HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MYOZYME safely and effectively. See full prescribing information for MYOZYME.

MYOZYME® (alglucosidase alfa)
Injectable for intravenous infusion
Initial U.S. Approval: 2006

WARNING: ANAPHYLAXIS, SEVERE ALLERGIC AND IMMUNE MEDIATED REACTIONS and RISK OF CARDIORESPIRATORY FAILURE

- **Life-threatening anaphylactic, severe allergic and immune mediated 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.
  See Warnings and Precautions (5)

----------INDICATIONS AND USAGE----------
MYOZYME® (alglucosidase alfa) is a lysosomal glycogen-specific enzyme 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. (1)

----------DOSAGE AND ADMINISTRATION----------
- The recommended dosage of MYOZYME 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.
- Dosage strength: 5 mg/mL. (3)

----------CONTRAINDICATIONS----------
- None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Life-threatening anaphylactic, severe allergic and immune mediated reactions: Ensure that appropriate medical support is readily available. If severe allergic or anaphylactic reactions occur, consider immediate discontinuation of MYOZYME 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. (5.3)
- Cardiac arrhythmias and sudden cardiac death during general anesthesia: Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for MYOZYME infusion. (5.4)

----------ADVERSE REACTIONS----------
- The most common serious treatment-emergent adverse reactions (occurring in > 10% of patients) observed in clinical studies with MYOZYME were pneumonia, respiratory failure, respiratory distress, catheter-related infection, respiratory syncytial virus infection, gastroenteritis and fever. (6.1)
- The most common reactions requiring intervention were infusion reactions. (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, 17)
- Nursing Mothers: Physicians are encouraged to enroll nursing patients in the Pompe Registry. (8.3, 17)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

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FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLAXIS, SEVERE ALLERGIC AND IMMUNE MEDIATED REACTIONS and RISK OF CARDIORESPIRATORY FAILURE

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

Risk of Cardiorespiratory Failure
Patients with compromised cardiac or respiratory function may be at risk for serious acute exacerbation of their cardiac or respiratory compromise due to infusion reactions, and require additional monitoring. ***[see Warnings and Precautions (5.2)]***

1 INDICATIONS AND USAGE

MYOZYME® (alglucosidase alfa) *[see Description (11)]* is a lysosomal glycogen-specific enzyme 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 (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dosage regimen of MYOZYME is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion.

2.2 Instructions for Use

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

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 1 below for the rate of infusion at each step, expressed as mL/hr based on the recommended infusion volume by patient weight.

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)
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

Reconstitution, dilution and administration

MYOZYME should be reconstituted, diluted and administered by a healthcare 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 1 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.

10. Administer MYOZYME using an in-line low protein-binding 0.2 μm filter.

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

MYOZYME does not contain any preservatives. Vials are single-use only. Discard any unused product.

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Allergic Reactions

(see Boxed Warning)

Anaphylaxis and severe allergic reactions have been reported in some patients during and up to three hours after MYOZYME infusion, some of which were IgE-mediated. Some of the reactions were life-threatening and 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 *[see Adverse Reactions (6)]*.

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% of 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, decreased oxygen saturation; Cutaneous: angioedema, urticaria, rash, erythema, periorbital edema, pruritus, hyperhidrosis, cold sweat, livedo reticularis *[see Adverse Reactions (6)]*.

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. Some patients have been rechallenged and have continued to receive MYOZYME under close clinical supervision. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product *[see Adverse Reactions (6.3)]*.

5.2 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 mediated reactions *[see Adverse Reactions (6.3)]*. 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. Nephrotic syndrome secondary to membranous glomerulonephritis was observed in a few Pompe patients treated with alglucosidase alfa and who had persistently positive anti-rhGAA IgG antibody titers *[see Adverse Reactions (6.3)]*. In these patients renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption. It is therefore recommended to perform periodic urinalysis.

Patients should be monitored for the development of systemic immune mediated reactions involving skin and other organs while receiving MYOZYME. If immune mediated reactions occur, discontinuation of the administration of MYOZYME should be considered, and appropriate medical treatment initiated. The risks and benefits of re-administering alglucosidase alfa following an immune mediated reaction should be considered. Some patients have successfully been rechallenged and have continued to receive alglucosidase alfa under close clinical supervision.

5.3 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 (2.2)]*. Patients with acute underlying respiratory illness, compromised cardiac function and/or sepsis may be at risk of serious exacerbation of their cardiac or respiratory compromise during infusions. 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 *[see Dosage and Administration (2.2)]*.

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

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

administering general anesthesia for the placement of a central venous catheter intended for MYOZYME infusion. Ventricular arrhythmias 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 during general anesthesia for central venous catheter placement.

5.5 Infusion Reactions

Infusion reactions occurred in 20 of 39 (51%) patients treated with MYOZYME in clinical studies *[see Adverse Reactions (6)]*. 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.

If an infusion reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of antihistamines and/or antipyretics may ameliorate the symptoms. If severe infusion or allergic reactions occur, immediate discontinuation of the administration of MYOZYME should be considered, and appropriate medical treatment should be initiated

[see Adverse Reactions (6.1)]. Severe infusion reactions are generally managed with infusion interruption, administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. Patients who have experienced infusion reactions should be treated with caution when they are re-administered MYOZYME.

5.6 Monitoring: Laboratory Tests

Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter. Testing for IgG titers may also be considered if patients develop allergic or other immune mediated reactions. Patients who experience anaphylactic or allergic reactions may also be tested for IgE antibodies to alglucosidase alfa and other mediators of anaphylaxis.

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. Liver enzymes should be evaluated prior to the initiation of MYOZYME treatment and periodically thereafter.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

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

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 and Warnings and Precautions (5.1)]*.

Acute cardiorespiratory failure has been observed in a few infantile-onset Pompe disease patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of alglucosidase alfa *[see Boxed Warning and Warnings and Precautions (5.2) and Instructions for Use (2.2)]*.

The most common serious treatment-emergent adverse reactions occurring in > 10% of patients 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 adverse reactions requiring intervention in clinical trials were infusion reactions *[see Warnings and Precautions (5.4)]*. Twenty of 39 patients (51%) treated with MYOZYME in clinical studies developed infusion reactions. Infusion reactions, defined as an adverse reaction occurring during the infusion or within 2 hours after completion of the infusion, that occurred 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.

The most common treatment-emergent adverse reactions occurring in ≥ 20% of patients were fever, diarrhea, rash, vomiting, cough, pneumonia, otitis media, upper respiratory tract infection, gastroenteritis and decreased oxygen saturation.

Table 2 enumerates treatment-emergent adverse reactions 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 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 reactions observed with MYOZYME treatment in this study were headache (4.1%), pharyngitis (9.1%), upper abdominal pain (15.2%), malaise (6.1%) and rhinitis (6.1%).

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for 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 (12.3)]*.

Some patients who developed IgG antibodies to alglucosidase alfa in clinical studies or in the postmarketing setting were evaluated for the presence of inhibitory antibodies and tested positive for inhibition of enzyme activity and/or uptake in *in vitro* assays.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to alglucosidase alfa with the incidence of antibodies to other products may be misleading.

The effect of antibody development on the long-term efficacy of MYOZYME is not fully understood. However, CRIM-negative infants have shown poorer clinical response in the presence of high sustained IgG antibody titers and positive inhibitory antibodies.

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 and Precautions (5.4)]*.

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

6.3 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of MYOZYME. 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 causal relationship to drug exposure.

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 and Warnings and Precautions (5.1)]*. 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 and Warning and Precautions (5.2)]*. 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, respiratory arrest, apnea, stridor, pharyngeal edema, peripheral edema, chest pain, chest discomfort, muscle spasm, fatigue and conjunctivitis *[see Warnings and Precautions (5.1) and (5.4)]*. Additional adverse drug reactions included proteinuria and nephrotic syndrome *[see Warnings and Precautions (5.5)]*.

Systemic and cutaneous immune mediated reactions, including ulcerative and necrotizing skin lesions, and nephrotic syndrome secondary to membranous glomerulonephritis have been reported in postmarketing safety experience with alglucosidase alfa *[see Warnings and Precautions (5.5)]*.

7 DRUG INTERACTIONS

7.1 Interference with Other Drugs

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B. Reproduction studies have been performed in pregnant mice at intravenous doses up to 40 mg/kg/day (plasma AUC of 64.6 mg•min/mL, 0.4 times the human steady-state exposure at the recommended bi-weekly dose) and pregnant rabbits at intravenous doses up to 40 mg/kg/day (plasma AUC of 85 mg•min/mL, 0.5 times the human steady-state exposure at the recommended bi-weekly dose) and have 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 Registry *[see Patient Counseling Information (17)]*.

8.2 Labor and Delivery

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

8.3 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. Nursing women are encouraged to enroll in the Pompe Registry *[see Patient Counseling Information (17)]*.

8.4 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 (14)]*. 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.

8.5 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 *[see Clinical Studies (14)]*.

10 OVERDOSAGE

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

11 DESCRIPTION

MYOZYME (alglucosidase alfa), a lysosomal glycogen-specific enzyme, 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. The MYOZYME manufacturing process differs from that for LUMIZYME®, resulting in differences in some product attributes. 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 110 kilo 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.

12 CLINICAL PHARMACOLOGY

12.1 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.

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.

12.3 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. Based on the pharmacokinetic blood samples collected for 12 hours after a 4-hr intravenous infusion of 20 mg/kg (n=5), the estimated mean AUC was 811 mcg•hr/mL with 17% coefficient of variation [CV], C_{max} 162 mcg/mL with 19% CV, clearance 25 mL/hr/kg with 16% CV, and half-life 2.3 hr with 17% CV.

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.

13 NONCLINICAL TOXICOLOGY

13.1 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 (plasma AUC of 64.6 mg•min/mL, 0.4 times the human steady-state exposure at the recommended bi-weekly dose) had no effect on fertility and reproductive performance in mice.

14 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).

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 were reported through a median

follow-up of 20 months. Survival without invasive ventilatory support was greater in the MYOZYME-treated patients (83%) as compared with overall survival in the historical control group (2%). 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 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 was an 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

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.

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.

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17 PATIENT COUNSELING INFORMATION

17.1 Pompe Registry

Patients and their caregivers should be informed that a registry for patients with Pompe disease (the Pompe Registry) has been established in order to better understand the variability and progression of Pompe disease and to continue to monitor and evaluate long-term treatment effects of alglucosidase alfa. The Pompe Registry will also monitor the effects of alglucosidase alfa on pregnant women and their offspring *[see Use in Specific Populations (8)]*. Patients and their caregivers are encouraged to participate in the Pompe Registry and should be advised that their participation is voluntary and may involve long-term follow-up. For information regarding the registry program visit www.pomperegistry.com or call 1-800-745-4447.

17.2 General Clinical Recommendations

Patients and caregivers should be informed that anaphylactic reactions, severe allergic reactions, and immune mediated reactions have been observed in some patients having received MYOZYME infusions. Patients and caregivers should also be warned of the risk for acute cardiorespiratory failure, cardiac

arrhythmias, and infusion reactions *[see Boxed Warning and Warnings and Precautions (5)]*.

MYOZYME is manufactured and distributed by:
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