LUMIZYM® (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)

Dosage and Administration, Instructions for Use (2.2) 5/2022

INDICATIONS AND USAGE

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

DOSE AND ADMINISTRATION

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

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

See full prescribing information for complete boxed warning.

- 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, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia. (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: 05/2022
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 cardiac or respiratory compromise due to fluid overload, and require additional monitoring [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

LUMIZYME® (alglucosidase alfa) [see Description (11)] is a hydrolitic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α-glucosidase [GAA] deficiency).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

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

2.2 Instructions for Use

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

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 stepwise 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 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, alglucosidase alfa may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed or temporarily stopped in the event of mild to moderate hypersensitivity reactions. In the event of anaphylaxis or severe hypersensitivity reaction, 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.

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 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>
</tr>
<tr>
<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>600</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>

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 onto 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. Infusion-related reactions are generally managed with infusion interruption, administration of antihistamines, corticosteroids, ophthalmic solutions for eye irritation, and discontinuation of the infusion. Storage of 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 portion.

2 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, wheezing, tachypnea, cyanosis, decreased oxygen saturation, convulsions, pruritus, rash, urticaria, nausea, dizziness, hypotension/ increased blood pressure, flushing/feeling hot, erythema, pyrexia, pallor, peripheral coldness, restlessness, nervousness, headache, back pain, and paresthesia. Some of these reactions were IgE-mediated. If anaphylaxis or severe hypersensitivity reaction occurs continue 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 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 infusion of alglucosidase alfa infusions. Skin biopsy in one patient demonstrated deposition of anti-iHGA 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 one Pompe disease patients treated with alglucosidase alfa who had persistently positive anti-iHGA 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 occur, consider 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 LUMIZYMÉ may also aid 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 readily available during 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 (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-positive patients. CRIM status has been shown to be associated with immunogenicity and patients' responses to enzyme replacement therapies. CRIM-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 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 reduced clinical response 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 serious adverse reactions are described below and elsewhere in the labeling:

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

In clinical trials, the most common adverse reactions (≥5%) following alglucosidase alfa treatment were hypersensitivity reactions, and included anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia.

Clinical Trials in Infantile-Onset and Juvenile-Onset Pompe Disease
Two multicenter, open-label clinical trials were conducted in 39 infantile-onset Pompe disease patients, ages 1 month to 3 years old. Approximately half of the patients (54%) were male. Patients were treated with alglucosidase alfa 20 or 40 mg/kg every other week for periods ranging from 1 to 106 weeks (mean: 61 weeks). The most serious adverse reactions reported with alglucosidase alfa treatment included anaphylaxis and acute cardiorespiratory failure. The most common adverse reactions requiring intervention in clinical trials were hypersensitivity reactions, occurring in 20 of 39 (51%) patients treated with alglucosidase alfa, and included rash, pyrexia, urticaria, flushing, decreased oxygen saturation, cough, tachypnea, tachycardia, hypertension/increased blood pressure, paller, rigors, vomiting, cyanosis, agitation, and tremor. These reactions were more likely to occur with higher infusion rates. Some patients who were pretreated with antihistamines, antipyrretics and/or corticosteroids still experienced hypersensitivity reactions.

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 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, retching, increased lacrimation, ventricular extrasystoles, 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, hypotension, 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% of 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 fatique, myalgia, and nausea. Patients should be counseled about the possibility of delayed-onset hypersensitivity reactions and given proper follow-up instructions.

Table 2 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.
Precautions

Approximately in inhibition is not fully understood. The clearance values for 4 of these 5 patients were treatment under close clinical supervision experienced hypersensitivity reactions were able to be rechallenged with alglucosidase.

For patients who experienced moderate to severe or recurrent hypersensitivity reactions, for which [see Clinical Pharmacology (5.2)] as compared to in the absence of inhibitory antibodies (Week 0) Pharamacokinetic (PK) samples, 5 patients tested positive for uptake inhibition. The clinical relevance of this uptake activity and/or uptake in clinical effect in the presence of high sustained IgG antibody titers with inhibitory activity [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 vitro assays. Furthermore, CRIM-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 activity or uptake. 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 CRIM 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. The following adverse reactions have been identified during post approval use of 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 infantile-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 palpitations, 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 necrotic skin lesions have been reported in postmarketing safety experience with alglucosidase alfa [see Warnings and Precautions (5.2)].

7.4 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 LUMIZYME-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 late gestation; 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. Pregnancy women and women of reproductive potential should be encouraged to enroll in the Pompe patient registry. The registry will monitor the effect of LUMIZYME on pregnant women and their offspring. For more information, visit www registryntx.com or call 1-800-745-4447, extension 15500.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

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

Data

Animal data

Reproductive studies included pretreatment with diphenhydramine to prevent or minimize hypersensitivity reactions. The effects of alglucosidase alfa were evaluated based on comparison to a control group treated with diphenhydramine alone. Daily intravenous administration of alglucosidase alfa up to 40 mg/kg in mice and rabbits (0.4 and 0.5 times the human steady-state AUC, respectively, at the recommended biweekly dose) during the period of organogenesis had no effects on embryo-fetal development. Administration of 40 mg/kg intravenously every other day in mice (0.4 times the human steady-state AUC at the recommended biweekly dose) during the period of organogenesis therefore lactation produced an increase in mortality of offspring during the lactation period.

8.2 Lactation

Risk Summary

Available published literature suggests the presence of alglucosidase alfa in human milk. The effects of alglucosidase alfa on the breastfed infant are not known. 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 LUMIZYME and any potential adverse effects on the breastfed child from LUMIZYME or from the underlying maternal condition.

Lactating women with Pompe disease treated with LUMIZYME should be encouraged to enroll in the Pompe disease registry [use in Specific Populations (8.1)].

Clinical Considerations

Pediatric use

The 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-naive 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-infantile) onset Pompe disease in a 2003-2005, 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 hydrolitic lysosomal glycogen-specific enzyme encoded by the predominant of nine observed haplotypes of the human α-1,4-glucosidase (GAA) gene. Alglucosidase alfa is produced by recombinant DNA technology in a Chinese hamster ovary cell line [see Clinical Pharmacology (3.2)]. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6-glycosidic linkages of lysosomal glycogen.

Alglucosidase alfa is a glycoprotein with a calculated mass of 99,377 Daltons for the polypeptide chain, and a total mass of approximately 109,000 Daltons, including carbohydrates. Alglucosidase alfa has a specific activity of 3.6 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 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 carbonate di basic heptahydrate, and 31.2 mg sodium phosphate monobasic monohydrate. Reconstituted solutions contain 0.2 mg/mL alglucosidase alfa and a total available volume of 10 mL at 5 mg/mL 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 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 as a 4-hour intravenous) or 40 mg/kg (approximately as a 4-hour intravenous) 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 pharmacokinetic data collected for 12 hours after a 4-hour intravenous infusion of 20 mg/kg alglucosidase alfa every 2 weeks, the mean (± standard deviation) area under the curve (AUC) from 0 to 12 hours (AUC 0–12) was 11,965 ± 714 mcg·hr/mL. The mean terminal half-life of alglucosidase alfa was about 11.1 hours (11.4 ± 1.8 hours).

The pharmacokinetics of alglucosidase alfa was also evaluated in a separate trial of 14 patients with late-onset Pompe disease, aged 6 months to 3.15 years, who received 20 mg/kg of alglucosidase alfa as a 4-hour intravenous 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 20 mg/kg or 40 mg/kg of alglucosidase alfa as a 4-hour infusion every 2 weeks. 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.

The pharmacokinetics of alglucosidase alfa was evaluated in another trial of 10 adult and 10 pediatric patients with Pompe disease who received a single dose of 200 mg/kg of alglucosidase alfa as a 4-hour infusion. In pediatric patients, aged 7 months to 13.7 years, the estimated mean AUC was 1,110 mcg·hr/mL with 68% CV and Cmax was 204 mcg/mL with 46% CV. In adult patients, aged 19 to 57 years, the estimated mean AUC was 1,890 mcg·hr/mL with 51% CV and Cmax was 307 mcg/mL with 47% CV.

13 NONCLINICAL TOXICOLGY
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.

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 month 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 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 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. Eleven 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 2 was an international, multicenter, open-label clinical trial that enrolled 21 infantile-onset patients aged 3 months to 3.5 years at first infusion. Sixteen patients were free of invasive ventilatory support at the time of first infusion; of these, 8 died, 4 required invasive ventilatory support, and 4 were free of invasive ventilatory support after 52 weeks of treatment. 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 ambulatory (some required assistive walking devices), did not require invasive ventilator 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 tests were excluded from the study. A total of 81 of 90 patients completed the trial. Of the 9 patients who discontinued, 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).
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

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.

PATIENT COUNSELING INFORMATION
Anaphylaxis, Hypersensitivity, and Immune-Mediated Reactions
Advising 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
Advising 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
Informing 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 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 1-850-745-4447, extension 15500.

LUMIZYME is manufactured and distributed by: Genzyme Corporation Cambridge, MA 02142 1-800-745-4447 (phone)

U.S. License Number: 1596

LUMIZYME and GENZYME are registered trademarks of Genzyme Corporation.