per minute under the specified assay conditions). MYOZYME is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with 10.3 mL Sterile Water for Injection, USP. Each 50 mg vial contains 52.5 mg alglucosidase alfa, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate, 31.2 mg sodium phosphate monobasic monohydrate. Following reconstitution as directed, each vial contains 10.5 mL reconstituted solution and a total extractable volume of

10 mL at 5.0 mg/mL alglucosidase alfa. MYOZYME does not contain preservatives; each vial is for single use only.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

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

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

Pharmacokinetics

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

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

Pharmacokinetic Parameter	20 mg/kg (n=5)	40 mg/kg (n=8)
Cmax (mcg/mL)	162 ± 31	276 ± 64
AUC_{∞} (mcg-hr/mL)	811 ± 141	1781 ± 520
CL (mL/hr/kg)	25 ± 4	24 ± 7
Vss (mL/kg)	96 ± 16	119 ± 28
$t_{1/2}$ (hr)	2.3 ± 0.4	2.9 ± 0.5

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

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

CLINICAL STUDIES

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

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

Efficacy was assessed by comparing the proportions of MYOZYME-treated patients who died or needed invasive ventilator support with the mortality experience of an

historical cohort of untreated infantile-onset Pompe patients with similar age and disease severity. In the historical cohort, 61 untreated patients with infantile-onset Pompe disease diagnosed by age 6 months, born between 1982 and 2002, were identified by a retrospective review of medical charts. By the age of 18 months, only one of the 61 historical control patients was alive (98% mortality), indicating the poor outcome of patients who are left untreated.

Within the first 12 months of treatment, 3 of 18 MYOZYME-treated patients required invasive ventilatory support (17%, with 95% confidence interval 4% to 41%); there were no deaths. With continued treatment beyond 12 months, 4 additional patients required invasive ventilatory support, after receiving between 13 and 18 months of MYOZYME treatment; 2 of these 4 patients died after receiving 14 and 25 months of treatment, and after receiving 11 days and 7.5 months of invasive ventilatory support, respectively. No other deaths have been reported through a median follow-up of 20 months, and all 16 surviving patients continue to be followed. Survival without invasive ventilatory support was substantially greater in the MYOZYME-treated patients in this study than would be expected compared to the poor survival of the historical control patients. No differences in outcome were observed between patients who received 20 mg/kg versus 40 mg/kg.

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

Changes from baseline to Month 12 in left ventricular mass index (LVMI), an evaluation of bioactivity, were measured by echocardiography. For the 15 patients with both baseline and Month 12 echocardiograms, all had

decreases from baseline in LVMI (mean decrease 118 g/m^2, range 45 to 193 g/m^2). The magnitude of the decrease in LVMI did not correlate with the clinical outcome measure of ventilator-free survival.

Study 2 is an ongoing, international, multicenter, non-randomized, open-label clinical trial that enrolled 21 patients who were ages 3 months to 3.5 years at first treatment. All patients received 20 mg/kg MYOZYME every other week for up to 104 weeks. Five of 21 patients were receiving invasive ventilatory support at the time of first infusion.

The primary outcome measure was the proportion of patients alive at the conclusion of treatment. At the 52–week interim analysis, 16 of 21 patients were alive. Sixteen patients were free of invasive ventilatory support at the time of first infusion: of these, 4 died, 2 required invasive ventilatory support, and 10 were free of invasive ventilatory support after 52 weeks of treatment. For the 5 patients who were receiving invasive ventilatory support at baseline, 1 died, and 4 remained on invasive ventilatory support at Week 52. The status of patients at Week 52 overlapped with that of an untreated historical group of patients, and no effect of MYOZYME treatment could be determined.

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

None known.

WARNINGS

Anaphylaxis and Allergic Reactions (see BOXED WARNING)

Life-threatening and severe allergic reactions have been reported in some patients during and within three hours after MYOZYME infusion. Reactions have included anaphylactic shock, cardiac arrest, respiratory distress, hypotension, bradycardia, hypoxia, bronchospasm, throat tightness, dyspnea, angioedema, and urticaria.

Interventions have included cardiopulmonary resuscitation, mechanical ventilatory support, oxygen supplementation, intravenous (IV) fluids, hospitalization, treatment with inhaled beta-adrenergic agonists, epinephrine, and IV corticosteroids.

In clinical trials and postmarketing safety experience with MYOZYME, approximately 1% of patients developed anaphylactic shock and/or cardiac arrest during MYOZYME infusion that required life-support measures. In clinical trials and expanded access programs with MYOZYME, approximately 14% patients treated with MYOZYME have developed allergic reactions that involved at least 2 of 3 body systems, cutaneous, respiratory or cardiovascular systems. These events included: Cardiovascular: hypotension, cyanosis, hypertension, tachycardia, ventricular extrasystoles, bradycardia, pallor, flushing, nodal rhythm, peripheral coldness; Respiratory: tachypnea, wheezing/bronchospasm, rales, throat tightness, hypoxia, dyspnea, cough, respiratory tract irritation, oxygen saturation decreased; Cutaneous: angioedema, urticaria, rash, erythema, periorbital edema, pruritus, hyperhidrosis, cold sweat, livedo reticularis (see **ADVERSE REACTIONS**).

If anaphylactic or other severe allergic reactions occur, immediate discontinuation of the administration of MYOZYME should be considered, and appropriate medical treatment should be initiated. Because of the potential for severe allergic reactions, appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when MYOZYME is administered.

The risks and benefits of re-administering MYOZYME following an anaphylactic or severe allergic reaction should be considered. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product.

Risk of Acute Cardiorespiratory Failure (see BOXED WARNING)

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed up to 72 hours after infusion with MYOZYME in infantile-onset Pompe disease patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous

administration of MYOZYME (see **Instructions for Use: Reconstitution, dilution and administration** for information on appropriate infusion volumes). Patients with an acute illness at the time of MYOZYME infusion may be at greater risk for experiencing acute cardiorespiratory failure. Appropriate medical support and monitoring measures should be readily available during MYOZYME infusion, and infants with cardiac dysfunction may require prolonged observation times that should be individualized based on the needs of the patient.

Risk of Cardiac Arrhythmia and Sudden Cardiac Death During General Anesthesia for Central Venous Catheter Placement

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

Caution should be used when administering general anesthesia for the placement of a central venous catheter in infantile-onset Pompe disease patients with cardiac hypertrophy.

Infusion Reactions

Infusion reactions occurred in 20 of 39 (51%) of patients treated with MYOZYME in clinical studies (see **ADVERSE REACTIONS**). Some reactions were severe. Severe infusion reactions reported in more than 1 patient in clinical studies and the expanded access program included fever, decreased oxygen saturation, tachycardia, cyanosis and hypotension. Other infusion reactions reported in more than 1 patient in clinical studies and the expanded access program included rash, flushing, urticaria, fever, cough, tachycardia, decreased oxygen saturation, vomiting, tachypnea, agitation, increased blood pressure/hypertension, cyanosis, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face edema, feeling hot, headache, hyperhidrosis, increased lacrimation, livedo reticularis, nausea, periorbital edema, restlessness and wheezing. Some patients were pre-

treated with antihistamines, antipyretics and/or steroids. Infusion reactions occurred in some patients after receiving antipyretics, antihistamines, or steroids. Infusion reactions may occur at any time during, or up to 2 hours after, the infusion of MYOZYME, and are more likely with higher infusion rates.

Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from infusion reactions. Therefore, these patients should be monitored more closely during administration of MYOZYME. Patients with an acute illness at the time of MYOZYME infusion may be at greater risk for infusion reactions. Careful consideration should be given to the patient's clinical status prior to administration of MYOZYME.

Patients may be treated with antipyretics and/or antihistamines prior to infusion. If an infusion reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of antihistamines, and/or antipyretics may ameliorate the symptoms (see **ADVERSE REACTIONS**). If severe infusion reactions occur, immediate discontinuation of the administration of MYOZYME should be considered, and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. Because of the potential for severe infusion reactions, appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when MYOZYME is administered. Patients who have experienced infusion reactions should be treated with caution when readministered MYOZYME.

PRECAUTIONS

Immune Mediated Reactions

Severe cutaneous and systemic immune mediated reactions have been reported in postmarketing safety experience with MYOZYME in at least 2 patients, including ulcerative and necrotizing skin lesions, and possible type III immune complex-mediated reactions. These reactions occurred several weeks to 3 years after initiation of MYOZYME infusions. Skin biopsy in one

patient demonstrated deposition of anti-rh-GAA antibodies in the lesion. Another patient developed severe inflammatory arthropathy in association with fever and elevated erythrocyte sedimentation rate. Patients should be monitored for the development of systemic immune complex-mediated reactions involving skin and other organs while receiving MYOZYME.

Information for Patients

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

Laboratory Tests

Patients should be monitored for IgG antibody formation every 3 months. There are no marketed tests for antibodies against alglucosidase alfa. Contact your local Genzyme representative or Genzyme Corporation at 1-800-745-4447 for information on testing and to obtain a sample collection box.

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

Drug Interactions

No drug interaction studies have been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

Pregnancy: Teratogenic Effects: Pregnancy Category B.

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

ADVERSE REACTIONS

The most serious adverse reactions reported with MYOZYME were anaphylactic reactions, acute cardiorespiratory failure, and cardiac arrest.

Anaphylactic reactions have been reported during and within 3 hours after MYOZYME infusion (see **BOXED WARNING: Risk of Anaphylaxis** and **WARNINGS: Anaphylaxis and Allergic Reactions**).

Acute cardiorespiratory failure, possibly associated with fluid overload, has been reported in infantile-onset Pompe disease patients, and pre-existing cardiac hypertrophy likely contributed to the severity of the reaction (see **BOXED WARNING: Risk of Cardiorespiratory Failure** and **WARNINGS: Risk of Acute Cardiorespiratory Failure** and **Instructions for Use: Reconstitution, dilution and administration** for information on appropriate infusion volumes).

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

The most common treatment-emergent adverse reactions (regardless of relationship) were fever, diarrhea, rash, vomiting, cough, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis and decreased oxygen saturation.

The most common adverse reactions requiring intervention were infusion reactions (see **WARNINGS: Infusion Reactions**). Twenty of 39 patients (51%) treated with MYOZYME in clinical studies developed infusion reactions during the infusion or during the 2 hours following infusion. The majority of infusion reactions were mild to moderate. Infusion reactions reported in more than 1 patient in clinical studies and the expanded access program include rash, flushing, urticaria, fever, cough, tachycardia, decreased oxygen saturations, vomiting,

tachypnea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face edema, feeling hot, headache, hyperhidrosis, increased lacrimation, livedo reticularis, nausea, periorbital edema, restlessness and wheezing. Most infusion reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administration of antipyretics, antihistamines, or steroids.

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

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

Table 2 enumerates treatment-emergent adverse reactions (regardless of relationship) that occurred in at least 20% of patients treated with MYOZYME in clinical trials described above. Reported frequencies of adverse events have been classified by MedDRA terms.

Table 2. Summary of Adverse Reactions (regardless of relationship) by System Organ Class and Preferred Term Occurring in at Least 20% of Patients Treated 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

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

In postmarketing experience with MYOZYME, severe and serious infusion reactions have been reported, some of which were life-threatening, including anaphylactic shock (see **BOXED WARNING: Risk of Anaphylaxis**, and **WARNINGS: Anaphylaxis and Allergic Reactions**). Acute cardiorespiratory failure, possibly associated with fluid overload, has been reported in infantile-onset Pompe disease patients with pre-existing hypertrophic cardiomyopathy (see **BOXED WARNING: Risk of Cardiorespiratory failure** and **WARNINGS: Risk of Acute Cardiorespiratory Failure**). In addition to the infusion reactions reported in clinical trials and expanded access programs, the following infusion reactions have been reported in patients during postmarketing use of MYOZYME; cardiac arrest, pharyngeal edema, peripheral edema, chest pain, chest discomfort, muscle spasm, fatigue and conjunctivitis (see **WARNINGS: Anaphylaxis and Allergic Reactions** and **Infusion Reactions**). Systemic and cutaneous immune mediated reactions, including ulcerative and necrotizing skin lesions have been reported (see **PRECAUTIONS: Immune Mediated Reactions**).

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a casual relationship to drug exposure.

Immunogenicity

The majority of patients (34 of 38; 89%) in the two clinical trials tested positive for IgG antibodies to alglucosidase alfa. The data reflect the percentage of patients whose test results were considered positive for antibodies to alglucosidase alfa using an enzyme-linked immunosorbent assay (ELISA) and radioimmunoprecipitation (RIP) assay for alglucosidase

alfa-specific IgG antibodies. Most patients who develop antibodies do so within the first 3 months of exposure. There is evidence to suggest that patients developing sustained titers ≥12,800 of anti-alglucosidase alfa antibodies may have a poorer clinical response to treatment, or may lose motor function as antibody titers increase. Treated patients who experience a decrease in motor function should be tested for neutralization of enzyme uptake or activity. Five patients with antibody titers ≥ 12,800 at Week 12 had an average increase in clearance of 50% from Week 1 to Week 12 (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

The effect of antibody development on the long-term efficacy of MYOZYME is not fully understood. There is an observation that some patients who develop high and sustained anti-alglucosidase alfa antibody titers, including those who possess 2 null mutations, have a poorer clinical response.

Some IgG-positive patients in clinical trials and on commercial therapy who were evaluated for the presence of inhibitory antibodies tested positive for inhibition of enzyme activity and/or uptake in *in vitro* assays.

Infusion reactions were reported in 20 of 39 patients (51%) treated with MYOZYME in clinical studies and appear to be more common in antibody-positive patients: 8 of 15 patients with high antibody titers experienced infusion reactions whereas none of 3 antibody-negative patients experienced infusion reactions (see **WARNINGS: Infusion Reactions**).

Patients in clinical trials, expanded access programs and on commercial therapy have undergone testing for MYOZYME-specific IgE antibodies. Testing was performed for infusion reactions, especially moderate to severe or recurrent reactions, for which mast-cell activation was suspected. A small number of these patients tested positive for MYOZYME-specific IgE-binding antibodies, some of whom experienced an anaphylactic reaction (see **BOXED WARNING: Risk of Anaphylaxis** and **WARNINGS: Anaphylaxis and Allergic Reactions**).

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

Table 3. 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)
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
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	1000	50	150	250	350

Instructions for Use

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

Reconstitution, dilution and administration

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

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

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

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

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

   Example: Patient weight (16 kg) x dose (20 mg/kg) = patient dose (320 mg)

   320 mg divided by 50 mg/vial = 6.4 vials; therefore, 7 vials should be reconstituted

   Remove the required number of vials from the refrigerator and allow them to reach room temperature prior to reconstitution (approximately 30 minutes).

2. Reconstitute each MYOZYME vial by **slowly** injecting 10.3 mL of Sterile Water for Injection, USP to the inside wall of each vial. Each vial will yield 5 mg/mL. The total extractable dose per vial is 50 mg per 10 mL. Avoid forceful impact of the water for injection on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilized cake. Tilt and roll each vial gently. Do not invert, swirl, or shake.

3. The reconstituted MYOZYME solution should be protected from light.

4. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection opaque particles are observed or if the solution is discolored

do not use. The reconstituted solution may occasionally contain some alglucosidase alfa particles (typically less than 10 in a vial) in the form of thin white strands or translucent fibers subsequent to the initial inspection. This may also happen following dilution for infusion. These particles have been shown to contain alglucosidase alfa and may appear after the initial reconstitution step and increase over time. Studies have shown that these particles are removed via in-line filtration without having a detectable effect on the purity or strength.

5. MYOZYME should be diluted in 0.9% Sodium Chloride for Injection, USP, immediately after reconstitution, to a final MYOZYME concentration of 0.5 to 4 mg/mL. See Table 3 for the recommended total infusion volume based on patient weight.

6. Slowly withdraw the reconstituted solution from each vial. Avoid foaming in the syringe.

7. Remove airspace from the infusion bag to minimize particle formation due to the sensitivity of MYOZYME to air-liquid interfaces.

8. Add the reconstituted MYOZYME solution slowly and directly into the sodium chloride solution. Do not add directly into airspace that may remain within the infusion bag. Avoid foaming in the infusion bag.

9. Gently invert or massage the infusion bag to mix. Do not shake.

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

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

Storage

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

The reconstituted and diluted solution should be administered without delay. If immediate use is not possible, the reconstituted and diluted solution is stable for up to 24 hours at 2° to 8°C (36° to 46°F). Storage of the reconstituted solution at room temperature is not recommended. The reconstituted and diluted MYOZYME solution should be protected from light. DO NOT FREEZE OR SHAKE.

HOW SUPPLIED

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

NDC 58468-0150-1
Rx Only

MYOZYME is manufactured and distributed by:
Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
1-800-745-4447

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