HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NEXVIAZYME® safely and effectively. See full prescribing information for NEXVIAZYME.

**NEXVIAZYME® (avalglucosidase alfa-ngpt) for injection, for intravenous use**

**WARNING: SEVERE HYPERSENSITIVITY REACTIONS, INFUSION-ASSOCIATED REACTIONS, and RISK OF ACUTE CARDIORESPIRATORY FAILURE IN SUSCEPTIBLE PATIENTS**

See full prescribing information for complete boxed warning.

### Hypersensitivity Reactions Including Anaphylaxis
- Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available. If a severe hypersensitivity reaction occurs, NEXVIAZYME should be discontinued immediately and appropriate medical treatment should be initiated. (5.1)

### Infusion-Associated Reactions (IARs)
- If severe IARs occur, consider immediate discontinuation and initiation of appropriate medical treatment. (5.2)

### Risk of Acute Cardiorespiratory Failure in Susceptible Patients
- Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function, may be at risk of serious exacerbation of their cardiac or respiratory status during NEXVIAZYME infusion. (5.3)

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**INDICATIONS AND USAGE**

NEXVIAZYME is a hydrolytic lysosomal glycogen-specific enzyme indicated for the treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency). (1)

**DOSAGE AND ADMINISTRATION**

- Consider administering antihistamines, antipyretics, and/or corticosteroids prior to NEXVIAZYME administration to reduce the risk of IARs. (2.1)
- Must be reconstituted and diluted prior to use.
- See full prescribing information for administration instructions including the recommended infusion rate schedule. (2.1, 2.3, 2.4)
- NEXVIAZYME is administered as intravenous infusion. For patients weighing (2.1):
  - ≥30 kg, the recommended dosage is 20 mg/kg (of actual body weight) every two weeks.
  - <30 kg, the recommended dosage is 40 mg/kg (of actual body weight) every two weeks.
- See the full prescribing information for dosage modifications due to hypersensitivity reactions or IARs. (2.2)

**DOSAGE FORMS AND STRENGTHS**

For injection: 100 mg of avalglucosidase alfa-ngpt as a lyophilized powder in a single-dose vial for reconstitution. (3)

**CONTRAINDICATIONS**

None. (4)

**WARNINGS AND PRECAUTIONS**

See boxed warning. (5.1, 5.2, 5.3)

**ADVERSE REACTIONS**

The most common adverse reactions (>5%) were headache, fatigue, diarrhea, nausea, arthralgia, dizziness, myalgia, pruritus, vomiting, dyspnea, erythema, paresthesia and urticaria. (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

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FULL PRESCRIBING INFORMATION: CONTENTS*

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Revised: 04/2023
Dilute the reconstituted solution without delay. If immediate use is not possible, the reconstituted solution can be stored up to 24 hours in a refrigerator, 36°F to 46°F (2°C to 8°C). Do not freeze.

### Dilution of the Reconstituted Solution

1. Draw the total infusion volume (reconstituted solution and additional diluent) into a sterile tube or syringe.
2. Add the reconstituted solution slowly and directly into 5% Dextrose Injection. See Table 1 for the recommended total infusion volume based on the patient’s weight.

### Administration Instructions

1. Prior to the initial dose of NEXVIAZYME, perform a complete visual inspection of the reconstituted solution in vials for particulate matter and discoloration. If any particulate matter or discoloration is present, do not use the solution.
2. Infuse the solution into a large peripheral vein or with a 20-gauge catheter or above. Avoid administering the solution through a subcutaneous or intramuscular route.
3. Discard any unused reconstituted solution after 9 hours.

### Storage of the Diluted Solution

- **If the diluted solution is not used immediately, refrigerate at 36°F to 46°F (2°C to 8°C) for up to 24 hours. Do not freeze.**
- **Completely infuse the diluted solution within 9 hours after removal from the refrigerator.**
- **If the diluted solution is removed from the refrigerator, it must not be restored in the refrigerator.**
- **Discard the diluted solution if refrigerated more than 24 hours or if the diluted solution is not able to be completely infused within 9 hours after removal from the refrigerator.**

### Table 1: Projected Intravenous Infusion Volume for NEXVIAZYME Administration According to Patient Weight

<table>
<thead>
<tr>
<th>Patient Weight Range</th>
<th>Total Infusion Volume (mL) for 20 mg/kg</th>
<th>Total Infusion Volume (mL) for 40 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to 9.9</td>
<td>N/A</td>
<td>100</td>
</tr>
<tr>
<td>10 to 19.9</td>
<td>N/A</td>
<td>200</td>
</tr>
<tr>
<td>20 to 29.9</td>
<td>N/A</td>
<td>300</td>
</tr>
<tr>
<td>30 to 34.9</td>
<td>200</td>
<td>N/A</td>
</tr>
<tr>
<td>35 to 49.9</td>
<td>250</td>
<td>N/A</td>
</tr>
<tr>
<td>50 to 59.9</td>
<td>300</td>
<td>N/A</td>
</tr>
<tr>
<td>60 to 99.9</td>
<td>500</td>
<td>N/A</td>
</tr>
<tr>
<td>100 to 119.9</td>
<td>600</td>
<td>N/A</td>
</tr>
<tr>
<td>120 to 140</td>
<td>700</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Dosage and Administration Modifications Due to Hypersensitivity Reactions or Infusion-Associated Reactions

- **In the event of a severe hypersensitivity reaction (including anaphylaxis) or a severe infusion-associated reaction (IAR), immediately discontinue NEXVIAZYME administration and initiate appropriate medical treatment [see Warnings and Precautions (5.1)].**
- **In the event of a mild to moderate hypersensitivity reaction or a moderate IAR, consider temporarily holding or slowing the infusion rate and initiating appropriate medical treatment [see Warnings and Precautions (5.1, 5.2)]. If symptoms:**
  - Persist despite temporarily holding the infusion, wait at least 30 minutes for symptoms to resolve before deciding to stop the infusion for the day.
  - Subside, resume the infusion for 30 minutes at half the rate at which the reaction occurred, and subsequently increase the infusion rate by 50% for 15 to 30 minutes. If symptoms do not recur, increase the infusion rate to the rate at which the reaction occurred and consider continuing to increase the rate in a stepwise manner.

### Reconstitution and Dilution Instructions

Reconstitute and dilute NEXVIAZYME in the following manner. Use aseptic technique during preparation.

1. **Reconstitute the Lyophilized Powder**
   - Determine the number of vials to be reconstituted based on individual patient’s weight and the recommended dose [see Dosage and Administration (2.1)].
   - Remove the required number of vials needed for the infusion from the refrigerator and set aside for approximately 30 minutes to allow them to reach room temperature.
   - Reconstitute each vial by injecting 10 mL of Sterile Water for Injection, USP, into each vial by a slow drop-wise addition of the diluent down the side of the vial and not directly onto the lyophilized powder. Tilt and roll each vial gently. Avoid forcing the diluent onto the lyophilized powder and avoid foaming. Do not invert, swirl, or shake. Allow the solution to become dissolved. After reconstitution, each vial will yield 100 mg/10 mL (10 mg/mL) of avalglucosidase alfa-ngpt.

2. **Perform an immediate visual inspection of the reconstituted solution in vials for particulate matter and discoloration.**

### Warnings and Precautions

1. **Hypersensitivity Reactions Including Anaphylaxis**
   - Prior to NEXVIAZYME administration, consider pretreating with antihistamines, antipetietics, and/or corticosteroids. Appropriate medical support measures, including cardipulmonary resuscitation equipment, should be readily available during NEXVIAZYME administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, NEXVIAZYME should be discontinued immediately and appropriate medical treatment should be initiated. In patients with severe hypersensitivity reaction, a desensitization procedure to NEXVIAZYME may be considered [see Warnings and Precautions (5.1)].

2. **Infusion-Associated Reactions (IARs)**

   - **Patients treated with NEXVIAZYME have experienced life-threatening hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardipulmonary resuscitation equipment, should be readily available during NEXVIAZYME administration. If a severe hypersensitivity reaction occurs, NEXVIAZYME should be discontinued immediately and appropriate medical treatment should be initiated. In patients with severe hypersensitivity reaction, a desensitization procedure to NEXVIAZYME may be considered [see Warnings and Precautions (5.1)].**

   - **The initial recommended infusion rate is 1 mg/kg/hour. Gradually increase the infusion rate every 30 minutes if there are no signs of infusion-associated reactions (IARs) [see Dosage and Administration (2.4)].**

   - **In the event of a severe infusion-associated reaction (IAR), immediately discontinue NEXVIAZYME administration and initiate appropriate medical treatment [see Warnings and Precautions (5.1)].**

   - **In the event of a mild to moderate infusion-associated reaction (IAR), consider temporarily holding or slowing the infusion rate and initiating appropriate medical treatment [see Warnings and Precautions (5.1, 5.2)]. If symptoms:**
     - Persist despite temporarily holding the infusion, wait at least 30 minutes for symptoms to resolve before deciding to stop the infusion for the day.
     - Subside, resume the infusion for 30 minutes at half the rate at which the reaction occurred, and subsequently increase the infusion rate by 50% for 15 minutes to 30 minutes. If symptoms do not recur, increase the infusion rate to the rate at which the reaction occurred and consider continuing to increase the rate in a stepwise manner.

3. **Reconstitute and dilute NEXVIAZYME in the following manner. Use aseptic technique during preparation.**

   - **Reconstitute the Lyophilized Powder**
     - **1. Determine the number of vials to be reconstituted based on individual patient’s weight and the recommended dose [see Dosage and Administration (2.1)].**
     - **2. Remove the required number of vials needed for the infusion from the refrigerator and set aside for approximately 30 minutes to allow them to reach room temperature.**
     - **3. Reconstitute each vial by injecting 10 mL of Sterile Water for Injection, USP, into each vial by a slow drop-wise addition of the diluent down the side of the vial and not directly onto the lyophilized powder. Tilt and roll each vial gently. Avoid forcing the diluent down the inside of the vial and not directly onto the lyophilized powder. Tilt and roll each vial gently. Avoid forcing the diluent onto the lyophilized powder and avoid foaming. Do not invert, swirl, or shake. Allow the solution to become dissolved. After reconstitution, each vial will yield 100 mg/10 mL (10 mg/mL) of avalglucosidase alfa-ngpt.**
     - **4. Perform an immediate visual inspection of the reconstituted solution in vials for particulate matter and discoloration.**

### Warnings and Precautions

1. **Hypersensitivity Reactions Including Anaphylaxis**
   - Prior to NEXVIAZYME administration, consider pretreating with antihistamines, antipetietics, and/or corticosteroids. Appropriate medical support measures, including cardipulmonary resuscitation equipment, should be readily available during NEXVIAZYME administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, NEXVIAZYME should be discontinued immediately and appropriate medical treatment should be initiated. In patients with severe hypersensitivity reaction, a desensitization procedure to NEXVIAZYME may be considered. If the decision is made to readminister NEXVIAZYME following severe IARs, consider immediate discontinuation of NEXVIAZYME, initiation of appropriate medical treatment, and the benefits and risks of readministering NEXVIAZYME following severe IARs. Patients with an acute underlying illness at the time of NEXVIAZYME infusion may be at greater risk for IARs. Patients with advanced Pompe disease may have compromised cardiac and respiratory function, which may predispose them to a higher risk of severe complications from IARs [see Warnings and Precautions (5.2)].

2. **Risk of Acute Cardiorespiratory Failure in Susceptible Patients**
   - Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function for whom fluid restriction is indicated may be at risk of serious exacerbation of their cardiac or respiratory status during NEXVIAZYME infusion. More frequent monitoring of vitals should be performed during NEXVIAZYME infusion in such patients [see Warnings and Precautions (5.3)].

3. **Indications and Usage**
   - NEXVIAZYME is indicated for the treatment of patients 1 year of age and older with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency).
IAXES® (NEXVIAZYME®), ensure the patient tolerates the infusion. If the patient tolerates the infusion, the dosage (dose and/or the rate) may be increased to reach the recommended approved dosage.

- If a mild or moderate hypersensitivity reaction occurs, the infusion rate may be slowed or temporarily stopped.

Adverse Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>NEXVIAZYME (N=51)</th>
<th>Alglucosidase Alfa (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>11 (22%)</td>
<td>16 (33%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (18%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (12%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (12%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (10%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (10%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (10%)</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (8%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>3 (6%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Paralysis</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>3 (6%)</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

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 antibodies (including neutralizing antibody) 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.

The incidence of anti-alglucosidase alfa-ntg antibodies (antidrug antibodies, ADA) in NEXVIAZYME-treated patients with Pompe disease is shown in Table 3. In NEXVIAZYME-treated patients (mean of 26 months, up to 85 months of treatment), the incidence of IARs was 62% (8/13) in those with an ADA peak titer ≥12,800, compared with incidences of 19% (8/43) in those with ADA peak titer <12,800 and 33% (1/3) in those who were ADA-negative. One (1) treatment-related death occurred in an ADA-negative patient. Patients who developed ADA compared to patients who were ADA-negative. One (1) treatment-related death occurred in an ADA-negative patient.

Table 3: Incidence of Anti-Alglucosidase Alfa-ntg Antibodies in Patients with Pompe Disease

<table>
<thead>
<tr>
<th>Treatment-Exposed Patients Alglucosidase Alfa-ntg ADA (N=74)</th>
<th>Adults/ Pediatrics 20 mg/kg every two weeks (N=61)</th>
<th>Adults 20 mg/kg every two weeks (N=58)</th>
<th>PEDIATRICS 20 mg/kg every two weeks (N=6)</th>
<th>PEDIATRICS 40 mg/kg every two weeks (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults 20 mg/kg every two weeks (N=58)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Adults 40 mg/kg every two weeks (N=10)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
</tbody>
</table>

ADA at baseline

2 (3%) 43 (74%) 1 (17%) 1 (10%)
Table 3: Incidence of Anti-Avalglucosidase Alfa-ngpt Antibodies in Patients with Pompe Disease (continued)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>NEXVIAZYME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-Naive Patients</td>
<td></td>
</tr>
<tr>
<td>Adults/</td>
<td>Adults 20 mg/kg every two weeks (N=58)</td>
</tr>
<tr>
<td>Pediatrics (N=61)</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>ADA after treatment</td>
<td>58 (95%)</td>
</tr>
<tr>
<td>Neutralizing Antibody (NAb)</td>
<td></td>
</tr>
<tr>
<td>Both NAb types</td>
<td>13 (21%)</td>
</tr>
<tr>
<td>Inhibition of enzyme activity</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>Inhibition of enzyme cellular uptake</td>
<td>24 (39%)</td>
</tr>
</tbody>
</table>

*Includes one pediatric patient
†Treatment naive: only treated with avalglucosidase alfa-ngpt
‡Treatment experienced: previously treated with alglucosidase alfa.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary

Available data from case reports of NEXVIAZYME use in pregnant women are insufficient to evaluate for a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. However, available data from postmarketing reports and published case reports on alglucosidase alfa (another hydrolytic lysosomal glycosidase-specific enzyme replacement therapy) use in pregnant women have not identified a drug-associated risk of adverse pregnancy outcomes. The continued 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].

Embryo-fetal toxicity studies performed in pregnant mice resulted in maternal toxicity related to an immunologic response (including an anaphylactoid response) and embryo-fetal loss at 17 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for LOPD patients weighing ≥30 kg or 10 times the human steady-state AUC at the recommended biweekly dose of 40 mg/kg for LOPD patients weighing <30 kg. Avalglucosidase alfa-ngpt did not cross the placenta in mice, therefore, the adverse effects were likely related to the immunologic response in the mothers. Embryo-fetal toxicity studies performed in pregnant rabbits showed no adverse effects on the fetuses at exposure up to 91 times the human steady-state AUC at the recommended biweekly dosage of 20 mg/kg for LOPD patients weighing ≥30 kg or 50 times the human steady-state AUC at the recommended biweekly dose of 40 mg/kg for LOPD patients weighing <30 kg [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, miscarriage, 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 exposed to NEXVIAZYME, or their healthcare providers, should report NEXVIAZYME exposure by calling 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.

Data

Animal data

The majority of reproductive toxicity studies in mice included the pretreatment with diphenhydramine (DPH) to prevent or minimize hypersensitivity reactions. The effects of NEXVIAZYME were evaluated based on a biweekly treatment with DPH alone. Rabbits tested in reproductive toxicity studies were not pretreated with DPH because hypersensitivity reactions were not observed.

Embryo-fetal toxicity studies performed in pregnant mice at doses of 0, 10, 20, or 50 mg/kg/day administered intravenously once daily on gestational days 6 through 15 resulted in an immunologic response, including an anaphylactoid response, in some dams at the highest dose of 50 mg/kg/day (17 times the human steady-state AUC at the recommended biweekly dose of 20 mg/kg for LOPD patients weighing ≥30 kg or 10 times the human steady-state AUC at the recommended biweekly dose of 40 mg/kg for LOPD patients weighing <30 kg). Increased postimplantation loss and mean number of late resorptions were observed in this group. Placental transfer studies determined that avalglucosidase alfa-ngpt was not transported from the maternal to the fetal circulation in mice, suggesting that the embryo-fetal effects were due to maternal toxicity relating to the immunologic response. The maternal no observed adverse effect level (NOAEL) was 50 mg/kg/day intravenously (17 times the human AUC) and the developmental NOAEL was 20 mg/kg/day intravenously (4.8 times the human AUC).

Embryo-fetal toxicity studies performed in rabbits at doses of 0, 30, 60, and 100 mg/kg/day and administered intravenously once daily on gestational days 6 through 19 resulted in no adverse effects in the fetuses at the highest dose (100 mg/kg/day; 91 times the human steady-state AUC at the recommended biweekly dosage of 20 mg/kg for LOPD patients weighing ≥30 kg or 50 times the human steady-state AUC at the recommended biweekly dosage of 40 mg/kg for LOPD patients weighing <30 kg). Administration of NEXVIAZYME intravenously every other day in mice from gestational day 6 through postpartum day 20 did not produce adverse effects in the offspring at the highest dose of 50 mg/kg (maternal exposure not evaluated).

8.2 Lactation

Risk Summary

There are no data on the presence of avalglucosidase alfa-ngpt in human or animal milk. The effects on the breastfed infant, or the effects on milk production. Available literature suggests the presence of alglucosidase alfa (another hydrolytic lysosomal glycosidase-specific enzyme replacement therapy) in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for NEXVIAZYME and any potential adverse effects on the breastfed child from NEXVIAZYME or from the underlying maternal condition.

Lactating women exposed to NEXVIAZYME, or their healthcare providers, should report NEXVIAZYME exposure by calling 1-800-745-4447, extension 15500.

8.4 Pediatric Use

The safety and effectiveness of NEXVIAZYME for the treatment of late-onset Pompe disease have been established in pediatric patients 1 year of age and older. Use of NEXVIAZYME for this indication is supported by evidence from two clinical studies which included adults with LOPD, and 1 pediatric patient with LOPD (16 years of age) and from safety data in 19 pediatric patients with infantile-onset Pompe disease (IOPD) (1 to 12 years of age) treated with NEXVIAZYME [see Clinical Studies (14.1)]. NEXVIAZYME is not approved for the treatment of IOPD.

The safety profile of NEXVIAZYME in pediatric patients 1 to 12 years old with Pompe disease was similar to the safety profile of NEXVIAZYME in older pediatric adult patients with LOPD. The safety and effectiveness of NEXVIAZYME have not been established in pediatric patients younger than 1 year of age.

8.6 Geriatric Use

Clinical studies with NEXVIAZYME included 14 patients 65 to 74 years of age and 3 patients 75 years of age and older. The recommended dosage in geriatric patients is the same as the recommended dosage in younger adult patients [see Adverse Reactions (6.1)].

11 DESCRIPTION

Avalglucosidase alfa-ngpt is a hydrolytic lysosomal glycosidase-specific recombinant human α-glucosidase enzyme conjugated with multiple synthetic bis-mannose-6-phosphate (bis-M6P)-glucosidase (GAA), which results in intralysosomal accumulation of glycogen in various tissues. Avalglucosidase alfa-ngpt has a molecular weight of approximately 124 kDa.

NEXVIAZYME (avalglucosidase alfa-ngpt) for injection is a sterile white to pale-yellow lyophilized powder for intravenous use after reconstitution and dilution. Each single-dose vial contains 100 mg of avalglucosidase alfa-ngpt, glycine (200 mg), L-Histidine (10.7 mg), L-Histidine HCl monohydrate (6.5 mg), mannitol (200 mg), and polysorbate 80 (1 mg). After reconstitution with 10 mL of Sterile Water for Injection, USP, the resultant concentration is ≤ 100 mg/mL (10 mg/mL) with a pH of approximately 6.2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pompe disease (also known as glycogen storage disease type II, acid maltase deficiency, or glycogen storage disease type II) is an inherited disorder of glycogen metabolism caused by a deficiency of the lysosomal enzyme α-glucosidase (GAA), which results in intralysosomal accumulation of glycogen in various tissues. Avalglucosidase alfa-ngpt provides an exogenous source of GAA. The M6P on avalglucosidase alfa-ngpt mediates binding to M6P receptors on the cell surface with high affinity. After binding, it is internalized and transported into lysosomes where it undergoes proteolytic cleavage that results in increased GAA enzymatic activity. Avalglucosidase alfa-ngpt then exerts enzymatic activity in clearing glycogen.

12.2 Pharmacodynamics

In patients with Pompe disease, excess of glycogen is degraded to hexose tetrasaccharide (Hex4) which is then excreted in urine. The urinary Hex4 assay measures its major component, glucose tetrasaccharide (Gi4C). In clinical studies, treatment with NEXVIAZYME resulted in reductions of urinary Glc4 concentrations normalized by urine creatinine and reported as mmol Gi4C/mol creatinine in patients with Pompe disease.

In Study 1, the baseline mean urinary Glc4 concentration was 12.7 mmol/mol and 8.7 mmol/mol in NEXVIAZYME and alglucosidase alfa treatment groups, respectively, in treatment-naive LOPD patients with a mean age of 38.7 years [see Clinical Studies (14.1)]. The mean percentage (SD) change in urinary Glc4 concentrations from baseline to Week 49 was -54% (24) and -11% (32) in the NEXVIAZYME and alglucosidase alfa treatment groups, respectively.

12.3 Pharmacokinetics

The avalglucosidase alfa-ngpt exposure increases in an approximately proportional manner with increasing doses over a range from 5 to 20 mg/kg (0.25 to 1 time the approved recommended dosage in LOPD patients weighing ≥30 kg or 0.125 to 0.5 times the approved recommended dosage in LOPD patients weighing <30 kg) without accumulation when observed following every two weeks dosing. Following intravenous infusion of 20 mg/kg of NEXVIAZYME every two weeks in LOPD patients weighing ≥30 kg, the mean ± SD plasma Cmax of avalglucosidase alfa-ngpt at Week 1 and Week 49 was 259 ± 72 µg/mL and 242 ± 81 µg/mL, respectively; the mean ± SD plasma AUC of avalglucosidase alfa-ngpt at Week 1 and Week 49 was 720 ± 420 µg·h/mL and 1230 ± 453 µg·h/mL, respectively. Patients weighing <30 kg are expected to have similar AUC following intravenous infusion of 40 mg/kg of NEXVIAZYME every two weeks.

Distribution

The volume of distribution of avalglucosidase alfa-ngpt was 3.4 L in LOPD patients.
Endpoints and Results from the 49-Week Active-Controlled Period in Study 1

Baseline was 62.1% (range from 32 to 85%), and mean 6MWT at baseline was 388.9 meters (95% CI: 1.3, 58.7) favoring NEXVIAZYME (Table 5). Figure 2 presents the LS mean change from baseline in 6MWT distance over time by treatment group.

Specific Populations

Population pharmacokinetic analyses indicated that age and sex did not significantly influence the pharmacokinetics of avalglucosidase alfa-ngpt in patients with Pompe disease aged 1 to 78 years.

In 16 patients aged 1 to 12 years with Pompe disease, following a 4-hour intravenous infusion of NEXVIAZYME 20 mg/kg every two weeks and 7-hour intravenous infusion of NEXVIAZYME 40 mg/kg every two weeks, the mean Cmax ranged from 175 to 189 µg/mL and 250 to 403 µg/mL, respectively. The mean AUClast ranged from 805 to 923 µg·hr/mL for 20 mg/kg every two weeks and 1,720 to 2,630 µg·hr/mL for 40 mg/kg every two weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential or studies to evaluate mutagenic potential have not been performed with avalglucosidase alfa-ngpt. Intravenous administration of avalglucosidase alfa-ngpt every other day at doses up to 50 mg/kg (exposure not evaluated) had no adverse effects on fertility in male or female mice.

14.1 Clinical Trial in Patients with Late-Onset Pompe Disease

Study 1 (NCT02782741) was a randomized, double-blinded, multinational, multicenter trial comparing the efficacy and safety of NEXVIAZYME to alglucosidase alfa in 100 treatment-naive patients with LOPD. Patients were randomized in a 1:1 ratio based on baseline forced vital capacity (FVC), gender, age, and country to receive 20 mg/kg of NEXVIAZYME or alglucosidase alfa administered intravenously once every two weeks for 49 weeks. The trial included an open-label, long-term, follow-up phase of up to 5 years, in which patients in the alglucosidase alfa arm were switched to NEXVIAZYME treatment. Of the 100 randomized patients, 52 were males, the baseline median age was 49 years old (range from 16 to 78), median baseline weight was 76.4 kg (range from 38 to 139 kg), median length of time since diagnosis was 6.9 months (range from 0.3 to 328.4 months), mean age at diagnosis was 46.4 years old (range from 11 to 78), mean FVC (%) predicted at baseline was 62.1% (range from 32 to 85%), and mean 6MWT at baseline was 388.9 meters (range from 118 to 630 meters).

Endpoints and Results from the 49-Week Active-Controlled Period in Study 1

The primary endpoint of Study 1 was the change in FVC (%) predicted in the upright position from baseline to Week 49. At Week 49, the least squares (LS) mean change in FVC (%) predicted for patients treated with NEXVIAZYME and alglucosidase alfa was 2.9% and 0.5%, respectively. The estimated treatment difference was 2.4% (95% CI: -0.1, 5.0) favoring NEXVIAZYME (see Table 4). Figure 1 presents the LS mean change from baseline in FVC (%) predicted over time by treatment group up to Week 49.

Table 4: Summary Results of FVC (%) Predicted in Upright Position in Treatment-Naive Patients with LOPD (Study 1)

<table>
<thead>
<tr>
<th></th>
<th>NEXVIAZYME (n=51)</th>
<th>Alglucosidase Alfa (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment baseline Mean (SD)</td>
<td>62.5 (14.4)</td>
<td>61.6 (12.4)</td>
</tr>
<tr>
<td>Week 49 Mean (SD)</td>
<td>65.5 (17.4)</td>
<td>61.2 (13.5)</td>
</tr>
<tr>
<td>Estimated change from baseline to week 49 LS mean (SE)</td>
<td>2.9* (0.9)</td>
<td>0.5* (0.9)</td>
</tr>
<tr>
<td>Estimated difference between groups in change from baseline to week 49 LS mean (95% CI)</td>
<td>2.4† (1.5)</td>
<td>-0.1, 5.0</td>
</tr>
</tbody>
</table>

*All randomized patients
†Estimated using a mixed model for repeated measures (MMRM) including baseline FVC (% predicted, as continuous), sex, baseline age (years), treatment group, visit, and treatment-by-visit interaction term as fixed effects.
‡Noninferiority margin of 1.1% (p=0.0074). Statistical superiority of NEXVIAZYME over alglucosidase alfa was not achieved (p=0.06).

Figure 1: Plot of LS Mean (SE) Change from Baseline of FVC (%) predicted in Upright Position over Time in Treatment-Naive Patients with LOPD (Study 1)

Figure 2: Plot of LS Mean (SE) Change from Baseline of 6MWT (distance walked, in meters) over Time in Treatment-Naive Patients with LOPD (Study 1)

*All randomized patients
†The MMRM model for 6MWT distance adjusts for baseline FVC (% predicted), baseline 6MWT (distance walked in meters), baseline age (years), gender, treatment group, visit, and treatment-by-visit interaction as fixed effects.
‡p-value at nominal level, without multiplicity adjustment (p=0.04).
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 from volume overload during NEXVIAZYME infusion [see Warnings and Precautions (5.3)].

NEXVIAZYME Exposure During Pregnancy or Lactation

Pregnant or lactating women exposed to NEXVIAZYME, or their healthcare providers, should report NEXVIAZYME exposure by calling 1-800-745-4447, extension 15500.

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 effects of NEXVIAZYME. 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.registynxt.com or call 1-800-745-4447, extension 15500.

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