HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XENPOZYME safely and effectively. See full prescribing information for XENPOZYME.
XENPOZYME® (olipudase alfa-rpcp) for injection, for intravenous use
Initial U.S. Approval: 2022

WARNING: SEVERE HYPERSENSITIVITY REACTIONS
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, XENPOZYME should be discontinued immediately and appropriate medical treatment should be initiated. (5.1)

RECENT MAJOR CHANGES
Dosage and Administration, Preparation Instructions (2.6) 3/2023
Dosage and Administration, Important Recommendations (2.1) 7/2023

INDICATIONS AND USAGE
XENPOZYME is a hydrolytic lysosomal sphingomyelin-specific enzyme indicated for treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients. (1)

DOSAGE AND ADMINISTRATION
• Prior to initiating treatment, verify pregnancy status in females of reproductive potential and obtain baseline transaminase levels. (2.1)
• Consider pretreating with antihistamines, antipyretics, and/or corticosteroids. (2.1)
• Adults: Recommended starting dose is 0.1 mg/kg administered as an intravenous infusion. (2.1, 2.2, 2.3, 2.5, 2.6, 2.7)
• Pediatrics: Recommended starting dose is 0.03 mg/kg administered as an intravenous infusion. (2.3)
• See Full Prescribing Information for the recommended dose escalation and maintenance dosage, dosage modifications to reduce the risk of adverse reactions, and preparation and administration instructions. (2.1, 2.2, 2.3, 2.5, 2.6, 2.7)

ADVERSE REACTIONS
Most common adverse reactions in adult patients (incidence ≥10%) are headache, cough, diarrhea, hypotension, and ocular hyperemia. (6.1)
Most common adverse reactions in pediatric patients (incidence ≥20%) are pyrexia, cough, diarrhea, rhinitis, abdominal pain, vomiting, headache, urticaria, nausea, rash, arthralgia, pruritus, fatigue, and pharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 07/2023

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**1 INDICATIONS AND USAGE**

XENPOZYME is indicated for treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients.

**2 DOSAGE AND ADMINISTRATION**

**2.1 Important Recommendations**

**Laboratory Testing**

* Before initiating XENPOZYME:
  - Obtain baseline transaminase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) levels in all patients within 1 month prior to treatment initiation [see Warnings and Precautions (5.3)].
  - Verify pregnancy status in females of reproductive potential [see Use in Specific Populations (8.1, 8.3)].

**Weight-Based Dosing Information**

The recommended adult and pediatric dosages of XENPOZYME for the dose escalation and maintenance phases [see Dosage and Administration (2.2, 2.3)] are based on body weight as follows for patients with a body mass index (BMI):

- Less than or equal to 30, the dosage is based on actual body weight (kg)
- Greater than 30, the dosage is based on adjusted body weight (kg). Calculate an adjusted body weight (kg) based on height in meters as described below:

  \[
  \text{Adjusted body weight (kg)} = \left( \frac{\text{height in m}}{30} \right)^2 \times 30
  \]

**Dosage**

Treatment with XENPOZYME should always be initiated via a dose escalation regimen followed by a maintenance dose. For missed doses, see Missed Doses (2.4).

In order to avoid dosing errors including overdose [see Overdose (10)], follow all instructions for dosage and administration, including for preparation and handling, below.

**2.2 Recommended Dosage in Adult Patients**

**Dose Escalation Phase**

The recommended starting dose of XENPOZYME in adults is 0.1 mg/kg.

In order to reduce the risk of hypersensitivity and infusion-associated reactions or elevated transaminase levels, follow the dose escalation regimen in Table 1 [see Warnings and Precautions (5.1, 5.2, 5.3)].

Administer XENPOZYME via intravenous infusion every 2 weeks.

**Maintenance Phase**

The recommended maintenance dosage of XENPOZYME in adults is 3 mg/kg via intravenous infusion every 2 weeks.

In order to reduce the risk of hypersensitivity and infusion-associated reactions or elevated liver enzyme elevations, follow the dose escalation regimen in Table 2 [see Warnings and Precautions (5.1, 5.2, 5.3)].

Administer XENPOZYME via intravenous infusion every 2 weeks.

**2.3 Recommended Dosage in Pediatric Patients**

**Dose Escalation Phase**

The recommended starting dose of XENPOZYME in pediatric patients is 0.03 mg/kg.

In order to reduce the risk of hypersensitivity and infusion-associated reactions or elevated liver enzyme elevations, follow the dose escalation regimen in Table 2 [see Warnings and Precautions (5.1, 5.2, 5.3)].

Administer XENPOZYME via intravenous infusion every 2 weeks.

**Maintenance Phase**

The recommended maintenance dosage of XENPOZYME in pediatric patients is 3 mg/kg via intravenous infusion every 2 weeks.

**2.4 Missed Doses**

A dose is considered missed when it is not administered within 3 days of the scheduled date. When a dose of XENPOZYME is missed, refer to Table 3. Follow the instructions in the “Escalation Phase” or “Maintenance Phase” depending on which phase the patient misses the dose.

**Table 1: XENPOZYME Dose Escalation Regimen for Adult Patients**

<table>
<thead>
<tr>
<th>Adult Patients (18 years and older)</th>
<th>Dose Escalation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose (Day 1/Week 0)</td>
<td>0.1 mg/kg</td>
</tr>
<tr>
<td>Second dose (Week 2)</td>
<td>0.3 mg/kg</td>
</tr>
<tr>
<td>Third dose (Week 4)</td>
<td>0.3 mg/kg</td>
</tr>
<tr>
<td>Fourth dose (Week 6)</td>
<td>0.6 mg/kg</td>
</tr>
<tr>
<td>Fifth dose (Week 8)</td>
<td>0.6 mg/kg</td>
</tr>
<tr>
<td>Sixth dose (Week 10)</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>Seventh dose (Week 12)</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Eighth dose (Week 14)</td>
<td>3 mg/kg (recommended maintenance dose)</td>
</tr>
</tbody>
</table>

*Use actual body weight for patients with a BMI less than or equal to 30. For patients with a BMI greater than 30, calculate adjusted body weight (kg) = \( (\text{actual height in m})^2 \times 30 \) [see Dosage and Administration (2.1)].

†The dose escalation phase includes the first 3 mg/kg dose.

**Table 2: XENPOZYME Dose Escalation Regimen for Pediatric Patients**

<table>
<thead>
<tr>
<th>Pediatric Patients (0 to 17 years)</th>
<th>Dose Escalation Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>First dose (Day 1/Week 0)</td>
<td>0.03 mg/kg</td>
</tr>
<tr>
<td>Second dose (Week 2)</td>
<td>0.1 mg/kg</td>
</tr>
<tr>
<td>Third dose (Week 4)</td>
<td>0.3 mg/kg</td>
</tr>
<tr>
<td>Fourth dose (Week 6)</td>
<td>0.3 mg/kg</td>
</tr>
<tr>
<td>Fifth dose (Week 8)</td>
<td>0.6 mg/kg</td>
</tr>
<tr>
<td>Sixth dose (Week 10)</td>
<td>0.6 mg/kg</td>
</tr>
<tr>
<td>Seventh dose (Week 12)</td>
<td>1 mg/kg</td>
</tr>
<tr>
<td>Eighth dose (Week 14)</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Ninth dose (Week 16)†</td>
<td>3 mg/kg (recommended maintenance dose)</td>
</tr>
</tbody>
</table>

*Use actual body weight for patients with a BMI less than or equal to 30. For patients with a BMI greater than 30, calculate adjusted body weight (kg) = \( (\text{actual height in m})^2 \times 30 \) [see Dosage and Administration (2.1)].

†The dose escalation phase includes the first 3 mg/kg dose.

**Maintenance Phase**

The recommended maintenance dosage of XENPOZYME in pediatric patients is 3 mg/kg via intravenous infusion every 2 weeks.

**2.5 Dosage and Administration Modifications and Monitoring**

* In the event of a severe hypersensitivity reaction (e.g., anaphylaxis) or a severe infusion-associated reaction [see Warnings and Precautions (5.1, 5.2)], immediately discontinue XENPOZYME administration and initiate appropriate medical treatment [see Warnings and Precautions (5.1, 5.2)].

†In the event of a mild to moderate hypersensitivity reaction or a mild to moderate IAR, consider temporarily holding or slowing the infusion rate, and/or reducing the XENPOZYME dose. If dose is reduced, re-escalate following dose escalation described in Tables 1 and 2 for adult and pediatric patients, respectively [see Warnings and Precautions (5.1, 5.2)].

‡If transaminase levels are elevated above baseline and >2 times the ULN prior to the next scheduled administration, the XENPOZYME dose can be adjusted (prior dose repeated or reduced) or treatment can be temporarily withheld until the liver transaminases return to the patient’s baseline value [see Warnings and Precautions (5.3)].

**2.6 Preparation Instructions**

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

1. **Reconstitution and Dilution Instructions**

   1. Determine the number of XENPOZYME vials to be reconstituted based on the calculated dose [see Dosage and Administration (2.2, 2.3)].
   2. Remove XENPOZYME vials from refrigeration and set aside for approximately 20 to 30 minutes to allow vials to reach room temperature.
   3. Reconstitute each vial with:
      * 1.1 mL of Sterile Water for Injection, USP into the 4 mg vial
      * 5.1 mL of Sterile Water for Injection, USP into the 20 mg vial
   4. Gently roll and tilt vials to reconstitute XENPOZYME and avoid foaming. Each reconstituted vial will yield a 4 mg/mL clear, colorless solution.
5. Visually inspect the reconstituted solution in the vials for particulate matter and discoloration. The solution should be clear and colorless. Discard if the solution is discolored or if visible particulate matter is present.

6. Withdraw the required volume of XENPOZYME from the vial(s) and dilute the XENPOZYME solution for infusion with 0.9% Sodium Chloride Injection, USP in a syringe or infusion bag depending on the volume of infusion (see Table 4).
   - For patients who weigh less than 10 kg receiving 0.03 mg/kg and 0.1 mg/kg and patients who weigh between 10 to 20 kg receiving 0.03 mg/kg dose, the volume of infusion will vary to achieve a fixed final concentration of 0.1 mg/mL (see Table 4).
   - Prepare the required dose diluted to a final concentration of 0.1 mg/mL in a syringe for infusion.
   - For all other patient weights and doses, the final concentration will vary to achieve a fixed total volume (see Table 4).
      - For total volume less than or equal to 20 mL prepare a syringe for infusion:
         - Inject the required volume of the reconstituted XENPOZYME solution (4 mg/mL) from step 3 slowly down the inside wall of the syringe.
         - Add slowly the quantity sufficient of 0.9% Sodium Chloride Injection, USP to obtain the required total infusion volume (avoid foaming within the syringe).
      - For a total volume of greater than or equal to 50 mL prepare an infusion bag: Add slowly the required volume of the reconstituted XENPOZYME solution (4 mg/mL) from step 3 into the appropriate size 0.9% Sodium Chloride Injection, USP infusion bag (avoid foaming within the bag) to achieve a fixed total volume per Table 4.

7. Gently invert the syringe or the infusion bag to mix. Do not shake. Because this is a protein solution, slight flocculation (described as thin translucent fibers) occurs occasionally after dilution.

8. Vials are for single dose only. Discard any unused solution.

Storage and Handling of the Reconstituted and Diluted Solutions
- If the reconstituted XENPOZYME vials are not used immediately, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature at 20°C to 25°C (68°F to 77°F) for up to 6 hours.
- If the diluted solution is not administered immediately, store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature at 20°C to 25°C (68°F to 77°F) for up to 12 hours (including infusion time).
- Do not freeze.

**Table 4: XENPOZYME Infusion Volumes for Pediatric and Adult Patients Based on Body Weight**

<table>
<thead>
<tr>
<th>XENPOZYME Dosage</th>
<th>Total Infusion Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body Weight</strong></td>
<td><strong>Pediatric Patients (0 to 17 years)</strong></td>
</tr>
<tr>
<td>≥2 kg and &lt;10 kg</td>
<td>Actual volume will vary³  (0.6 mL to 3 mL)</td>
</tr>
<tr>
<td>0.03 mg/kg</td>
<td>5 mL</td>
</tr>
<tr>
<td>0.1 mg/kg</td>
<td>10 mL</td>
</tr>
<tr>
<td>0.3 mg/kg</td>
<td>10 mL</td>
</tr>
<tr>
<td>0.6 mg/kg</td>
<td>20 mL</td>
</tr>
<tr>
<td>1.0 mg/kg</td>
<td>50 mL</td>
</tr>
<tr>
<td>2.0 mg/kg</td>
<td>75 mL</td>
</tr>
<tr>
<td>3.0 mg/kg</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

³Use actual or adjusted body weight based on BMI. Refer to section 2. [see Dosage and Administration (2.2, 2.3)].

**Table 5: XENPOZYME Infusion Rates for Adult Patients**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Infusion Rate</th>
<th>step 1</th>
<th>step 2</th>
<th>step 3</th>
<th>step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03 mg/kg</td>
<td>0.1 mg/kg/hour for the full length of the infusion</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>0.1 mg/kg</td>
<td>0.3 mg/kg/hour</td>
<td>0.6 mg/kg/hour</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>0.3 mg/kg</td>
<td>0.6 mg/kg/hour</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>0.6 mg/kg</td>
<td>0.9 mg/kg/hour</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>1.5 mg/kg/hour</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>2.2 mg/kg/hour</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>3.0 mg/kg/hour</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

NA: Not applicable.

Start infusion at step 1 and in absence of infusion-associated reactions increase infusion rate sequentially per the steps of infusion.

**Table 6: XENPOZYME Infusion Rates for Pediatric Patients**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Infusion Rate</th>
<th>step 1</th>
<th>step 2</th>
<th>step 3</th>
<th>step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg/kg</td>
<td>0.1 mg/kg/hour</td>
<td>0.3 mg/kg/hour</td>
<td>0.6 mg/kg/hour</td>
<td>1 mg/kg/hour</td>
<td></td>
</tr>
</tbody>
</table>

NA: Not applicable.

Start infusion at step 1 and in absence of infusion-associated reactions increase infusion rate sequentially per the steps of infusion.

**5.2 Infusion-Associated Reactions**

Anaphylactoid, antitibodies, and/or corticosteroids may be given prior to XENPOZYME administration to reduce the risk of infusion-associated reactions (IARs). However, IARs may still occur in patients after receiving pretreatment.

- If severe IARs occur, discontinue XENPOZYME immediately and initiate appropriate medical treatment. Consider the risks and benefits of re-administering XENPOZYME following severe
IARs. One patient has been rechallenged using slower infusion rates at a dose lower than the recommended dose. If a patient tolerates the infusion, the dose may be increased to reach the recommended dose.

- If a mild or moderate IAR occurs, the infusion rate may be slowed or temporarily withheld, and/or the XENPOZYME dosage may be reduced [see Dosage and Administration (2.5)].

IARs occurred in approximately 75% of pediatric and 50% of adult XENPOZYME-treated patients in the clinical trials; a severe IAR occurred in one (12.5%) of the pediatric patients. The most frequent IARs in:

- ≥10% of adult patients were headache, pruritus, vomiting, and urticaria
- ≥20% of pediatric patients were urticaria, pruritus, nausea, pyrexia, and vomiting

Acute phase reaction (APR), an acute inflammatory response accompanied by elevations in inflammatory serum protein concentrations, was observed in one XENPOZYME-treated adult and one XENPOZYME-treated pediatric patient. Most of the APRs occurred at 48 hours post infusion during the dose escalation phase. Elevations of C-reactive protein, calcium, and IL-6, and reductions of serum iron were observed. The most common clinical symptoms associated with APRs were pyrexia, vomiting, and diarrhea. All events can be managed as other IARs.

5.3 Elevated Transaminase Levels

XENPOZYME may be associated with elevated transaminases (ALT, AST, or both) within 24 to 48 hours after infusion. Elevated transaminase levels were reported in 4 (13%) XENPOZYME-treated adults and 1 (13%) XENPOZYME-treated pediatric patient during the dose escalation phase in clinical trials. The time of the next scheduled infusion, these elevated transaminase levels generally returned to levels observed prior to the XENPOZYME infusion [see Adverse Reactions (6.1)].

To manage the risk of elevated transaminase levels, assess ALT and AST within one month prior to initiation of XENPOZYME, within 72 hours prior to any infusion during dose escalation, which includes the first 3 mg/kg dose outlined in Tables 1 and 2, or prior to the next scheduled XENPOZYME infusion upon resuming treatment following a missed dose.

If either the baseline or pre-infusion transaminase level (during the dose escalation phase) is ≥2 times the ULN, repeat transaminase levels within 72 hours after the end of the infusion. If the pre-infusion transaminase levels are elevated above baseline and ≥2 times the ULN prior to the next scheduled administration of XENPOZYME, the dose can be reduced (repeat prior lower dose or reduce the dose). XENPOZYME can be temporarily withheld until the liver transaminases return to the patient’s baseline value.

Upon reaching the recommended maintenance dose, transaminase testing is recommended to be continued as part of routine clinical management of ASMD.

5.4 Risk of Fetal Malformations During Dosage Initiation or Escalation in Pregnancy

There is no evidence that olipudase alfa-rpcp crosses the human placenta. However, published literature reports that early embryonic exposure to a metabolite of sphingomyelin (ceramide) or the S1P receptor modulator fingolimod can produce exencephaly in chicks and mice, respectively. In animal reproduction studies, exencephaly, a neural tube defect occurring in the first trimester of pregnancy, was observed in mouse fetuses at exposures less than the exposure at the maximum recommended human dose of olipudase alfa-rpcp. XENPOZYME dosage initiation or escalation, at any time during pregnancy, is not recommended as it may lead to elevated sphingomyelin metabolite levels that may increase the risk of fetal malformations [see Use in Specific Population (8.1), Clinical Pharmacology (12.2)]. The decision to continue or discontinue XENPOZYME maintenance dosing in pregnancy should consider the female’s need for XENPOZYME, the potential drug-related risks to the fetus, and the potential adverse outcomes from untreated maternal ASMD disease.

Verify the pregnancy status in females of reproductive potential prior to initiating XENPOZYME treatment. Advise females of reproductive potential to use effective contraception during treatment and for 14 days after the last dose if XENPOZYME is discontinued [see Warnings and Precautions (5.1)].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity Reactions Including Anaphylaxis [see Warnings and Precautions (5.1)]
- Infusion-Associated Reactions (IARs) [see Warnings and Precautions (5.2)]
- Elevated Transaminase Levels [see Warnings and Precautions (5.3)]

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 practice.

The pooled safety analysis from 3 clinical trials included a total of 38 XENPOZYME-treated patients (30 adult and 8 pediatric patients) aged range from 1.5 to 59 years old receiving infusions every 2 weeks up to 3 mg/kg every 2 weeks [see Clinical Studies (14.2)]. The median exposure duration was 2.5 years (range: 0.4 to 3.7 years) in adult patients and 2.7 years (range: 2.5 to 3.2 years) in pediatric patients. Serious adverse reactions of anaphylactic reaction were reported in 2 (25%) XENPOZYME-treated pediatric patients. Most frequently reported adverse drug reactions in adults (incidence ≥10%) were headache, cough, diarrhea, hypotension, and urticaria. Most frequently reported adverse drug reactions in pediatric patients (incidence ≥20%) were pyrexia, cough, diarrhea, rhinitis, abdominal pain, vomiting, headache, urticaria, nausea, rash, arthralgia, pruritus, fatigue, and pharyngitis.

Adult patients with ASMD type B and type A/B (Trial 1)

In Trial 1, 13 adult patients received XENPOZYME once every 2 weeks for 52 weeks (primary analysis period (PAP)) at dosages escalating from 0.1 mg/kg to a target dose of 3 mg/kg [see Clinical Studies (14.2)].

Adverse reactions that occurred in at least 7% of XENPOZYME-treated adult patients during the PAP are described in Table 7.

Table 7: Adverse Reactions Occurring at ≥7% in Adult Patients with ASMD During the 52-Week Primary Analysis Period in Trial 1

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XENPOZYME N=13</th>
<th>Placebo N=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7 (54%)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (31%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (15%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (15%)</td>
<td>2 (11%)</td>
</tr>
</tbody>
</table>

Adverse reactions that occurred in at least 13% of pediatric patients are described in Table 8.

Table 8: Adverse Reactions Occurring at ≥13% in XENPOZYME-Treated Pediatric Patients with ASMD in Trial 2 and 3 for an Overall Observation Period of 2.5 to 3.2 Years

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XENPOZYME N=8</th>
<th>Placebo N=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>8 (100%)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>6 (75%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (75%)</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>6 (75%)</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (63%)</td>
<td></td>
</tr>
<tr>
<td>Urticaria</td>
<td>4 (50%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (38%)</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3 (38%)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (38%)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (25%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (25%)</td>
<td></td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2 (25%)</td>
<td></td>
</tr>
<tr>
<td>C-reactive protein increased</td>
<td>1 (13%)</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (13%)</td>
<td></td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>1 (13%)</td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 (13%)</td>
<td></td>
</tr>
<tr>
<td>Infusion site swelling</td>
<td>1 (13%)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1 (13%)</td>
<td></td>
</tr>
<tr>
<td>Pharyngeal swelling</td>
<td>1 (13%)</td>
<td></td>
</tr>
</tbody>
</table>

Abdominal pain includes abdominal pain and abdominal pain upper. Fatigue includes fatigue and asthenia. Rash includes rash and erythema.

Duration of treatment in Trial 2 was 64 weeks. All patients continued into Trial 3.

Treatment related serious adverse reactions, hypersensitivity reactions including anaphylaxis, and IARs occurred within 24 hours of infusion and were observed in a higher percentage of pediatric patients than in adult patients.

Laboratory Adverse Reaction

Elevated transaminase levels ranging from 3 to 14 times the upper limit of normal (ULN) were reported in 4 (13%) adults and 1 (13%) pediatric patient during the XENPOZYME dose escalation phase in clinical trials.

Immunogenicity: Antidrug Antibody-Associated Adverse Reactions

In Trial 1, one XENPOZYME-treated pediatric patient (18-month-old) experienced an anaphylactic reaction during the sixth infusion and developed IgE ADE and the highest IgG ADE titers (ADA peak titer 1,600) of the patients in this trial. After treatment discontinuation, XENPOZYME was resumed four months later using a diluted drug solution and a desensitization procedure.
8.1 Pregnancy

Risk Summary

Based on findings from animal reproduction studies, XENPOZYME may cause embryo-fetal harm when administered to a pregnant female. XENPOZYME dosage initiation or escalation, at any time during pregnancy, may lead to elevated sphingomyelin metabolite levels that may increase the risk of fetal malformations [see Data], [see Clinical Pharmacology (12.2)]. However, the decision to continue or discontinue XENPOZYME maintenance dosing in pregnancy should consider the female’s need for XENPOZYME, the potential drug-related risks to the fetus, and the potential adverse outcomes from untreated maternal ASMD disease.

In an embryo-fetal toxicity study in pregnant mice, a rare malformation (exencephaly) was observed in offspring at an exposure less than the exposure at the maximum recommended human dose (MRHD) of olipudase alf-prcp [see Data].

There are no available data on XENPOZYME use in pregnant females to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Advise the pregnant female of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for 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.

8.2 Lactation

Risk Summary

There are no data on the presence of olipudase alfa-prcp in human milk, the effects on the breastfed infant, or the effects on milk production. Olipudase alfa-prcp is present in animal milk. [see Data]. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The development of breast feeding should be considered along with the mother’s clinical need for XENPOZYME and any potential adverse effects on the breastfed infant from XENPOZYME or from the underlying maternal condition.

Data

Olipudase alfa-prcp was administered as a single intravenous dose (3 mg/kg) to lactating CD1 mice on post-partum day 7. Milk was not evaluated until post-partum day 5, at which time concentrations of olipudase alfa-prcp detected were approximately 1.3% the estimated maximal maternal plasma concentration.

8.3 Females and Males of Reproductive Potential

XENPOZYME may cause embryo-fetal harm when administered during the first trimester of pregnancy [see Use in Specific Populations (8.1)].

Pregnancy Testing

Verify the pregnancy status in females of reproductive potential prior to initiating XENPOZYME.

Contraception

Advise females of reproductive potential to use effective contraception during treatment and for 14 days after the last dose of XENPOZYME is discontinued.

8.4 Pediatric Use

The safety and effectiveness of XENPOZYME for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) have been established in pediatric patients down to birth.

Use of XENPOZYME for this indication is supported by evidence from an adequate, and well-controlled trial (Trial 1) in adults with supportive efficacy, safety, and tolerability data in pediatric patients (Trial 2 and Trial 3) [see Adverse Reactions (6.1) and Clinical Studies (14.2, 14.3, 14.4)].

Compared to adults, a higher percentage of pediatric patients experienced treatment related serious adverse reactions, anaphylaxis, hypersensitivity reactions, and IARs that occurred within 24 hours of infusion [see Adverse Reactions (6.1)]. Two pediatric patients, an 18 month old receiving XENPOZYME and a 16 month old with ASMD type A that received a version of olipudase alfa manufactured from a different process developed anaphylaxis [see Warnings and Precautions (5.1)].

8.5 Geriatric Use

Of the total number of XENPOZYME-treated adult patients in these trials, 1 (3%) was 65 to 74 years of age, and none were 75 years of age and older [see Clinical Studies (14)]. Clinical trials of XENPOZYME did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

10 OVERDOSAGE

A limited number of cases of overdose of XENPOZYME have been reported in pediatric patients during dose escalation. Some of these patients experienced serious adverse events within 24 hours of treatment initiation, including death. The main clinical findings included respiratory failure, hypotension, marked elevations in liver function tests, and gastrointestinal bleeding.

There is no known specific antidote for Xenozyme overdose. In the event of overdose, immediately stop the infusion, and monitor the patient closely in a hospital setting for the development of IARs including acute phase reactions. For the management of adverse reactions, see Warnings and Precautions (5.1, 5.2, 5.3) and Adverse Reactions (6.1).

12.1 Mechanism of Action

ASMD is a lysosomal storage disease that results from reduced activity of the enzyme acid sphingomyelinase (ASM), caused by pathogenic variants in the sphingomyelin phosphodiesterase 1 gene. ASM degrades sphingomyelin to ceramide and phosphocholine. The deficiency of ASM causes an intra-lysosomal accumulation of sphingomyelin (as well as cholesterol and other cell membrane lipids) in various tissues. XENPOZYME provides an exogenous source of ASM.

XENPOZYME is not expected to cross the blood-brain barrier or modulate the CNS manifestations of ASMD.

12.2 Pharmacodynamics

Plasma Lysosphingomyelin Levels

Lysosphingomyelin is substantially elevated in plasma of adult and pediatric patients with ASMD. Plasma lysosphingomyelin levels decreased after repeated administration of XENPOZYME and were approximately 50% of baseline levels by Week 52 following treatment with XENPOZYME.

12.3 Pharmacokinetics

In adult patients with ASMD in Trial 1 [see Clinical Studies (14.2)], the mean (standard deviation, SD) plasma lysosphingomyelin concentration was 379 (204) mcg/L at baseline and decreased to 200 (120) mcg/L at Week 52 following treatment with XENPOZYME.

In pediatric patients with ASMD in Trial 2 [see Clinical Studies (14.3)], the mean (SD) plasma lysosphingomyelin concentration was 47.0 (9.9) mcg/L at baseline and decreased to 1.8 (0.3) mcg/L at Week 52 following treatment with XENPOZYME.

Lever Sphingomyelin Content

In adult patients, the liver sphingomyelin content, as assessed by histopathology, decreased from baseline to Week 52 in the XENPOZYME treatment group compared to an increase in the placebo group.

12.4 Metabolism

The metabolic pathway of olipudase alfa-prcp has not been characterized. Olipudase alfa-prcp is expected to be metabolized into small peptides and amino acids via catabolic pathways.

12.5 Elimination

The metabolic pathway of olipudase alfa-prcp has not been characterized. Olipudase alfa-prcp is expected to be metabolized into small peptides and amino acids via catabolic pathways.
Following 2.5 to 3.2 years of XENPOZYME treatment in Trial 2 and 3 (see Clinical Studies (14.3)), 6 out of 9 (75%) XENPOZYME-treated pediatric patients with ASMD developed IgG ADA. The median time to seroconversion from first XENPOZYME infusion was 10 weeks. One out of the 6 (17%) pediatric patients developed NAb that inhibited olipudase alfa-rpcp enzyme activity. None of these 6 patients had NAb that inhibited the cellular uptake of olipudase alfa-rpcp.

Infusion-associated reactions (including hypersensitivity reactions) occurred in a higher percentage in XENPOZYME-treated patients who developed ADA compared to those who did not develop ADA (see Warnings and Precautions (5.1) and Adverse Reactions (6.1)). There was no identified clinically significant effect of ADA on pharmacokinetics of XENPOZYME.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Studies to evaluate the carcinogenic potential of olipudase alfa-rpcp have not been conducted.

Mutagenesis

Studies to evaluate the mutagenic potential of olipudase alfa-rpcp have not been conducted.

Impairment of Fertility

Intravenous administration of olipudase alfa-rpcp every other day at doses up to 30 mg/kg had no adverse effects in a combined study of fertility in male and female mice. Exposures at this dose, based on the embryo-fetal development study, were estimated to be approximately 1.5-fold those of the MRHD of olipudase alfa-rpcp.

13.2 Animal Toxicology and/or Pharmacology

In acid sphingomyelinase knock-out (ASMKO) mice (a disease model of ASMD), mortality was observed after a single dose ≥10 mg/kg administered as an IV bolus injection. Observations (lethargy, coolness to touch, and unwillingness to move), combined with the adrenal hemorrhage, suggested that hypotensive shock may be the cause of death. These findings were accompanied by necrosis and apoptosis in the liver and subcutaneous gland, elevations of ceramide, sphingosine and sphinganine 1-phosphate in the serum, catabolites of accumulated sphingomyelin as well as elevations in the serum concentrations of inflammatory mediators, such as cytokines and acute phase proteins.

In ASMKO mice, a dose-dependent reduction in heart rate accompanied by a decrease in motor activity and followed by a slow decline in blood pressure was noted after a single IV administration at 3, 10, and 20 mg/kg. After 2 doses of olipudase alfa-rpcp at 3 and 10 mg/kg to ASMKO mice, a slight decline in heart rate was noted following the second administration.

Repeated dose studies in adult ASMKO mice show that administration of olipudase alfa-rpcp via a dose escalation regimen (3 mg/kg administered IV every other day, followed by a single IV dose of 20 mg/kg 3 days later) did not result in toxicity. The lack of adverse findings in BALB/c, C57BL/6 mice, rats, dogs, and monkeys at comparable olipudase alfa-rpcp doses suggested that the dose-related toxicity observed in ASMKO mice may be due to the rate and amount of substrate degradation.

14 CLINICAL STUDIES

14.1 Overview of Clinical Trials

The efficacy of XENPOZYME for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) has been evaluated in 3 clinical trials involving a total of 61 patients with ASMD:

• Trial 1 in adult patients (NCT02004691),
• Trial 2 in pediatric patients (NCT02262964), and
• Trial 3 a long-term trial in pediatric patients (NCT0204704).

14.2 Clinical Trial in Adult Patients with ASMD

Trial 1 was a multicenter, randomized, double-blinded, placebo-controlled, repeat-dose phase II/III trial in adult patients with ASMD (clinical diagnosis consistent with ASMD type B and A/B). In this trial, patients enrolled in the trial received either XENPOZYME or placebo. Follow-up included 4 groups as an intravenous infusion once every 2 weeks. XENPOZYME was dosed as follows: 0.1 mg/kg (Day 1, Week 0), 0.3 mg/kg (Week 1, 2, 3, and 4), 0.6 mg/kg (Weeks 5 and 6), 1 mg/kg (Week 10), 2 mg/kg (Week 12), and then a maintenance dose of 3 mg/kg (Week 14 onwards). The trial was divided into 2 consecutive periods: a randomized placebo-controlled, double-blinded primary analysis period (PAP) which lasted to Week 52, followed by an extension treatment period (ETP) for up to 4 years. Patients randomized to the placebo arm in the PAP crossed over to receive XENPOZYME treatment in the ETP to reach the targeted dose of 3 mg/kg, while patients in the original XENPOZYME arm continued treatment.

Patients enrolled in the trial had an initial 0.1 mg/kg dose and then had a cumulative dose of 3 mg/kg (Week 14 onwards). The trial was conducted in 24 centers in the USA and included patients with ASMD who met the criteria for inclusion in the trial. The trial population included 87% White, 7% Asian, and 12% Black patients. Patients were included if they had a diagnosis of ASMD type B, A/B, and were at least 18 years of age. The median time to seroconversion from first XENPOZYME infusion was 10 weeks. One out of the 6 (17%) pediatric patients developed NAb that inhibited olipudase alfa-rpcp enzyme activity. None of these 6 patients had NAb that inhibited the cellular uptake of olipudase alfa-rpcp.

14.3 Clinical Trial in Pediatric Patients with ASMD

Trial 2 was a multicenter, randomized, double-blinded, placebo-controlled, repeat-dose phase II/III trial in pediatric patients with ASMD: patients with ASMD with a diffusion capacity of the lungs for carbon monoxide (DLco) greater than or equal to 70% of the predicted normal value and a spleen volume of more than 90% of the predicted normal value at baseline. The trial included patients who were at least 1 year old and had a diagnosis of ASMD type B or A/B. In this trial, patients enrolled in the treatment group received XENPOZYME for 52 weeks (in the PAP) started or continued treatment with XENPOZYME, and followed by a slow decline in blood pressure was noted after a single IV administration at 3, 10, and 20 mg/kg. After 2 doses of olipudase alfa-rpcp at 3 and 10 mg/kg to ASMKO mice, a slight decline in heart rate was noted following the second administration.

Repeated dose studies in adult ASMKO mice show that administration of olipudase alfa-rpcp via a dose escalation regimen (3 mg/kg administered IV every other day, followed by a single IV dose of 20 mg/kg 3 days later) did not result in toxicity. The lack of adverse findings in BALB/c, C57BL/6 mice, rats, dogs, and monkeys at comparable olipudase alfa-rpcp doses suggested that the dose-related toxicity observed in ASMKO mice may be due to the rate and amount of substrate degradation.

14.4 Clinical Trial in Pediatric Patients with ASMD Type B, A/B on XENPOZYME or Placebo (Trial 3)

Trial 3 was a long-term trial in pediatric patients (NCT02004704) for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD). The trial included patients who were at least 1 year old and had a diagnosis of ASMD with a diffusion capacity of the lungs for carbon monoxide (DLco) greater than or equal to 70% of the predicted normal value and a spleen volume of more than 90% of the predicted normal value at baseline. The trial was conducted in 20 centers in the USA and included patients with ASMD who met the criteria for inclusion in the trial. The trial population included 87% White, 7% Asian, and 12% Black patients. Patients were included if they had a diagnosis of ASMD type B, A/B, and were at least 1 year old. The median time to seroconversion from first XENPOZYME infusion was 10 weeks. One out of the 6 (17%) pediatric patients developed NAb that inhibited olipudase alfa-rpcp enzyme activity. None of these 6 patients had NAb that inhibited the cellular uptake of olipudase alfa-rpcp.

The efficacy of XENPOZYME for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) has been evaluated in 3 clinical trials involving a total of 61 patients with ASMD:

• Trial 1 in adult patients (NCT02004691),
• Trial 2 in pediatric patients (NCT02262964), and
• Trial 3 a long-term trial in pediatric patients (NCT0204704).

Endpoints in Adult Patients with ASMD Type B, A/B on XENPOZYME or Placebo (Trial 1)

Table 9: Observed Value and Percentage Change from Baseline to Week 52 in Key Endpoints in Adult Patients with ASMD Type B, A/B on XENPOZYME or Placebo (Trial 1)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>XENPOZYME</th>
<th>Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean platelet count (10⁹/L)</td>
<td>115.6</td>
<td>109.3</td>
<td>NA</td>
</tr>
<tr>
<td>Mean platelet count at 10⁹/L at baseline</td>
<td>115.6</td>
<td>109.3</td>
<td>NA</td>
</tr>
<tr>
<td>Mean platelet count at 10⁹/L at Week 52 (SD)</td>
<td>120.2</td>
<td>126.4</td>
<td>NA</td>
</tr>
<tr>
<td>Mean platelet count at Platelet Count from baseline to Week 52 (SE)</td>
<td>2.7 (4.5)</td>
<td>18.3 (5.0)</td>
<td>+15.6 (6.7) [1.8, 29.4]</td>
</tr>
</tbody>
</table>

Nominal p value: *p value = 0.0003; †p value <0.0001; ‡p value = 0.0280

Seventeen of 18 patients previously receiving placebo and 13 of 13 patients previously treated with XENPOZYME for 52 weeks (in the PAP) started or continued treatment with XENPOZYME, respectively, for up to 4 years. At Week 104, patients initially randomized to placebo had received XENPOZYME for 52 weeks and demonstrated the following LS mean (SE) percent changes in clinical parameters from baseline (before first administration of XENPOZYME): increase in % predicted DLco was 26.8% (6.2) (Figure 1); reduction in spleen volume (MN) was 36.5% (2.5) (Figure 2); reduction in liver volume (MN) was 29.5 (2.6); and increase in platelet count was 19.5 (6.7).

Patients in the previous XENPOZYME group demonstrated improvement from baseline to Week 104 in the following parameters: LS mean (SE) percent increase in % predicted DLco was 34.1% (7.9) (Figure 1); LS mean (SE) percent reduction in spleen volume (MN) was 48.3 (2.9) (Figure 2); LS mean (SE) percent reduction in liver volume (MN) was 51.7 (2.9); LS mean (SE) percent increase in platelet count was 24.0 (8.2).

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>XENPOZYME</th>
<th>Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean % predicted DLco at baseline (SD)</td>
<td>48.5 (10.8)</td>
<td>49.1 (9.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Mean % predicted DLco at Week 52 (SD)</td>
<td>49.9 (11.1)</td>
<td>59.4 (9.6)</td>
<td>NA</td>
</tr>
</tbody>
</table>
The vertical bars represent the 95% CIs for the LS means.
The LS means and 95% CIs are based on a mixed model for repeated measures approach, using data up to Week 104. Patients in placebo/XENPOZYME group received placebo by Week 52 and switched to XENPOZYME thereafter.

Figure 2: Plot of the LS means (95% CI) of the Percentage Change in Spleen Volume (MN) from Baseline to Week 104 in Patients with ASMD (Trial 1)

The vertical bars represent the 95% CIs for the LS means.
The LS means and 95% CIs are based on a mixed model for repeated measures approach, using data up to Week 104. Patients in placebo/XENPOZYME group received placebo by Week 52 and switched to XENPOZYME thereafter.

Figure 2: Plot of the LS means (95% CI) of the Percentage Change in Spleen Volume (MN) from Baseline to Week 104 in Patients with ASMD (Trial 1)