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 re-
  actions 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)
• Infante-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
Dosage and Administration, Instructions for Use (2.2) 5/2022

INDICATIONS AND USAGE
LUMIZYME® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indi- 
cated for patients with Pompe disease (GAA deficiency). (1)

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

FULL PRESCRIBING INFORMATION: CONTENTS*
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FULL PRESCRIBING INFORMATION

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

Life-threatening anaphylactic reactions and severe hypersensitivity reactions, presenting as respiratory distress, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, angioedema (including tongue or lip swelling, periorbital edema, and face edema), and urticaria, 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 [see Warnings and Precautions (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 cardio or respiratory compromise due to fluid overload, and require additional monitoring [see Warnings and Precautions (5.3)].

<table>
<thead>
<tr>
<th>Patient Weight Range (kg)</th>
<th>Total Infusion Volume (mL)</th>
<th>Step 1 1 mg/kg/hr (mL/hr)</th>
<th>Step 2 3 mg/kg/hr (mL/hr)</th>
<th>Step 3 5 mg/kg/hr (mL/hr)</th>
<th>Step 4 7 mg/kg/hr (mL/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25 to 2.5</td>
<td>25</td>
<td>1.25</td>
<td>3.75</td>
<td>6.25</td>
<td>6.6</td>
</tr>
<tr>
<td>2.6 to 10</td>
<td>50</td>
<td>3</td>
<td>8</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>10.1 to 20</td>
<td>100</td>
<td>5</td>
<td>15</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>20.1 to 30</td>
<td>150</td>
<td>8</td>
<td>23</td>
<td>38</td>
<td>53</td>
</tr>
<tr>
<td>30.1 to 35</td>
<td>200</td>
<td>10</td>
<td>30</td>
<td>50</td>
<td>70</td>
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<td>35.1 to 50</td>
<td>250</td>
<td>13</td>
<td>38</td>
<td>63</td>
<td>88</td>
</tr>
<tr>
<td>50.1 to 60</td>
<td>300</td>
<td>15</td>
<td>45</td>
<td>75</td>
<td>105</td>
</tr>
<tr>
<td>60.1 to 100</td>
<td>500</td>
<td>25</td>
<td>75</td>
<td>125</td>
<td>175</td>
</tr>
<tr>
<td>100.1 to 120</td>
<td>800</td>
<td>30</td>
<td>90</td>
<td>150</td>
<td>210</td>
</tr>
<tr>
<td>120.1 to 140</td>
<td>700</td>
<td>35</td>
<td>105</td>
<td>175</td>
<td>245</td>
</tr>
<tr>
<td>140.1 to 160</td>
<td>800</td>
<td>40</td>
<td>120</td>
<td>200</td>
<td>280</td>
</tr>
<tr>
<td>160.1 to 180</td>
<td>900</td>
<td>45</td>
<td>135</td>
<td>225</td>
<td>315</td>
</tr>
<tr>
<td>180.1 to 200</td>
<td>1,000</td>
<td>50</td>
<td>150</td>
<td>250</td>
<td>350</td>
</tr>
</tbody>
</table>

Patient weight (kg) × 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 (68 kg) × dose (20 mg/kg) = 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 drop-wise addition of the water for injection down the inside of the vial and not directly on the lyophilized cake. Tilt and roll each vial gently. Do not invert, swirl, 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 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.
e. Alglucosidase alfa should be diluted in 0.9% Sodium Chloride for Injection, USP, immediately after reconstitution, to a final alglucosidase alfa concentration of 0.5 to 4 mg/mL. See Table 1 for the recommended total infusion volume based on patient weight.

f. Slowly withdraw the reconstituted solution from each vial. Avoid foaming in the syringes.
g. Remove airspace from the infusion bag to minimize particle formation due to the sensitivity of alglucosidase alfa to air-liquid interfaces.
h. Add the reconstituted alglucosidase alfa solution slowly and directly into the sodium chloride infusion. Do not add directly into airspace that may remain within the infusion bag. Avoid foaming in the injection port.
i. Gently invert or massage the infusion bag to mix. Do not shake.
j. Administer alglucosidase alfa using an in-line low protein binding 0.2 µm filter.
k. Do not infuse alglucosidase alfa in the same intravenous line with other products.

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 refrigerated up to 5°C (41°F) to 30°C (86°F) for 24 hours. The reconstituted solution at room temperature is not recommended. The reconstituted and diluted alglucosidase alfa solution should be protected from light. Do not freeze or shake.

Alglucosidase alfa does not contain any preservatives. Vials are single dose only. Discard any unused product.

3 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.

4 CONTRAINDICATIONS

None.

5 Warnings and Precautions

5.1 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, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, 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, pruritus, rash, hyperhidrosis, nausea, dizziness, hypertension/increased blood pressure, flushing/feeling hot, anythema, pyrexia, pallor, peripheral coldness, restlessness, nervousness, headache, back pain, and paresthesia. Some of these reactions were IgE-mediated.

If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue administration of alglucosidase alfa, and initiate appropriate medical treatment. 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.

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.

Immune-mediated cutaneous reactions have been reported with alglucosidase alfa including necrotizing 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 hyperglycemia and hepatic encephalopathy in association with antiphospholipid antibodies and increased 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 deposition. Patients improved following treatment interruption. Therefore, patients receiving alglucosidase alfa should undergo periodic urinalysis [see Adverse Reactions (6.3)].

Patients should be monitored for the development of systemic immune-mediated reactions involving skin and other organs while receiving alglucosidase alfa. If immune-mediated reactions are considered to be due to discontinuation of the administration of alglucosidase alfa, and initiate appropriate medical treatment. The risks and benefits of readministering alglucosidase alfa following an immune-mediated reaction should be considered. Some patients have been able to be rechallenged and have continued to receive alglucosidase alfa under close clinical supervision. Immune tolerance induction administered in conjunction with LUMIZYM™ may also aide tolerability of alglucosidase alfa under the management of a clinical specialist knowledgeable in immune tolerance induction in pediatric Pompe disease.

5.3 Risk of Acute Cardiorespiratory Failure

Patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their cardiac or respiratory compromise during infusions. Appropriate medical support and monitoring measures should be undertaken during the first alglucosidase alfa infusion, and some patients may require prolonged observation times that should be individualized based on the needs of the patient. Acute cardiorespiratory failure has been observed in infantile-onset Pompe disease patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of alglucosidase alfa [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. 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 Risk of Antibody Development

Patients with infantile-onset Pompe disease should have a cross-reactive immunologic material (CRM) assessment at the start of their disease course and be managed by an early 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 aide tolerability of alglucosidase alfa in CRM-negative patients. CRM status has been shown to be associated with immuno- nogenicity and patients’ responses to enzyme replacement therapies. CRM-negative infants with infantile-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 CRM-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 CRM-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 reduced clinical response may also be tested for antibody formation. Patients who experience anaphylactic or hypersensitivity reactions may also be tested for IgG antibodies to alglucosidase alfa and other mediators of anaphylaxis [see Adverse Reactions (6.2)].

Testing services for antibodies against alglucosidase alfa are available through Genzyme Corporation. Contact Genzyme Corporation at 1-800-745-4447 for information on testing.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the 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 following severe adverse reactions are described below and elsewhere in the labeling:

- Anaphylaxis and hypersensitivity reactions [see Warnings and Precautions (5.1)].

In clinical studies, adverse reactions (≥2%) following alglucosidase alfa treatment were hypersensitivity reactions, and included anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, increased blood pressure, pallor, rigor, tremor, vomiting, fatigue, and myalgia.

Clinical Trials in Infantile-Onset and Juvenile-Onset Pompe Disease

Table 2: Adverse Reactions That Occurred in at Least 5% of Infantile-Onset Patients Treated with Alglucosidase Alfa in Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Number of Patients (N=39) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>20 (51)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>17 (44)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Flushing</td>
<td>13 (33)</td>
</tr>
<tr>
<td>Hypertension/Increased Blood Pressure</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Decreased Oxygen Saturation</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Erythema</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Rigors</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Pallor</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Agitation</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Tremor</td>
<td>5 (13)</td>
</tr>
</tbody>
</table>

An open-label, single-center trial was conducted in 18 treatment-naive infantile-onset Pompe disease patients who were treated exclusively with alglucosidase alfa. Adverse reactions observed in these patients were similar to those in infantile-onset Pompe disease patients who received alglucosidase alfa in other clinical trials.

Additional hypersensitivity reactions observed in infantile-onset Pompe disease patients treated in other clinical trials and expanded access programs with alglucosidase alfa included livedo reticularis, irritability, itching, increased lacrimation, ventilator extrasynto, nodal rhythm, rales, respiratory tract irritation, and cold sweat.

Safety was also evaluated in 99 patients (51 male, 48 females) with Pompe disease in an ongoing, open-label, prospective study in patients 12 months of age and older who were previously treated with the 160 L scale of alglucosidase alfa and switched to the 4000 L scale of alglucosidase alfa. Patients were aged 1 to 18 years with a median duration of treatment of 437 days (range 13 to 466 days). No new safety findings were observed following the switch to 4000 L scale of alglucosidase alfa.

Clinical Trials in Late-Onset Pompe Disease

Assessment of adverse reactions in patients with late-onset Pompe disease is based on the exposure of 90 patients (45 male, 45 female), aged 10 to 70 years, to 20 mg/kg alglucosidase alfa or placebo in a randomized, double-blind, placebo-controlled trial. The youngest alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo-treated patient was 10 years of age. All patients were naive to enzyme replacement therapy. Patients were randomized in a 2:1 ratio and received alglucosidase alfa or placebo every other week for 78 weeks (18 months). The study population included 34 males and 26 females (n=60) 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 angioedema, throat tightness and chest pain/discomfort. One patient with a history of Wolff-Parkinson-White syndrome experienced a serious adverse reaction of supraventricular tachycardia.

The most common adverse reactions (≥3%; 2 or more patients) observed in alglucosidase alfa-treated patients were hypersensitivity reactions and included anaphylaxis, headache, nausea, urticaria, dizziness, chest discomfort, vomiting, hyperhidrosis, flushing/feeling hot, increased blood pressure, paresthesia, pyrexia, local swelling, diarrhea, pruritus, rash, and throat tightness.

Delayed-onset reactions, defined as adverse reactions occurring 2 to 48 hours after completion of alglucosidase alfa infusion, that were observed in ≥3% more patients in the alglucosidase alfa-treated group compared to patients in the placebo-treated group in the controlled trial, included hyperhidrosis. 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 study described above.

Table 3: Adverse Reactions That Occurred in ≥3% of Late-Onset Patients Treated with Alglucosidase Alfa in Clinical Trials
Table 3: Adverse Reactions Occurring 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/Feeling Hot</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 Poplar</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>

In clinical trials, anaphylaxis and hypersensitivity reactions were managed with infusion interruption, deescalation, or discontinuation. Anaphylaxis is not always possible to reliably differentiate from severe, or severe enough, anaphylactic reactions or life-threatening anaphylactic reactions, for which 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 in 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 infant-onset patients, the majority of patients (34 of 38; 89%) tested positive for IgG antibodies to alglucosidase alfa. 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 (5.5)]. Some IgG-positive patients in clinical trials who were retrospectively evaluated for the presence of inhibitory antibodies tested positive for inhibition of enzyme activity and/or uptake in in vitro assays. Furthermore, CRM-negative infants have shown reduced clinical effect in the presence of high sustained IgG antibody titers with inhibitory activity [see Warnings and Precautions (5.5)]. 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, infant-onset Pompe disease patients suggest that the administration of an immune tolerance induction regimen individualized to alglucosidase alfa-naïve patients may be effective in preventing or reducing the development of high sustained antibody titer 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 patients 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.

None 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 inhibition of 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 1.6-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-specific IgE antibodies. Testing was performed in patients who experienced anaphylaxis or severe anaphylactic 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 positive for alglucosidase alfa-specific IgE antibodies and experienced hypersensitivity reactions 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 (5.1)]. Since patients who develop IgG 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 always 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 cardiorespiratory failure, possibly associated with fluid overload, has been reported in infant-onset Pompe disease patients with pre-existing hypertrophic cardiomyopathy [see Boxed Warning and Warnings and Precautions (5.3)].

Recurrent reactions consisting of flu-like illness or a combination of events such as pyrexia, rash, 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, hypoxia, dyspnea, wheezing, convulsions, peripheral coldness, restlessness, nervousness, back pain, stridor, pharyngeal edema, abdominal pain, apnea, 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 postmarketing safety experience with alglucosidase alfa [see Warnings and Precautions (5.2)].

7.2 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

Risk Summary

Data from postmarketing reports and published case reports with alglucosidase alfa use in pregnant women have not identified a LUMIZYM®-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. The continuation of treatment for Pompe disease during pregnancy should be individualized to the pregnant woman.

Untreated Pompe disease may result in worsening disease symptoms in pregnant women [see Clinical Considerations]. Reproduction studies performed in mice and rabbits at doses resulting in exposures up to 0.4 or 0.5 times the human steady-state AUC (area under the plasma concentration-time curve), respectively, during the period of organogenesis revealed no evidence of effects on embryo-fetal development. In mice there was an increase in pup mortality during lactation at maternal exposures 0.4 times the human steady-state AUC (see Data). The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Pregnant women and women of reproductive potential should be encouraged to enroll in the Pompe patient registry. The registry will monitor the effect of LUMIZYM® on pregnant women and their offspring. For more information, visit www.registerzym.com or call 1-800-745-4447, extension 15500.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

Untreated Pompe disease has been associated with worsening respiratory and musculoskeletal symptoms in some pregnant women.

8.2 Lactation

Risk Summary

Available published literature suggests the presence of alglucosidase alfa in human milk. In pregnant women, the reports of adverse events in neonates born to treated mothers are not sufficient to comment on the potential adverse effects of alglucosidase alfa on the breastfed infant. There is no information on the effects of alglucosidase alfa on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LUMIZYM® and any potential adverse effects on the breastfed child from LUMIZYM®. The benefits of nursing the breastfed infant must be considered against the potential risks to the breastfed infant of inadequate nutrition from human milk, the possible adverse effects of alglucosidase alfa on the breastfed infant, and the potential benefits to the mother of breastfeeding.

Lactating women with Pompe disease treated with LUMIZYM® should be encouraged to enroll in the Pompe disease registry [see Use in Specific Populations (8.1)].

Clinical Considerations

Pregnancy

A woman may consider interrupting breastfeeding, pumping and discarding breast milk during treatment and for 24 hours after LUMIZYM® administration in order to minimize drug exposure to a breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of alglucosidase alfa have been established in pediatric patients with Pompe disease [see Adverse Reactions (6.2)]. The safety and effectiveness of alglucosidase alfa were assessed in 57 treatment-naïve infant-onset Pompe disease patients, aged 0.2 months to 3.5 years at first infusion, in three separate clinical trials [see Clinical Studies (14.1)].
The safety and effectiveness of alglucosidase alfa were assessed in pediatric patients with late (non-infant-onset) Pompe disease in a randomized, double-blind, placebo-controlled study in 90 patients, including 2 patients 16 years of age or less [see Clinical Studies (14.2)].

Anaphylaxis, hypersensitivity reactions, and acute cardiorespiratory failure have occurred in pediatric patients [see 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)].

8.5 Geriatric Use

The randomized, double-blind, placebo-controlled study of alglucosidase alfa did not include sufficient numbers (n=4) of patients aged 65 years and over to determine whether they respond differently from younger patients [see Clinical Studies (14.1)].

11 DESCRIPTION

Alglucosidase alfa is a hydrolytic lysosomal glycogen-specific enzyme encoded by the predominant of nine observed haplotypes of the human acid 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-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 108,000 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 the hydrolysis of 1 micromole of synthetic substrate per minute under specified assay conditions). Alglucosidase alfa is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with 10.5 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, and 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 10.5 mL. 5 mL of alglucosidase alfa. Alglucosidase alfa does not contain preservatives; each vial is for single-dose only.

12 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 Pharmacokinetics

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 0.4 times the human AUC at the recommended biweekly dose) 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.

In the open-label, single-center trial in 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 ventilator 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 16 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=60) in the alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. At baseline, all patients were CRIM positive (some required assisted walking devices). 10 patients 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 ventilator support.

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At study entry, the mean 6 minute walk test (6MWT) among all patients was about 330 meters. After 78 weeks, the mean 6MWT increased by 25 meters for alglucosidase alfa-treated patients and decreased by 3 meters for placebo-treated patients indicating an alglucosidase alfa treatment effect of 28 meters (95% confidence interval: [-1 to 52 meters]; p=0.06) (see Figure 2).

Figure 2: Mean Six Minute Walk Test Total Distance Walked Over Time

16 HOW SUPPLIED/STORAGE AND HANDLING
LUMIZYME 50 mg vials are supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder in single-dose vials.
NDC 58468-0160-1 (Carton of one single-dose vial)
NDC 58468-0160-2 (Carton of ten single-dose vials)
Store LUMIZYME under refrigeration between 2°C and 8°C (36°F and 46°F). Do not use LUMIZYME after the expiration date on the vial.

17 PATIENT COUNSELING INFORMATION
Anaphylaxis, Hypersensitivity, and Immune-Mediated Reactions
Advise the patients and caregivers that reactions related to administration and infusion may occur during and after alglucosidase alfa treatment, including life-threatening anaphylaxis, hypersensitivity reactions, and immune-mediated reactions. Patients who have experienced anaphylaxis or hypersensitivity reactions may require close observation during and after alglucosidase alfa administration. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek medical care should signs and symptoms occur.
Risk of Acute Cardiorespiratory Failure
Advise patients and caregivers that patients with underlying respiratory illness or compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Patients with compromised cardiac or respiratory function may require close observation during and after alglucosidase alfa administration.
Pompe Registry
Inform patients and their caregivers that 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 effect of alglucosidase alfa on pregnant women and their offspring [see Use in Specific Populations (8.1)]. Patients and their caregivers should be encouraged to participate in the Pompe Registry and advised that their participation is voluntary and may involve long-term follow-up. For more information regarding the registry program, visit www.registrynxt.com or call 1-800-745-4447, extension 15500.

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