

About Myozyme

What is Myozyme?

Myozyme® (alglucosidase alfa) is an enzyme replacement therapy that works by replacing acid alpha-glucosidase (GAA), an enzyme that is either missing or does not function properly in people with Pompe disease. Myozyme, recombinant human GAA, is administered intravenously. Myozyme received approval from the U.S. Food and Drug Administration (FDA) on April 28, 2006. It is the first and only approved treatment for Pompe disease. Pompe disease affects both children and adults. Though age of onset and rate of disease progression vary widely among patients, Pompe disease is generally characterized by progressive skeletal and respiratory muscle weakness, as well as cardiomyopathy in infants. Clinical manifestations can present at any age.

Myozyme 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.

The product labeling includes a **boxed warning** increasing the prominence of information about the potential risk of hypersensitivity reactions. The boxed statement includes the following information: “Life-threatening anaphylactic reactions, including anaphylactic shock, have been observed in patients during Myozyme infusion. Because of the potential for severe infusion reactions, appropriate medical support measures should be readily available when Myozyme is administered.”

The most common serious treatment-emergent adverse events (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. Please see full prescribing information for complete product information.

How does Myozyme work?

Pompe disease is caused by a deficiency or absence of an enzyme that occurs naturally in cell lysosomes. This deficiency causes glycogen to accumulate within cell lysosomes, resulting eventually in lysosomal breakdown and consequently progressive muscle damage. Myozyme replaces the missing enzyme that causes Pompe disease, making it possible for patients to process glycogen.

Myozyme is administered through an IV infusion over approximately 4 hours. The recommended dosage regimen of Myozyme is 20 mg/kg body weight every two weeks.

What clinical studies were conducted to gain approval for Myozyme?

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/m², range 45 to 193 g/m²). 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.

How long has Myozyme been studied?

Genzyme Corporation began development of Myozyme in 2001 and clinical studies were initiated in 2003.

What are the possible side effects of Myozyme?

In clinical trials and expanded access programs with Myozyme, 38 of 280 (approximately 14%) patients treated with Myozyme have developed infusion reactions that involved at least two of three 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: angioneurotic edema, urticaria, rash, erythema, periorbital edema, pruritus, hyperhidrosis, cold sweat, livedo reticularis. Of these cases, 8 patients experienced severe or significant hypersensitivity reactions.

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.

Acute cardiorespiratory failure requiring intubation and inotropic support has been observed after infusion with Myozyme in one infantile-onset Pompe disease patient with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of Myozyme. (See full prescribing information for information on appropriate infusion volumes.)

The most common adverse reactions requiring intervention were infusion-related reactions which occurred in 20 of 39 (51%) of patients treated with Myozyme in clinical studies. Some reactions were severe. Severe infusion reactions reported in more than one patient in clinical studies and the expanded access program included pyrexia, decreased oxygen saturation, tachycardia, cyanosis, and hypotension. Other infusion reactions reported as mild to moderate in more than one patient in clinical studies and the expanded access program included rash, flushing, urticaria, pyrexia, cough, tachycardia, decreased oxygen saturation, vomiting, tachypnea, agitation, increased blood pressure, cyanosis, hypertension, irritability, pallor, pruritus, retching, rigors, tremor, hypotension, bronchospasm, erythema, face edema, feeling hot, headache, hyperhidrosis, lacrimation increased, 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 two 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.



Please see accompanying full prescribing information including boxed warning.

For more information on Pompe disease, please visit www.pompe.com. For information about Myozyme, please visit www.myozyme.com.

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