HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LUMIZYME safely and effectively. See full prescribing information for LUMIZYME. LUMIZYME® (alglucosidase alfa), for injection, for intravenous use

Initial U.S. Approval: 2010

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, AND RISK OF CARDIORESPIRATORY FAILURE

See full prescribing information for complete boxed warning.

• Life-threatening anaphylactic reactions and severe hypersensitivity reactions have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur. (5.1, 5.2)
• Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring. (5.3)

RECENT MAJOR CHANGES

Warnings and Precautions (5.2, 5.5, 5.6) 02/2020

INDICATIONS AND USAGE

LUMIZYME® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency). (1)

• 20 mg per kg body weight administered every 2 weeks as an intravenous infusion. (2)

DOSEAGE AND ADMINISTRATION

DOSAGE FORMS AND STRENGTHS

For injection: 50 mg of alglucosidase alfa as lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

• Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. Ensure that appropriate medical support measures, including cardiopulmonary resuscitation equipment, are readily available. If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue infusion and initiate appropriate medical treatment. (5.1)
• Immune-Mediated Reactions: Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs. (5.2)
• Risk of Acute Cardiorespiratory Failure: Patients with compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion. (5.3)
• Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement: Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion. (5.4)
• Risk of Antibody Development: Patients with infantile-onset Pompe disease should have a cross-reactive immunologic material (CRIM) assessment early in their disease course and be managed by a clinical specialist knowledgeable in immune tolerance induction in Pompe disease to optimize treatment. (5.5)

ADVERSE REACTIONS

The most frequently reported adverse reactions (≥5%) in clinical trials were hypersensitivity reactions and included: anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hypertension, pain, chest discomfort, nausea, cough, decreased oxygen saturation, tachycardia, rash, and dyspnea. (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.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2020
2.3 Reconstitution, Dilution, and Administration

Alglucosidase alfa should be reconstituted, diluted, and administered by a healthcare professional. Use aseptic technique during preparation. Do not use filter needles during preparation.

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

\[
\text{Patient weight (kg)} \times \text{dose (mg/kg)} = \text{patient dose (in mg)}
\]

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 (68 kg) \times \text{dose (20 mg/kg)} = \text{patient dose (1,360 mg)}

1,360 mg divided by 50 mg/vial = 27.2 vials; therefore, 28 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).

b. Reconstitute each alglucosidase alfa vial by slowly injecting 10.3 mL of Sterile Water for Injection, USP to the inside wall of each vial. Each vial will yield a concentration of 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-drip-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, swivel, or shake.

c. The reconstituted alglucosidase alfa solution should be protected from light.

d. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discoloration. If upon reconstituted alglucosidase alfa concentration of 0.5 to 4 mg/mL. See Table 1 for the recommended total infusion volume based on patient weight.

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

2.4 DOSAGE FORMS AND STRENGTHS

For injection: 50 mg of alglucosidase alfa is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder in a single-dose vial for reconstitution. After reconstitution, the resultant solution concentration is 5 mg/mL.

2.5 CONTRAINDICATIONS

None.

3.1 Anaphylaxis and Hypersensitivity Reactions

Anaphylaxis and hypersensitivity reactions have been observed in patients during and up to 3 hours after alglucosidase alfa infusion. Some of the reactions were life-threatening and included anaphylactic shock, cardiac arrest, respiratory arrest, respiratory distress, hypotension, anaphylaxis, angioedema (including tongue or lip swelling, periorbital edema, and face edema), and urticaria. Other accompanying reactions included chest discomfort/pain, wheezing, tachycardia, cyanosis, decreased oxygen saturation, convulsions, vomiting, diaphoresis, hypotension, increased blood pressure, flushing, feeling hot, erythema, pyrexia, pallor, peripheral coldness, restlessness, nervousness, headache, back pain, and pruritis. Some of the reactions were IgE-mediated.

If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue administration of alglucosidase alfa, and initiate appropriate medical treatment. Severe reactions are generally managed with infusion interruption, administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylaxis, epinephrine has been administered. Appropriate medical support, including cardiopulmonary resuscitation equipment, should be readily available when alglucosidase alfa is administered.

The risks and benefits of readministering alglucosidase alfa following an anaphylactic or hypersensitivity reaction should be considered. Some patients have been rechallenged and have continued to receive alglucosidase alfa under close clinical supervision. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to readminister the product [see Adverse Reactions (6.2)].

5.2 Immune-Mediated Reactions

Immune-mediated cutaneous reactions have been reported with alglucosidase alfa including necrolytic skin lesions [see Adverse Reactions (6.3)]. Systemic immune-mediated reactions, including possible type III immune-mediated reactions have been observed with alglucosidase alfa. These reactions occurred several weeks to 3 years after initiation of alglucosidase alfa infusions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion. Another patient developed severe inflammatory arthropathy in association with pyrexia and elevated erythrocyte sedimentation rate. Nephrotic syndrome secondary to membranous glomerulonephritis was observed in some Pompe disease patients treated with alglucosidase alfa who had persistently positive anti-rhGAA IgG antibody titers. In these patients, renal biopsy was consistent with immune complex glomerulonephritis. In some patients following alglucosidase alfa treatment, immune-mediated cutaneous reactions have been reported including necrosis, cutaneous vasculitis, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur [see Warnings and Precautions (5.3)].

Table 1: Recommended Infusion Volumes and Rates

<table>
<thead>
<tr>
<th>Patient Weight Range (kg)</th>
<th>Total infusion volume (mL)</th>
<th>Step 1 (mg/kg/hr)</th>
<th>Step 2 (mg/kg/hr)</th>
<th>Step 3 (mg/kg/hr)</th>
<th>Step 4 (mg/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25–10</td>
<td>50</td>
<td>3</td>
<td>8</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>10.1–20</td>
<td>100</td>
<td>5</td>
<td>15</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>20.1–30</td>
<td>150</td>
<td>8</td>
<td>23</td>
<td>38</td>
<td>53</td>
</tr>
<tr>
<td>30.1–35</td>
<td>200</td>
<td>10</td>
<td>30</td>
<td>50</td>
<td>70</td>
</tr>
<tr>
<td>35.1–50</td>
<td>250</td>
<td>13</td>
<td>38</td>
<td>63</td>
<td>88</td>
</tr>
<tr>
<td>50.1–60</td>
<td>300</td>
<td>15</td>
<td>45</td>
<td>75</td>
<td>105</td>
</tr>
<tr>
<td>60.1–100</td>
<td>500</td>
<td>25</td>
<td>75</td>
<td>125</td>
<td>175</td>
</tr>
<tr>
<td>100.1–120</td>
<td>600</td>
<td>30</td>
<td>90</td>
<td>150</td>
<td>210</td>
</tr>
<tr>
<td>120.1–140</td>
<td>700</td>
<td>35</td>
<td>105</td>
<td>175</td>
<td>245</td>
</tr>
<tr>
<td>140.1–160</td>
<td>800</td>
<td>40</td>
<td>120</td>
<td>200</td>
<td>280</td>
</tr>
<tr>
<td>160.1–180</td>
<td>900</td>
<td>45</td>
<td>135</td>
<td>225</td>
<td>315</td>
</tr>
<tr>
<td>180.1–200</td>
<td>1,000</td>
<td>50</td>
<td>150</td>
<td>250</td>
<td>350</td>
</tr>
</tbody>
</table>

3.4 RISK OF CARDIOPULMONARY ARREST DURING GENERAL ANESTHESIA FOR SURGICAL PROCEDURE

Patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring [see Warnings and Precautions (5.3)].
5.5 Risk of Antibody Development

Patients with infant-onset Pompe disease should have a cross-reactive immunologic material (CRIM) assessment early in their disease course and be managed by a clinical specialist knowledgeable in immune tolerance induction in Pompe disease to optimize treatment. Immune tolerance induction administered prior to and in conjunction with initiation of alglucosidase alfa has been reported to aid tolerability of alglucosidase alfa in CRIM-negative patients. CRIM status has been shown to be associated with immunogenicity and patients’ responses to enzyme replacement therapies. CRIM-negative infants with infant-onset Pompe disease treated with alglucosidase alfa have shown poorer clinical response in the presence of high sustained IgG antibody titers and positive inhibitory antibodies compared to CRIM-positive infants (see Adverse Reactions [6.2]).

In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment. There is evidence to suggest that some patients who develop high and sustained IgG antibody titers, including CRIM-negative patients (i.e., patients in whom no endogenous GAA protein was detected by Western blot analysis and/or predicted based on the genotype), may experience reduced clinical alglucosidase alfa treatment efficacy, such as loss of motor function, ventilator dependence, or death.

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 hypersensitivity reactions, other immune-mediated reactions, or lose clinical response. Patients who experience anaphylactic or hypersensitivity reactions, occurring in 20 of 39 (51%) patients treated with alglucosidase alfa or placebo every other week for 78 weeks (18 months). The study population included 24 males and 26 females (n=50) in the alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. Two patients receiving alglucosidase alfa discontinued the trial due to anaphylactic reactions.

Serious adverse reactions reported with alglucosidase alfa included anaphylaxis, which presented as complete respiratory failure and anaphylactic shock. Additional delayed-onset reactions occurring in alglucosidase alfa-treated patients included fatigue, myalgia, and nausea. Patients should be counseled about the possibility of delayed-onset hypersensitivity reactions and given proper follow-up instructions.

Table 3 summarizes the most common adverse reactions that occurred in at least 3% of alglucosidase alfa-treated patients and with a higher incidence than the placebo-treated patients during the randomized, double-blind, placebo-controlled trial described above.

### Table 2: Adverse Reactions Occurring in at Least 3% of Infantile-Onset Patients Treated with Alglucosidase Alfa in Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number of Patients (N=30) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperhidrosis</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>5 (16)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Chest Discomfort</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Muscle Twitching</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Flushing/Foam</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Increased Blood Pressure</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash Papular</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Throat Tightness</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

In clinical trials, anaphylaxis and hypersensitivity reactions were managed with infusion interruption, decreased infusion rate, administration of antihistamines, corticosteroids, inotropic fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reactions, epinephrine was administered. Patients who have experienced anaphylaxis or hypersensitivity reactions should be treated with caution when they are readministered alglucosidase alfa.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. 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

### Table 4: Adverse Reactions in at Least 3% of Alglucosidase Alfa-Treated Late-Onset Patients and with a Higher Incidence than the Placebo-Treated Patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Alglucosidase Alfa n=60 N (%)</th>
<th>Placebo n=30 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperhidrosis</td>
<td>5 (8.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>5 (8.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>4 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chest Discomfort</td>
<td>4 (6.7)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Muscle Twitching</td>
<td>4 (6.7)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (5.0)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Flushing/Foam</td>
<td>3 (5.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Increased Blood Pressure</td>
<td>3 (5.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (5.0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Edema, Peripheral</td>
<td>2 (3.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (3.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Rash Papular</td>
<td>2 (3.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Throat Tightness</td>
<td>2 (3.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and patient status. For these reasons, comparison of the incidence of antibodies to the studies described below with the incidence of antibodies in other studies or to other alglucosidase alfa products may be misleading.

In the two clinical trials in infantile-onset patients, the majority of patients (34 of 38; 89%) tested positive for IgG antibodies. There is evidence to suggest that some patients who develop high sustained titers of anti-alglucosidase alfa antibodies may experience reduced clinical efficacy to alglucosidase alfa treatment [see Warnings and Precautions (5.3)]. Some IgG-positive patients in clinical trials who were retrospectively evaluated for the presence of inhibitory antibodies tested positive for inhibition in vitro for uptake in CIR, and further evaluation indicated that they had shown reduced clinical effect in the presence of high sustained IgG antibody titers with inhibitory activity [see Warnings and Precautions (5.3)]. Alglucosidase alfa-treated patients who experience a decrease in motor function should be tested for the presence of inhibitory antibodies that neutralize enzyme uptake or activity.

Immunogenicity data from clinical trials and published literature in CRM-negative, infantile-onset Pompe disease patients suggest that the administration of an immune tolerance induction regimen individualized to alglucosidase alfa-naive patients may be effective in preventing or reducing the development of IgG antibodies against alglucosidase alfa. This protocol involved 150 mg/kg (n=13, 21.2 mg/kg sodium acetate) against alglucosidase alfa. In the randomized, double-blind, placebo-controlled trial in late-onset patients, all alglucosidase alfa-treated patients with available samples (n=59, 100%) developed IgG antibodies to alglucosidase alfa. These were all CRM positive, consistent with late-onset Pompe disease. Most patients who developed IgG antibodies did so within the first 3 months of exposure (median time to seroconversion was 4 weeks). There was no apparent association between mean or peak IgG antibody titers and the occurrence of adverse reactions.

Nine of the 59 evaluable patients tested positive for inhibition of enzyme activity. Antibody titers for cellular uptake inhibition were present in 18 of 59 (31%) patients by Week 78. All other patients tested negative for cellular uptake. Patients who tested positive for uptake inhibition tended to have higher IgG titers than patients who tested negative for uptake inhibition. Among the 32 patients with evaluable pharmacokinetic (PK) samples, 5 patients tested positive for uptake inhibition. The clinical relevance of this in vitro inhibition is not fully understood. The clearance values for 4 of these 5 patients were approximately 1.2-fold to 1.8-fold greater in the presence of inhibitory antibodies (Week 52) as compared to in the absence of inhibitory antibodies (Week 0) [see Clinical Pharmacology (12.3)]. Some patients in the clinical studies or in the postmarketing setting have undergone testing for alglucosidase alfa antibodies. Testing was performed in patients who experienced moderate to severe or recurrent hypersensitivity reactions, for which mast-cell activation was suspected. Some of the patients who tested positive for alglucosidase alfa-specific IgE antibodies experienced anaphylactic reactions [see Boxed Warning and Warnings and Precautions (5.1)]. Some patients who tested negative for alglucosidase alfa-specific IgE antibodies had recurrent hypersensitivity reactions that were able to be rechallenged with alglucosidase alfa using a slower infusion rate at lower starting doses and have continued to receive treatment under close clinical supervision [see Warnings and Precautions (5.3)]. Since patients who develop IgE antibodies to alglucosidase alfa appear to be at a higher risk for developing anaphylaxis and hypersensitivity reactions, these patients should be monitored more closely during administration of alglucosidase alfa.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of alglucosidase alfa. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In postmarketing experience with alglucosidase alfa, serious adverse reactions have been reported, including anaphylaxis [see Boxed Warning and Warnings and Precautions (5.1)]. Acute cardiopulmonary failure, possibly associated with fluid overload, has been reported in infantile-onset Pompe disease patients with pre-existing hypertrophic cardiomyopathy [see Boxed Warning and Warnings and Precautions (5.3)]. Recurrent infections consisting of flu-like illness or a combination of events such as pyrexia, chills, myalgia, arthralgia, pain, or fatigue occurring after completion of infusions and lasting usually for 1 to 3 days have been observed in some patients treated with alglucosidase alfa. The majority of patients were able to be rechallenged with alglucosidase alfa using lower doses and/or pretreatment with anti-inflammatory drugs and/or corticosteroids and were able to continue treatment under close clinical supervision.

In addition to the hypersensitivity reactions reported in clinical trials [see Adverse Reactions (6.1)], the following hypersensitivity reactions have been reported in at least 2 patients and included: anaphylactic shock, respiratory failure, respiratory arrest, cardiac arrest, hypotension, wheezing, convulsions, peripheral coldness, restlessness, nervousness, back pain, stridor, pharyngeal edema, abdominal pain, muscle spasm, and conjunctivitis. In addition, one case of hyperparathyroidism has been reported.

Systemic and cutaneous immune-mediated reactions, including proteinuria and nephrotic syndrome secondary to membranous glomerulonephritis, and necrotizing skin lesions have been reported in Systemic and cutaneous immune-mediated reactions, including proteinuria and nephrotic syndrome reported.

6.4 Pediatric Use

The safety and effectiveness of alglucosidase alfa have been established in pediatric patients with Pompe disease [see Warnings and Precautions (6.2)].

The safety and effectiveness of alglucosidase alfa were assessed in 57 treatment-naive infantile-onset Pompe disease patients aged 0.2 to 12.0 years of age who received alglucosidase alfa at a dose of 0.2 to 0.4 mg/kg (0.01 to 0.02 mg/kg) (median dose 0.3 mg/kg) every 2 weeks. Patients who received alglucosidase alfa for ≥12 months were eligible to continue treatment under close clinical supervision.

Anaphylaxis, hypersensitivity reactions, and acute cardiopulmonary failure have occurred in pediatric patients [see Boxed Warning, Warnings and Precautions (5.1, 5.3)]. Additionally, cardiac arrhythmia and sudden cardiac death have occurred in pediatric patients during general anesthesia for central venous catheter placement [see Warnings and Precautions (5.4)].

6.5 Geriatric Use

The randomized, double-blind, placebo-controlled study of alglucosidase alfa did not include sufficient numbers (n=6) of patients aged 65 years and over to determine whether they respond differently from younger patients [see Clinical Studies (14.1)].

DESCRIPTION

Alglucosidase alfa is a hydrolytic lysosomal glycogen-specific enzyme encoded by the predominant of the human α-glucosidase (GAA) gene. Alglucosidase alfa 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- glycoclastic 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 3.6 to 5.4 units/mg (one unit is defined as that amount of activity that results in a colorimetric change of 0.001 absorbance units at 540 nm per minute under specified assay conditions). Alglucosidase alfa is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, white for white, colorless or colorless to slightly yellow, liquid, for intravenous administration. The concentration of alglucosidase alfa is 162 mcg/mL with 19% coefficient of variation (CV), clearance was 25 mL/hr/kg with 16% CV, and half-life was 2.3 hours.

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Clinical pharmacodynamic studies have not been conducted for alglucosidase alfa.

12.3 Pharmacokinetics

The pharmacokinetics of alglucosidase alfa was evaluated in 13 patients with infantile-onset Pompe disease aged 1 month to 7 months who received 20 mg/kg (approximately a 4-hour infusion) or 50 mg/kg (approximately as a 6.5-hour infusion) of alglucosidase alfa 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 mean alglucosidase alfa concentration in plasma for 12 hours after a 4-hour 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} was 162 mcg/mL with 19% CV, clearance was 25 mL/hr/kg with 16% CV, and half-life was 2.3 hours with 17% CV.

The pharmacokinetics of alglucosidase alfa was also evaluated in a separate trial of 14 patients with infantile-onset Pompe disease, aged 6 months to 3.5 years, who received 20 mg/kg of alglucosidase alfa as a 4-hour infusion every 2 weeks. The pharmacokinetic parameters were similar to those observed for the infantile-onset Pompe disease patients aged 1 month to 7 months who received the 20 mg/kg dose.
Nineteen of 21 patients who received treatment with alglucosidase alfa 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 alglucosidase alfa. Intravenous administration of alglucosidase alfa every other day in mice at doses up to 40 mg/kg (0.4 times the human AUC at the recommended biweekly dose) had no effect on fertility and reproductive performance.

14 CLINICAL STUDIES

14.1 Clinical Trials in Infantile-Onset Pompe Disease

The safety and efficacy of alglucosidase alfa were assessed in 37 treatment-naive infantile-onset Pompe disease patients, aged 0.2 months to 3.5 years at first infusion, in three separate clinical trials. 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 1:1 to receive either 20 mg/kg or 40 mg/kg alglucosidase alfa every two weeks, with length of treatment ranging from 52 to 108 weeks. Enrollment was restricted to patients 7 months of age or younger at first infusion with clinical signs of Pompe disease and cardiac hypertrophy, and who did not require ventilatory support at study entry. Fourteen patients were Cross Reactive Immunologic Material (CRIM) positive and 4 patients were CRIM-negative.

Efficacy was assessed by comparing the proportions of alglucosidase alfa-treated patients who died or needed invasive ventilatory support at 18 months of age with the mortality experience of a historical cohort of untreated infantile-onset Pompe disease 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 18 months of age, 15 of 18 (83%) alglucosidase alfa-treated patients were alive without invasive ventilatory support and 3 (17%) required invasive ventilatory support, whereas only one of the 61 (2%) historical control patients was alive. 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), a measure of infant motor performance that assesses motor maturation of the infant through age 18 months. Although gains in motor function were noted in 13 patients, the motor function was substantially delayed compared to normal infants of comparable age in the majority of patients. Two of 9 patients who had initially demonstrated gains in motor function after 12 months of alglucosidase alfa treatment regressed despite continued treatment. Changes from baseline to Month 12 in left ventricular mass index (LVMI), a measure of pharmacodynamic effect, were evaluated by echocardiography. Fifteen patients who underwent both baseline and Month 12 echocardiograms demonstrated decreases from baseline in LVMI (mean decrease 118 g/m² range 45 to 193 g/m²). However, 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 infantile-onset patients aged 3 months to 3.5 years at first infusion. Eighteen patients were CRIM-positive and 3 patients were CRIM-negative. All patients received 20 mg/kg alglucosidase alfa 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.

Study 3 was an open-label, single-center trial in 18 infantile-onset Pompe disease patients who had a confirmed diagnosis of Pompe disease as identified through a newborn screening program. All patients were CRIM-positive. Patients were treated with alglucosidase alfa prior to 6 months of age (0.2 to 5.8 months at first infusion). Sixteen patients reached 18 months of age at the time of analysis, and all (100%) were alive without invasive ventilatory support.

14.2 Clinical Trials in Late-Onset Pompe Disease

The safety and efficacy of alglucosidase alfa were assessed in 90 patients with late-onset Pompe disease, aged 10 to 70 years, in a randomized, double-blind, placebo-controlled trial. The youngest alglucosidase alfa-treated patient was 10 years of age, and the youngest placebo-treated patient was 10 years of age. All patients were naive to enzyme replacement therapy. Patients were allocated in a 2:1 ratio and received 20 mg/kg alglucosidase alfa (n=60) or placebo (n=30) every other week for 78 weeks (18 months). The study population included 34 males and 26 females (n=80) in the alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. At baseline, all patients were ambulatory (some required assistive walking devices), did not require invasive ventilatory support or non-invasive ventilation while awake and sitting upright, and had a forced vital capacity (FVC) between 30 and 79% of predicted in the sitting position. Patients who could not walk 40 meters in 6 minutes or were unable to perform appropriate pulmonary and muscle function testing were excluded from the study.

A total of 81 of 90 patients completed the trial. Of the 9 patients who discontinued treatment, 5 were in the alglucosidase alfa group and 4 were in the placebo group. Three patients discontinued the study due to an adverse event: two patients were in the alglucosidase alfa treatment group and one patient was in placebo group.

At study entry, the mean % predicted FVC in the sitting position among all patients was about 55%. After 78 weeks, the mean % predicted FVC increased to 56.2% for alglucosidase alfa-treated patients and decreased to 52.8% for placebo-treated patients indicating an alglucosidase alfa treatment effect of 3.4% (95% confidence interval: [1.3% to 5.5%]; p=0.004). Stabilization of % predicted FVC in the alglucosidase alfa-treated patients was observed (see Figure 1).