▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – XENPOZYME® (OLIPUDASE ALFA)

1 NAME OF THE MEDICINE

Olipudase alfa

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 4 mg or 20 mg of olipudase alfa.

After reconstitution, each vial contains 4 mg of olipudase alfa per mL.

Olipudase alfa is a recombinant human acid sphingomyelinase and is produced in a Chinese Hamster Ovary (CHO) cell line by recombinant DNA technology.

For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

Powder for injection.

White to off-white lyophilised powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Xenpozyme is indicated as an enzyme replacement therapy for the treatment of non-central nervous system (CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in paediatric and adult patients with type A/B (Niemann-Pick type A/B) or type B (Niemann-Pick type B).

4.2 DOSE AND METHOD OF ADMINISTRATION

Xenpozyme treatment should be initiated and supervised by a physician experienced in the management of ASMD or other inherited metabolic disorders. Xenpozyme infusion should be administered by a healthcare professional with access to appropriate medical support to manage potential severe reactions, including serious systemic hypersensitivity reactions and anaphylaxis. Treatment with Xenpozyme should always be initiated via a dose escalation

regimen followed by a maintenance dose. The dose escalation regimens are different for adult and paediatric patients, see Table 1 and Table 2. For missed doses see Table 3.

A limited number of paediatric patients experienced serious adverse events, including death, when receiving higher than recommended doses of Xenpozyme during dose escalation. In order to avoid dosing errors including overdose, all instructions for dosage, administration, preparation and handling in Section 4.2 should be followed, also see Section 4.9 Overdose and Section 6.3 Shelf life.

Dose

The rapid metabolism of accumulated sphingomyelin (SM) by Xenpozyme generates pro-inflammatory breakdown products, which may induce infusion-associated reactions and/or transient liver enzyme elevations. A dose escalation regimen can minimise the majority of these adverse events (see Section 4.8 – Adverse Effects (Undesirable Effects)).

Xenpozyme dose (both escalation and maintenance phases) for adult and paediatric patients is calculated based on the body weight (see Table 1 for adults and Table 2 for paediatric patients):

- **Patients with a body mass index (BMI) ≤ 30: actual body weight is used**
- **Patients with a body mass index (BMI) > 30: an optimal body weight is used to calculate the dose via the following method**:
  Optimal body weight (kg) to be used for dose calculation = 30 x (actual height in m)^2

For example, a patient with:
BMI of 38
body weight of 110 kg
height of 1.70 m.
The dose to be administered will be calculated using a body weight of $30 \times 1.70^2 = 86.7$ kg

Adult Patients

Dose Escalation Phase

The recommended starting dose of Xenpozyme is 0.1 mg/kg for adults (also see missed doses subsection for additional guidance) and subsequently, the dose should be increased according to the dose escalation regimen presented in Table 1.

Table 1 - Dose escalation regimen in adults

Adult Patients (≥ 18 years old)	
First dose (day 1/week 0)	0.1 mg/kg
Second dose (week 2)	0.3 mg/kg
Third dose (week 4)	0.3 mg/kg
Fourth dose (week 6)	0.6 mg/kg
Fifth dose (week 8)	0.6 mg/kg

Adult Patients (≥ 18 years old)	
Sixth dose (week 10)	1 mg/kg
Seventh dose (week 12)	2 mg/kg
Eighth dose (week 14)	3 mg/kg (recommended maintenance dose)

Maintenance Phase

The recommended maintenance dosage of Xenpozyme is 3 mg/kg every 2 weeks.

Paediatric Patients

Dose Escalation Phase

The recommended starting dose of Xenpozyme is 0.03 mg/kg for paediatric patients and the dose should be subsequently increased according to the dose escalation regimen presented in Table 2.

Table 2 - Dose escalation regimen in paediatric patients

Paediatric Patients (0 to < 18 years old)	
First dose (day 1/week 0)	0.03 mg/kg
Second dose (week 2)	0.1 mg/kg
Third dose (week 4)	0.3 mg/kg
Fourth dose (week 6)	0.3 mg/kg
Fifth dose (week 8)	0.6 mg/kg
Sixth dose (week 10)	0.6 mg/kg
Seventh dose (week 12)	1 mg/kg
Eighth dose (week 14)	2 mg/kg
Ninth dose (week 16)	3 mg/kg (recommended maintenance dose)

Maintenance Phase

The recommended maintenance dosage of Xenpozyme is 3 mg/kg every 2 weeks.

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, administer the next dose as described below in Table 3 as soon as possible. Thereafter, administration should be scheduled every 2 weeks from the date of the last administration. Follow the instructions in the “Escalation Phase” or “Maintenance Phase” depending on which phase the patient misses the dose.

Table 3 - Dosing Recommendations for Xenpozyme Missed Doses*

Consecutive Missed Doses:	During the Escalation Phase	During the Maintenance Phase
1 missed dose	• First dose after a missed dose: Administer last tolerated dose • Second and subsequent doses after missed dose: Resume dose escalation at next infusion according to Table 1 for adult patients or Table 2 for paediatric patients	First and subsequent doses after missed dose: Administer maintenance dose and adjust the treatment schedule accordingly
2 consecutive missed doses	• First dose after missed dose: Administer 1 dose below last tolerated dose (using a minimal dose of 0.3 mg/kg) • Second and subsequent doses after missed dose: Resume dose escalation according to Table 1 for adults or Table 2 for paediatric patients	• First dose after missed dose: Administer 1 dose below the maintenance dose (i.e. 2 mg/kg) • Second and subsequent doses after missed dose: Resume the maintenance dose (3 mg/kg) every 2 weeks
3 or more consecutive missed doses	**Adult patients:** For adult patients who have not completed the dose escalation regimen, re-initiate the dose escalation regimen starting at 0.1 mg/kg and follow Table 1.	**Adult patients:** Restart dosing at 0.3 mg/kg and follow Table 1. For adult patients who have missed maintenance dosing for an extended period during which sphingomyelin could have reaccumulated, the treating physician may consider resuming dosing at 0.1 mg/kg and dose escalate according to Table 1.
	Paediatric patients: For paediatric patients who have not completed the dose escalation regimen, re-initiate the dose escalation regimen starting at 0.03 mg/kg and follow Table 2.	**Paediatric patients:** Restart dosing at 0.3 mg/kg and follow Table 2. For paediatric patients who have missed maintenance dosing for an extended period during which sphingomyelin could have reaccumulated, the treating physician may consider resuming dosing at 0.03 mg/kg and dose escalate according to Table 2.

*At the next scheduled infusion after a missed dose, if the dose administered is 0.3 or 0.6 mg/kg, administer that dose twice as per Table 1 and 2.

Monitoring of Transaminase Levels

Transaminase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) levels should be obtained prior to treatment initiation and monitored during any dose escalation phases (see Section 4.4 Special warnings and precautions for use). If the pre-infusion transaminase levels are elevated above baseline and > 2 times the upper limit of normal (ULN), the Xenpozyme dose can be adjusted (prior dose repeated or reduced) or treatment can be temporarily withheld in accordance with the degree of transaminase elevation. If a patient requires a dose adjustment or treatment interruption, treatment re-initiation should follow the dose escalation regimen described in Table 1 or Table 2 for adult and paediatric patients, respectively, and recommendations in case of missed doses (see missed doses section).

Method of Administration

Preparation for intravenous infusion

Xenpozyme should be reconstituted, diluted and administered under the supervision of a healthcare professional. Infusions should be administered in a stepwise manner preferably using an infusion pump as described in Table 5 and Table 6.

Preparation of the Dosing Solution

Xenpozyme must be reconstituted with sterile water for injections, diluted with sodium chloride 9 mg/mL (0.9%) solution for injection and then administered by intravenous infusion.

The reconstitution and dilution steps must be completed under aseptic technique. Filtering devices should not be used at any time during the preparation of the infusion solution. Avoid foaming during reconstitution and dilution steps.

a) Determine the number of vials to be reconstituted based on the individual patient's weight (BMI < 30) or an optimal body weight (BMI ≥ 30) and the prescribed dose:

Patient weight (kg) x dose (mg/kg) = patient dose (mg)

When using 20 mg vials, patient dose (mg) / 20 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.

b) Remove the required number of vials from the refrigerator and set aside for approximately 20 to 30 minutes to allow them to reach room temperature.

c) Reconstitute each vial by injecting:

- 1.1 mL of sterile water for injections into the 4 mg vial

- 5.1 mL of sterile water for injections into the 20 mg vial

using a slow drop-wise addition technique to the inside wall of the vial.

d) Tilt and roll each vial gently. Each vial will yield a 4 mg/mL clear, colourless solution.

e) Visually inspect the reconstituted solution in the vials for particulate matter and discolouration. Xenpozyme solution should be clear and colourless. Any vials exhibiting opaque particles or discolouration should not be used.

f) Withdraw the volume of reconstituted solution, corresponding to the prescribed dose, from the appropriate number of vials and dilute with sodium chloride 9 mg/mL (0.9%) solution for injection, in a syringe or infusion bag depending on the volume of infusion (see Table 4 for the recommended total infusion volume based on patients age and/or weight)

Table 4 - Recommended infusion volumes

	Body weight ≥ 3 kg to < 10 kg	**Body weight ≥ 10 kg to < 20 kg**	**Body weight ≥ 20 kg (paediatric patients < 18 years)**	**Adult patients (≥ 18 years)**
Dose (mg/kg)	Total infusion volume (mL)	Total infusion volume (mL)	Total infusion volume (mL)	Total infusion volume (mL)
0.03	Variable volume will vary based on body weight	Variable volume will vary based on body weight	5	N/A
0.1	Variable volume will vary based on body weight	5	10	20
0.3	5	10	20	100
0.6	10	20	50	100
1	20	50	100	100
2	50	75	200	100
3	50	100	250	100

- For variable final volumes of infusion based on body weight in paediatric patients (see Table 4):
    - Prepare an infusion solution at 0.1 mg/mL by adding 0.25 mL (1 mg) of the reconstituted solution prepared in step c and 9.75 mL of 0.9% sodium chloride for injection into an empty 10 mL syringe
    - Calculate the volume (mL) required to obtain the patient dose (mg)
      Example: 0.3 mg / 0.1 mg/mL = 3 mL

Dilution instructions for 5 mL ≤ total volume ≤ 20 mL using a syringe:

- Inject the required volume of the reconstituted solution slowly to the inside wall of the empty syringe
- Add slowly the sufficient quantity of sodium chloride 9 mg/mL (0.9%) solution for injection to obtain the required total infusion volume (avoid foaming with the syringe)

Dilution instructions for a total volume ≥ 50 mL using an infusion bag:

- Empty infusion bag:
    - Inject slowly the required volume of the reconstituted solution from step c) in the appropriate size sterile infusion bag
    - Add slowly the sufficient quantity of sodium chloride 9 mg/mL (0.9%) solution for injection to obtain the required total infusion volume (avoid foaming within the bag)
- Pre-filled infusion bag:
    - Withdraw from the infusion bag pre-filled with sodium chloride 9 mg/mL (0.9%) solution for injection the volume of normal saline to obtain a final volume as specified in Table 4
    - Add slowly the solution withdrawn in step c) into the infusion bag (avoid foaming within the bag)

g) 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 fibres) occurs occasionally after dilution.

h) The diluted solution must be filtered through an in-line low protein-binding 0.2 µm filter during administration.

i) After the infusion is complete, the infusion line should be flushed with sodium chloride 9 mg/mL (0.9%) solution for injection using the same infusion rate as the one used for the last part of the infusion.

Xenpozyme is for intravenous use only. Infusions should be administered in a stepwise manner preferably using an infusion pump.

After reconstitution and dilution, the solution is administered as an intravenous infusion. The infusion rates must be incrementally increased during the infusion only in the absence of infusion-associated reactions (in case of infusion-associated reactions see section 4.4 Special Warnings and Precautions for Use). The infusion rate and duration of infusion (± 5 min) for each step of infusion as detailed in Table 5 and Table 6.

Table 5 - Infusion rates and duration of infusion in adult patients

Dose (mg/kg)	**Infusion Rate Duration of Infusion**				**Approximate Duration of Infusion**
	Step 1	Step 2	Step 3	Step 4	
0.1	20 mL/hr for 20 min	60 mL/hr for 15 min	N/A	N/A	35 min
0.3 to 3	3.33 mL/hr for 20 min	10 mL/hr for 20 min	20 mL/hr for 20 min	33.33 mL/hr for 160 min	220 min

hr: hour; min: minute; N/A: not application

Table 6 - Infusion rates and duration of infusion in paediatric patients

Dose (mg/kg)	**Infusion Rate Duration of Infusion**				**Approximate Duration of Infusion**
	Step 1	Step 2	Step 3	Step 4	
0.03	0.1 mg/kg/hr for the full length of the infusion	N/A	N/A	N/A	18 min
0.1	0.1 mg/kg/hr for 20 min	0.3 mg/kg/hr onwards	N/A	N/A	35 min
0.3	0.1 mg/kg/hr for 20 min	0.3 mg/kg/hr for 20 min	0.6 mg/kg/hr onwards	N/A	60 min
0.6	0.1 mg/kg/hr for 20 min	0.3 mg/kg/hr for 20 min	0.6 mg/kg/hr for 20 min	1 mg/kg/hr onwards	80 min
1					100 min
2					160 min

3					220 min

hr: hour; min: minute; N/A: not application

Signs and symptoms of infusion-associated reactions (IARs), such as headache, urticaria, pyrexia, nausea and vomiting, and other signs or symptoms of hypersensitivity should be monitored during the infusion. Depending on the symptom severity, the infusion may be slowed, paused or discontinued and appropriate medical treatment initiated as needed.

In case of severe hypersensitivity and/or anaphylactic reaction, treatment with Xenpozyme should be discontinued immediately (see section 4.4 Special Warnings and Precautions for Use).

At the end of infusion (once the syringe or infusion bag is empty), the infusion line should be flushed with sodium chloride 9 mg/mL (0.9%) solution using the same infusion rate as the one used for the last part of the infusion.

Home Infusion During Maintenance Phase

Home infusion by a trained healthcare professional may be considered for individual patients on the maintenance dose after safety and tolerability has been established in the clinical setting.

The decision to have a patient move to home infusion should be made after careful consideration of the risks and benefits by the treating physician. Health professionals administering the product must be trained in recognising and managing serious infusion related reactions. The necessary equipment and protocols sufficient to initiate the management of acute hypersensitivity reactions including anaphylaxis are to be in place (see section 4.4 Special Warnings and Precautions for Use, Infusion associated reactions).

The dose and infusion rate used in the home settings should remain the same as the last dose and infusion rate used in the supervised clinical setting, and should not be changed without supervision of the prescribing physician (see Section 4.4 Special Warnings and Precautions for use and Section 4.9 Overdose). In case of missed doses or delayed infusion, the prescribing physician should be contacted as subsequent infusions may occur in a supervised clinical setting (see Section 6.3 Shelf life - diluted medicinal product for storage instructions).

Special Populations

Elderly Patients

No dose adjustment is recommended for patients over the age of 65 (see Section 5.2 Pharmacokinetic Properties – Special Populations: Elderly).

Hepatic Impairment

No dose adjustment is recommended in patients with hepatic impairment (see Section 5.2 Pharmacokinetic Properties – Special Populations: Hepatic Impairment).

Renal Impairment

No dose adjustment is recommended in patients with renal impairment (see Section 5.2 Pharmacokinetic Properties – Special Populations: Renal Impairment).

4.3 CONTRAINDICATIONS

Life-threatening hypersensitivity (anaphylactic reaction) to olipudase alfa or to any of the excipients in Section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Traceability

In order to improve the traceability of biological medicinal products, the name and batch number of the administered product should be clearly recorded.

Absence of blood-brain barrier transfer

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

Infusion associated reactions (IARs)

IARs occurred in approximately 60% of patients treated with Xenpozyme in clinical studies. These IARs included hypersensitivity reactions and acute phase reactions (see section 4.8 Adverse Effects (Undesirable Effects)). The most frequent IARs were headache, urticaria, pyrexia, nausea and vomiting (see Section 4.8 Adverse Effects (Undesirable Effects) - Immunogenicity). IARs typically occurred between the time of infusion and up to 24 hours after infusion completion during dose escalation and maintenance phases.

Serious adverse reactions, including death, have occurred following overdose during the dose escalation phase (see Section 4.2 Dose and method of administration and Section 4.9 Overdose).

Hypersensitivity/anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in Xenpozyme-treated patients (see Section 134.8 Adverse Effects (Undesirable Effects)). In clinical studies, hypersensitivity reactions occurred in 9 (22.5%) adult and 9 (45%) paediatric patients including one paediatric patient who experienced anaphylaxis.

Hypersensitivity IARs are more likely to occur during the initial dose escalation (see Section 4.8 Adverse Effects (Undesirable Effects)). Mild to moderate hypersensitivity reactions reported in more than one adult patient included urticaria, erythema, pruritus, rash, and angioedema (see Section 4.8 Adverse Effects (Undesirable Effects)). In paediatric patients, mild to moderate hypersensitivity reactions reported in more than one patient included urticaria, erythema, rash, and pruritus (see Section 4.8 Adverse Effects (Undesirable Effects)).

Management

Patients should be observed closely during and for an appropriate period of time after the infusion, based on clinical judgement. Patients must be informed of the potential symptoms of hypersensitivity/anaphylaxis and instructed to seek immediate medical care should symptoms occur. IARs management should be based on the severity of signs and symptoms and may include temporarily interrupting the Xenpozyme infusion, lowering the infusion rate, and/or appropriate medical treatment.

If severe hypersensitivity or anaphylaxis occurs, Xenpozyme should be discontinued immediately, and appropriate medical treatment should be initiated. The patient who experienced anaphylaxis in the clinical study underwent a tailored desensitisation regimen that enabled the patient to resume long term treatment with Xenpozyme at the recommended maintenance dose. The prescriber should evaluate the risks and benefits of Xenpozyme re administration following anaphylaxis or severe hypersensitivity reaction. If considering re-administration of Xenpozyme following anaphylaxis, the prescribing physician should contact Sanofi (see section 8 Sponsor for contact details) for advice on re-administration. In such patients, extreme caution should be exercised, with appropriate resuscitation measures available, when Xenpozyme is readministered.

If mild or moderate IARs occur, the infusion rate may be slowed or temporarily stopped, the duration of each step for an individual infusion increased, and/or the Xenpozyme dose reduced. If a patient requires a dose reduction, re-escalation should follow dose escalation described in Table 1 and Table 2 for adult and paediatric patients, respectively (see section 4.2 Dose and Method of Administration).

Patients may be pre-treated with antihistamines, antipyretics, and/or glucocorticoids to prevent or reduce allergic reactions.

Immunogenicity

Treatment-emergent antidrug antibodies (ADA) were reported in adult and paediatric patients during the clinical trials (see Section 4.8 Adverse Effects (Undesirable Effects)). IARs and hypersensitivity reactions may occur independent of the development of ADA. The majority of IARs and hypersensitivity reactions were mild or moderate and were managed with standard clinical practices.

IgE ADA testing may be considered for patients who experienced a severe hypersensitivity reaction to olipudase alfa.

While in clinical studies, no loss of efficacy was reported, IgG ADA testing may be considered in case of loss of response to therapy.

Transient transaminase elevation

Transient transaminase elevations (ALT or AST) within 24 to 48 hours after infusions were reported during the dose escalation phase with Xenpozyme in clinical studies (see section 4.8 Adverse Effects (Undesirable Effects)). At the time of the next scheduled infusion, these elevated transaminase levels generally returned to the levels observed prior to Xenpozyme infusion.

After 52 weeks of treatment, most patients with elevated transaminase levels at baseline had values within the normal range (see Section 4.8 Adverse Effects (Undesirable Effects)).

Transaminases (ALT and AST) levels should be obtained within 1 month prior to Xenpozyme treatment initiation (see Section 4.2 Dose and method of administration). During dose escalation or upon resuming treatment following missed doses, transaminase levels should be obtained within 72 hours prior to the next scheduled Xenpozyme infusion. If either the baseline or a pre-infusion transaminase level is > 2 times the ULN during dose escalation, then additional transaminase levels should be obtained within 72 hours after the end of the infusion. If the pre-infusion transaminase levels are elevated above baseline and > 2 times the ULN, the Xenpozyme dose can be adjusted (prior dose repeated or reduced) or treatment can be temporarily withheld in accordance with the degree of transaminase elevation (see Section 4.2 Dose and method of administration). Upon reaching the recommended maintenance dose, transaminase testing can be performed as part of routine clinical management of ASMD.

Sodium content

This medicinal product contains 3.02 mg sodium per vial, equivalent to 0.15% of the WHO recommended maximum daily intake of 2 g sodium for an adult or an adolescent, and ≤ 0.38% of the maximum acceptable daily intake of sodium for children below 16 years of age.

Use in the elderly

Clinical studies with Xenpozyme included 2 patients between 65 and 75 years of age. See Section 5.2 Pharmacokinetic Properties.

Paediatric use

See Section 5.2 Pharmacokinetic Properties.

Effects on laboratory tests

No data available.

Use in females of childbearing potential and pregnant women

Xenpozyme is not recommended during pregnancy and in women of childbearing potential not using effective contraception, unless the potential benefits to the mother outweigh the potential risks, including those to the fetus.

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, is not recommended as it may lead to elevated sphingomyelin metabolite levels that may increase the risk of fetal malformations. 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.

Verify the pregnancy status in females of reproductive potential prior to initiating Xenpozyme treatment see section 4.6 Fertility, Pregnancy and Lactation.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been performed. Because olipudase alfa is a recombinant human protein, no cytochrome P450 mediated drug-drug interactions are expected.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data are available to determine potential effects of Xenpozyme on fertility in males and females. Fertility was unaffected in male and female mice at intravenous doses up to 30 mg/kg of Xenpozyme every other day (1.5 times the clinical exposure based on AUC).

Use in pregnancy – Category D

It is recommended to perform a pregnancy test prior to treatment initiation with Xenpozyme.

Women of childbearing potential are advised to use effective contraception during treatment and for 14 days after the last dose if Xenpozyme is discontinued.

There are limited data on Xenpozyme use in pregnant women. Xenpozyme is not recommended during pregnancy and in women of childbearing potential not using effective contraception, unless the potential benefits to the mother outweigh the potential risks, including those to the fetus.

An increased incidence of exencephaly was observed when pregnant mice were treated daily with olipudase alfa at exposure levels less than the human exposure (based on AUC) at the recommended maintenance therapeutic dose and frequency. This incidence was slightly higher than historical control data. The relevance of this observation for humans is unknown. The daily intravenous administration of olipudase alfa to pregnant rabbits did not result in fetal malformations or variations at exposures 10 times the human exposure (based on AUC) at the recommended maintenance therapeutic dose and frequency.

Use in lactation

It is unknown whether olipudase alfa is excreted in human milk. Olipudase alfa was detected in the milk of lactating mice. A risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue Xenpozyme therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Because hypotension has been reported in clinical studies, Xenpozyme may have a minor influence on the ability to drive and use machines (see Section 4.8 Adverse Effects (Undesirable Effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the Safety Profile

Serious adverse reactions reported in patients treated with Xenpozyme were an event of extrasystoles in the context of a history of cardiomyopathy in 1 (2.5%) adult patient and anaphylactic reaction, urticaria, rash, hypersensitivity and alanine aminotransferase level increase, each in 1 (5%) paediatric patient. The incidence of serious hypersensitivity-related IARs were higher in paediatric patients compared to adults. One adult patient discontinued due to recurrent adverse events of rash.

The most frequently reported adverse drug reactions (ADRs) (occurring in ≤10% of Xenpozyme patients) were headache (31.7%), urticaria (26.7%), pyrexia (25%), pyrexia (25%), nausea (20%), abdominal pain (16.7%), vomiting (16.7%), pruritus (13.3%), myalgia (13.3%), rash (11.7%), abdominal pain upper (10%), erythema (10%) and C-reactive protein increased (11.7%).

Tabulated List of Adverse Reactions

The pooled safety analysis from 4 clinical studies (a tolerability study in adult patients, ASCEND, ASCEND-Peds and an extension study in adult and paediatric patients) included a total of 60 patients (40 adult and 20 paediatric patients) treated with Xenpozyme at doses up to 3 mg/kg every 2 weeks.

The median exposure duration was 4.95 years (range: 0.4 to 9.6 years) in adult patients and 6.15 years (range: 4.3 to 8.2 years) in paediatric patients.

Adverse reactions reported in the pooled safety analysis of clinical studies are listed in Table 5 per System Organ Class, presented by frequency categories: very common ≥ 10%; common ≥ 1 and < 10%; uncommon ≥ 0.1 and < 1%; rare ≥ 0.01 and < 0.1%; very rare < 0.01%; not known (cannot be estimated from available data).

Table 7 - Adverse drug reactions in patients treated with Xenpozyme in pooled analysis of completed clinical studies

System Organ Class	Frequency	
	Very common	**Common**
Immune system disorders		Anaphylaxis and hypersensitivity
Nervous system disorders	Headache	
Eye disorders		Ocular hyperaemia Ocular discomfort Eye pruritus
Cardiac disorders		Palpitations Tachycardia
Vascular disorders		Hypotension Hot flush Flushing

System Organ Class	Frequency	
	Very common	Common
Respiratory, thoracic and mediastinal disorders		Pharyngeal oedema Pharyngeal swelling Throat tightness Wheezing Larynx irritation Dyspnoea Throat irritation
Gastrointestinal disorders	Nausea Abdominal pain Vomiting Abdominal pain upper	Diarrhoea Abdominal discomfort Gastrointestinal pain
Hepatobiliary disorders		Hepatic pain
Skin and subcutaneous tissue disorders	Urticaria Pruritus Rash Erythema	Angioedema Fixed eruption Rash papular Rash macular Rash maculopapular Rash erythematous Rash pruritic Rash morbilliform Papule Macule
Musculoskeletal and connective tissue disorders	Myalgia	Bone pain Arthralgia Back pain
General disorders and administration site conditions	Pyrexia	Pain Chills Catheter site pain Catheter site related reaction Catheter site pruritus Catheter site swelling Fatigue Asthenia
Investigations	C-reactive protein increased	Alanine aminotransferase increased Aspartate aminotransferase increased Serum ferritin increased C-reactive protein abnormal Body temperature increased

Description of Selected Adverse Reactions

Infusion-associated reactions (IARs), including hypersensitivity/anaphylactic reactions

IARs were reported in 23 of 40 (57.5%) adult and 13 of 20 (65%) paediatric patients. IAR symptoms reported in at least 3 adult patients (≥7.5%) were headache (25%), nausea (17.5%), urticaria (17.5%), myalgia (12.5%), arthralgia (10%), pyrexia (10%), pruritus (10%), vomiting (7.5%), abdominal pain (7.5%), erythema (7.5%), and fatigue (7.5%). IAR symptoms reported in at least two paediatric patients (≥10%) were pyrexia (40%), urticaria (40%), vomiting (30%), C-reactive protein increased (20%), headache (20%), nausea (20%), erythema (15%), rash (15%), serum ferritin increased (15%), abdominal pain (10%), and pruritus (10%). IARs typically occurred between the time of infusion and 24 hours after infusion end. The majority of IARs were assessed as mild or moderate.

Hypersensitivity-related IARs, including anaphylaxis, occurred in 18 (30%) patients, 9 (22.5%) adult and 9 (45%) paediatric patients in clinical studies. The most frequently reported hypersensitivity-related IAR symptoms were urticaria (25%), pruritus (10%), erythema (10%), and rash (8.3%).

In both adult and paediatric patients, exposure adjusted incidence rates (EAIR) for IARs were higher during the dose escalation phase, compared to after initial dose escalation.

Adult participants

The EAIR for hypersensitivity-related IARs was higher during the initial dose escalation phase (13.57 participants per 100 person years), compared to after initial dose escalation (6.23 participants per 100 person years).

Paediatric participants

The EAIR for hypersensitivity-related IARs was higher during the initial dose escalation phase (46.61 participants per 100 person years), compared to after initial dose escalation (8.53 participants per 100 person years)

Among the most frequently reported IARs, the EAIR for urticaria was higher in paediatric than adult participants (9.22 versus 4.15 participants per 100 person years). The treatment emergent adverse event of urticaria as IAR occurred more frequently after initial dose escalation in paediatric participants (35%) with EAIR (8.37) as compared to adult participants (17.5%) with EAIR (4.57) than during initial dose escalation.

One paediatric patient in the clinical studies incurred a severe anaphylactic reaction. Also, independent of the clinical study program, a 16-month-old patient with ASMD type A treated with Xenpozyme experienced 2 anaphylactic reactions. In the post-marketing setting, a 32-month-old patient experienced an anaphylactic reaction. Anti-olipudase alfa IgE antibodies were detected in all 3 paediatric patients.

In 2 adult and 3 paediatric patients, IAR symptoms were associated with changes in laboratory parameters (e.g. C-reactive protein, ferritin value) indicative of acute phase reaction, as reported by the investigator. All events can be managed as other IARs (see Section 4.4 Special warnings and precautions for use).

Transaminase Elevations

Transient transaminase (ALT or AST) elevations within 24 to 48 hours after infusion occurred in some patients treated with Xenpozyme during the dose escalation phase in the clinical

studies. These elevations generally returned to the previous pre-infusion transaminase levels by the next scheduled infusion.

Overall, after 52 weeks of treatment with Xenpozyme, mean ALT decreased 46.9% and mean AST decreased 40.2%, compared to baseline levels. In adult patients, all 16 patients with an elevated baseline ALT had an ALT within the normal range and 10 of 12 adult patients with an elevated baseline AST had an AST within the normal range.

Immunogenicity

In adult patients, 19 out of 40 (47.5%) patients treated with Xenpozyme developed treatment-emergent antidrug antibodies (ADA). The median time to seroconversion from first Xenpozyme infusion was approximately 52 weeks. The majority of adult patients had a low ADA response (peak titre ≤400) except for three patients with an intermediate ADA response (peak titres ranging 800-6400). The median ADA peak titre was 200. Eight out of these 19 adult patients had neutralising antibodies (NAb) that inhibited the olipudase alfa activity, but only two patients had NAb at more than one time point. None of the patients developed NAb that inhibited the cellular uptake of olipudase alfa.

In paediatric patients, 15 out of 20 (75%) paediatric patients treated with Xenpozyme developed treatment-emergent ADA. The median time to seroconversion from first Xenpozyme infusion was 12 weeks. The majority of paediatric patients had a low ADA response except for four patients with an intermediate ADA response. The median ADA peak titre was 200. Nine out of the 15 paediatric patients developed NAb that inhibited olipudase alfa activity, but only three patients had NAb at more than one time point. None of the patients developed NAb that inhibited the cellular uptake of olipudase alfa. One paediatric patient experienced an anaphylactic reaction and developed IgE ADA, and IgG ADA with a peak titre of 1600.

No effect of ADA was observed on pharmacokinetics and efficacy of Xenpozyme in adult and paediatric populations. There was a higher percentage of patients with treatment-emergent IARs (including hypersensitivity reactions) in patients who developed treatment-emergent ADA versus those who did not (70.6% versus 46.2%). The IARs were manageable and did not result in discontinuation of treatment.

Paediatric Population

Except for a higher incidence of hypersensitivity-related IARs in paediatric patients compared to adults, the safety profile of Xenpozyme in paediatric and adult patients was similar.

Long-term Use

Overall, the pattern of adverse events observed in adult and paediatric patients in longer term use was consistent with that observed during the first year of treatment.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

A limited number of cases of overdose of Xenpozyme have been reported in paediatric 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 Xenpozyme overdose. In the event of overdose, the infusion should be stopped immediately, and the patient should be monitored closely in a hospital setting for the development of IARs including acute phase reactions. For the management of adverse reactions, see Section 4.4 Special warnings and precaution for use and Section 4.8 Adverse Effects (Undesirable Effects).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Alimentary tract and metabolism product - enzyme, ATC code: A16AB25.

Mechanism of action

Olipudase alfa is a recombinant human acid sphingomyelinase that reduces sphingomyelin (SM) accumulation in organs of patients with acid sphingomyelinase deficiency (ASMD).

Clinical Trials

The efficacy of Xenpozyme has been evaluated in 3 clinical studies (ASCEND study in adult patients, ASCEND-Peds study in paediatric patients and an extension study in adult and paediatric patients) involving a total of 61 patients with ASMD.

Clinical Study in Adult Patients

The ASCEND study is a multicentre, randomised, double-blinded, placebo-controlled, repeat-dose phase II/III study in adult patients with ASMD type A/B and B. A total of 36 patients were randomised in a 1:1 ratio to receive either Xenpozyme or placebo. Treatment was administered in both groups as an IV infusion once every 2 weeks. Patients receiving Xenpozyme were up-titrated from 0.1 mg/kg to a target dose of 3 mg/kg. The study was divided into 2 consecutive periods: a randomised 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 randomised to the placebo arm in the PAP crossed over to active treatment in the ETP to reach the targeted dose of 3 mg/kg, while patients in the original Xenpozyme arm continued treatment.

Patients with platelet count < $60x10^3/\mu L$, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 250 IU/L, international normalized ratio (INR) > 1.5 were excluded from the clinical study. Patients enrolled in the study had a diffusion capacity of the lungs for carbon monoxide (DLco) ≤ 70% of the predicted normal value, a spleen volume ≥ 6 multiples

of normal (MN) measured by magnetic resonance imaging (MRI) and scores ≥ 5 in splenomegaly related score (SRS). Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 30 years (range: 18 – 66). The mean (standard deviation, SD) age at ASMD diagnosis was 18 (18.4) years. At baseline, neurologic manifestations were seen in 9 out of 36 adult patients (25%) consistent with a clinical diagnosis of ASMD type A/B. The remaining 27 patients had a clinical diagnosis consistent with ASMD type B.

This study included 2 separate primary efficacy endpoints: the percentage change in DLco (in % predicted of normal) and spleen volume (in MN), as measured by MRI, from baseline to week 52. Secondary efficacy endpoints included the percentage change in liver volume (in MN) and platelet count from baseline to week 52. Pharmacodynamic parameters (ceramide and lyso-sphingomyelin [a deacylated form of SM] levels) were also assessed.

Improvements in mean percent change in % predicted DLco ($p = 0.0004$) and spleen volume ($p < .0001$) as well as in mean liver volume ($p < 0.0001$) and platelet count ($p = 0.0185$) were observed in the Xenpozyme group as compared to the placebo group during the 52-week primary analysis period. A significant improvement in mean percent change in % predicted DLco, spleen volume, liver volume and platelet count were noted at Week 26 of treatment, the first post-dose endpoint assessment.

The results from the PAP at week 52 are detailed in

Table 8.

Table 8 - Mean (SD) values for efficacy endpoints at baseline and least squares (LS) mean percentage change (SE) from baseline to Week 52

	Placebo (n = 18)	Xenpozyme (n = 18)	Difference [95% CI]	p value*
Primary Endpoints				
Mean % predicted DLco at baseline	48.5 (10.8)	49.4 (11.0)	N/A	N/A
Percent change in % predicted DLco from baseline to Week 52	3 (3.4)	22 (3.3)	19 (4.8) [9.3, 28.7]	0.0004
Mean spleen volume (MN) at baseline	11.2 (3.8)	11.7 (4.9)	N/A	N/A
Percent change in spleen volume from baseline to Week 52	0.5 (2.5)	-39.4 (2.4)	-39.9 (3.5) [-47.1, -32.8]	< 0.0001
Secondary Endpoints				
Mean liver volume (MN) at baseline	1.6 (0.5)	1.4 (0.3)	N/A	N/A
Percent change in liver volume from baseline to Week 52	-1.5 (2.5)	-28.1 (2.5)	-26.6 (3.6) [-33.9, -19.3]	< 0.0001
Mean platelet count (10^9/L) at baseline	115.6 (36.3)	107.2 (26.9)	N/A	N/A

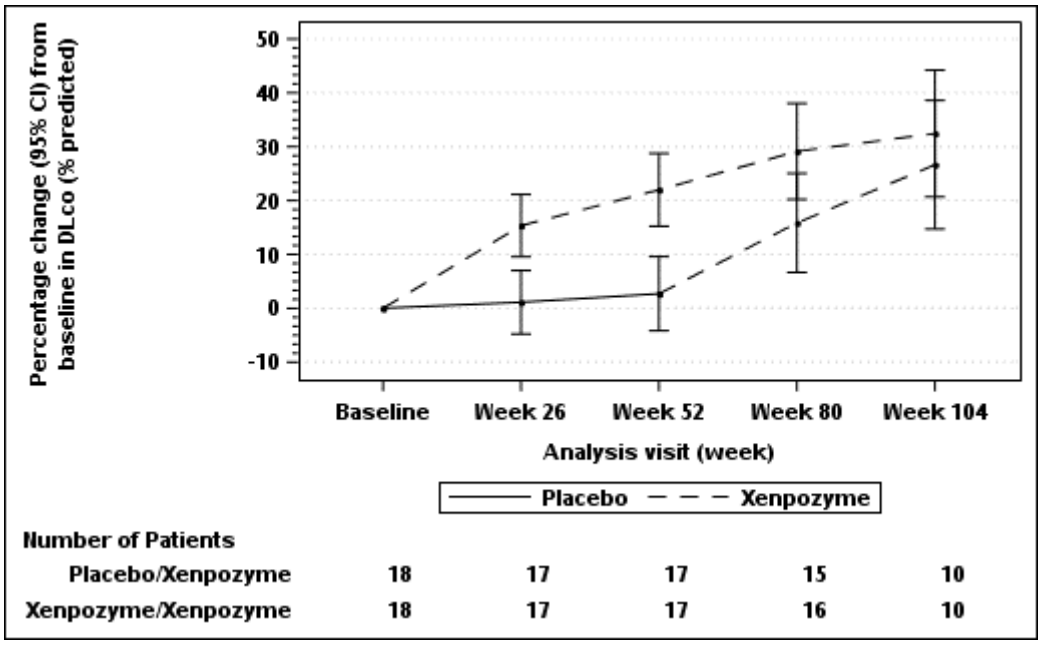
	Placebo (n = 18)	Xenpozyme (n = 18)	Difference [95% CI]	p value*
Percent change in platelet count from baseline to week 52	2.5 (4.2)	16.8 (4.0)	+ 14.3 (5.8) [2.6, 26.1]	0.0185

* statistically significant after multiplicity adjustment

In addition, lyso-sphingomyelin, which is substantially elevated in plasma of ASMD patients, declined significantly, reflecting reduction of sphingomyelin content in tissue. The LS mean percentage change from baseline to week 52 (SE) in pre-infusion plasma lyso-sphingomyelin level was 77.7 % (3.9) in the Xenpozyme treatment group compared to 5.0% (4.2) in the placebo group. The liver sphingomyelin content, as assessed by histopathology, decreased by 92.0% (SE: 8.1) from baseline to week 52 in the Xenpozyme treatment group (compared to +10.3% (SE: 7.8) in the placebo group).

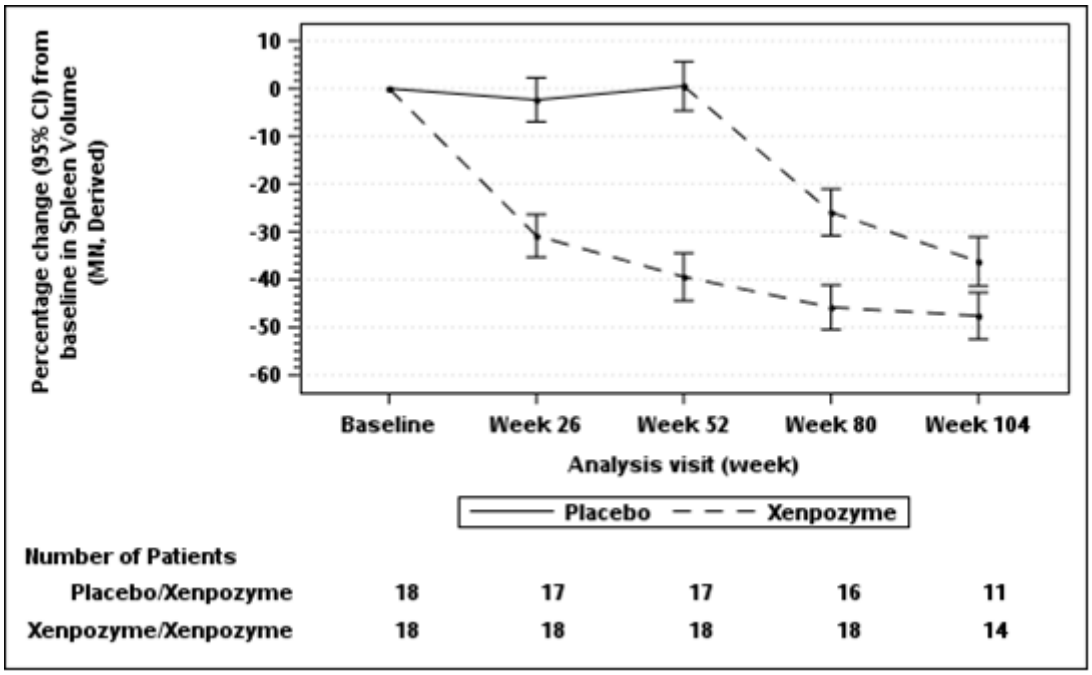
Seventeen of 18 patients previously receiving placebo and 18 of 18 patients previously treated with Xenpozyme for 52 weeks (PAP) started or continued treatment with Xenpozyme, respectively, for up to 4 years. Sustained effects of Xenpozyme on efficacy endpoints up to week 104 are presented in Figure 1 and Figure 2 and Table 9.

Figure 1 - Plot of the LS means (95% CI) of the percentage change in DL_{co} (% predicted) from baseline to Week 104 – mITT population



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 up to Week 52 and switched to Xenpozyme thereafter.
mITT: the modified intent-to-treat population included randomised patients who received at least 1 infusion (partial or total).

Figure 2 - Plot of the LS means (95% CI) of the percentage change in spleen volume (MN) from baseline to Week 104 – mITT population



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 up to Week 52 and switched to Xenpozyme thereafter.
mITT: the modified intent-to-treat population included randomised patients who received at least 1 infusion (partial or total).

Table 9 - LS mean percentage change (SE) from baseline to week 104 for liver volume (MN) and platelet count (10^9/L) in patients treated with Xenpozyme for 104 weeks

	Previous olipudase alfa group	
	Week 52 (ETP start)	**Week 104**
N	17	14
Percent change in liver volume (SD)	-27.8 (2.5)	-33.4 (2.2)
N	18	13
Percent change in platelet count (SD)	16.6 (4.0)	24.9 (6.9)

N: number of patients

Extension Study in Adult Patients

Five adult patients who participated in an open-label ascending dose study in ASMD patients continued treatment in an open-label extension study and received Xenpozyme for up to > 7 years.

Sustained improvements in % predicted DLco, spleen and liver volumes and platelet count, compared to baseline, were noted in adult over the course of the study (see Table 10).

Table 10 - Mean percentage change (SD) from baseline to month 78 of efficacy parameters

	Month 78 (n = 5)
Percent change in % predicted DLco (SD)	55.3% (48.1)
Percent change in spleen volume (SD)	-59.5% (4.7)
Percent change in liver volume (SD)	-43.7% (16.7)
Percent change in platelet count (SD)	38.5% (14.7)

N: number of patients

Clinical Study in Paediatric Patients

The ASCEND-Peds study (Phase 1/2 clinical study) is a multi-centre, open-label, repeated-dose study to evaluate the safety and tolerability of Xenpozyme administered for 64 weeks in paediatric patients aged < 18 years with ASMD (type A/B and B). In addition, exploratory efficacy endpoints related to organomegaly, pulmonary and liver functions, and linear growth were evaluated at week 52.

Patients with acute or rapidly progressive neurological abnormalities, or are homozygous for mutations of the SMPD1 gene p.Arg498Leu, p.Leu304Pro, or p.Phe333SerfsTer52 or any combination of these 3 mutations were excluded from the clinical study. A total of 20 patients (4 adolescents from 12 to < 18 years old, 9 children from 6 to < 12 years old, and 7 infants/children < 6 years old) were up-titrated with Xenpozyme via a dose escalation regimen from 0.03 mg/kg to a target dose of 3 mg/kg. Treatment was administered as an intravenous infusion once every 2 weeks for up to 64 weeks. Patients enrolled in the study had a spleen volume ≥ 5 MN measured by MRI. Patients were distributed across all ages from 1.5 to 17.5 years old, with both sexes equally represented. The mean (SD) age at ASMD diagnosis was 2.5 (2.5) years. At baseline, neurologic manifestations were seen in 8 out of 20 paediatric patients (40%) consistent with a clinical diagnosis of ASMD type A/B. The remaining 12 patients had a clinical diagnosis consistent with ASMD type B.

Treatment with Xenpozyme resulted in improvements in mean percent change in % predicted DLco, spleen and liver volumes, platelet counts, and linear growth progression (as measured by Height Z-scores) at week 52 as compared to baseline (see Table 11).

Table 11 - LS mean percentage change (SE) or change (SD) from baseline to Week 52 (all age cohort)

	Baseline value (n = 20)	Week 52 (n = 20)
Mean % predicted DLco (SD)	54.8 (14.2)	71.7 (14.8)
Percent change in % predicted DLco*		32.9 (8.3)
95% CI		13.4, 52.2
Mean spleen volume (MN) (SD)	19.0 (8.8)	9.3 (3.9)
Percent change in spleen volume (in MN)		-49.2 (2.0)
95% CI		-53.4, -45.0
Mean liver volume (MN) (SD)	2.7 (0.7)	1.5 (0.3)
Percent change in liver volume (in MN)		-40.6 (1.7)
95% CI		-44.1, -37.1
Mean platelet count (10^9/L) (SD)	137.7 (63.3)	173.6 (60.5)
Percent change in platelet count		34.0 (7.6)
95% CI		17.9, 50.1
Mean height z-scores (SD)	-2.1 (0.8)	-1.6 (0.8)
Change in height z-scores		0.6 (0.4)
95% CI		0.38, 0.73

* DLco was evaluated in 9 paediatric patients aged ≥ 5 years who were able to perform the test; change in height Z-score was evaluated in 19 paediatric patients
# nominal p value

In addition, LS mean pre-infusion plasma ceramide and lyso-sphingomyelin levels were reduced by 57% (SE: 5.1) and 87.2% (SE: 1.3), respectively, compared to baseline following 52 weeks of treatment.

The effects of Xenpozyme on spleen and liver volumes, platelets and height z-scores were seen across all paediatric age cohorts included in the study.

Extension Study in Paediatric Patients

Twenty paediatric patients who participated in ASCEND-Peds study continued treatment in an open-label extension study and received Xenpozyme for up to > 5 years.

Sustained improvements in efficacy parameters (% predicted DLco, spleen and liver volumes, platelet counts, height Z-scores and bone age) were noted in paediatric patients over the course of the study up to month 48 (see Table 12).

Table 12 - Mean percentage change or change (SD) from baseline to month 48 (all age cohort) of efficacy parameters

	Month 48
N	5
Percent change in % predicted DLco (SD)	60.3 (58.5)
N	7
Percent change in spleen volume (SD)	-69.1 (4.1)
N	7
Percent change in liver volume (SD)	-55.4 (11.0)
N	5
Percent change in platelet count (SD)	35.8 (42.4)
N	5
Change in height Z-scores (SD)	2.3 (0.8)
N	7
Change in bone age (months) (SD)	18.5 (19.0)

N: number of patients

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of olipudase alfa were assessed in 49 adult ASMD patients from all clinical studies, receiving single or multiple administrations. At the dose of 3 mg/kg administered once every 2 weeks, the mean (percent coefficient of variation, CV %) maximum concentration (C_{max}) and area under the concentration-time curve over a dosing interval ($AUC_{0-\tau}$) at steady state were 30.2 µg/mL (17%) and 607 µg.h/mL (20%) respectively.

Olipudase alfa exhibited linear pharmacokinetics over the dose range of 0.03 to 3 mg/kg. Following a dose escalation regimen from 0.1 to the maintenance dose of 3 mg/kg administered once every 2 weeks, there was minimal accumulation in plasma levels of olipudase alfa.

Absorption

There is no absorption since Xenpozyme is administered intravenously.

Distribution

The estimated mean (CV%) volume of distribution of olipudase alfa is 13.1 L (18%).

Metabolism

Olipudase alfa is a recombinant human enzyme and is expected to be eliminated via proteolytic degradation into small peptides and amino acids.

Excretion

Olipudase alfa is a recombinant human enzyme and is expected to be eliminated via proteolytic degradation into small peptides and amino acids.

The mean (CV%) clearance of olipudase alfa is 0.331 L/hr (22%). The mean terminal half-life ($t_{1/2}$) ranged from 31.9 to 37.6 hours.

Special Populations

Gender

There were no clinically relevant differences in olipudase alfa pharmacokinetics based on gender.

Race

Population pharmacokinetic analysis indicated that the exposure in Asian (n = 2) and other race patients (n = 2) were within the exposure ranges observed for Caucasian patients.

Elderly (≥ 65 years old)

Population pharmacokinetic analysis did not indicate a difference in exposure in elderly (only 2 patients between 65 and 75 years of age were included in clinical studies with Xenpozyme).

Paediatric

The pharmacokinetics of olipudase alfa were assessed in 20 paediatric patients including 4 adolescent patients, 9 child patients and 7 child/infant patients (see Table 13). Olipudase alfa exposures were lower in paediatric patients compared to those in adult patients. However, these differences were not considered to be clinically relevant.

Table 13 - Mean (CV%) of olipudase alfa PK parameters following administration of 3 mg/kg every 2 weeks in adolescent, child and child/infant patients with ASMD

Age group	Age (year)	C_{max} (µg/mL)	$AUC_{0-\tau}$ (µg.h/mL)
Adolescent (n = 4)	12, < 18	27.5 (8)	529 (7)
Child (n = 9)	6, <12	24.0 (10)	450 (15)
Child/infant (n = 7)	< 6	22.8 (8)	403 (11)

Descriptive statistics represent the post hoc estimates of steady-state exposures using population PK analysis.

$AUC_{0-\tau}$ area under the plasma concentration versus time curve over a dosing interval; C_{max}: maximum plasma concentration; n = total number of patients

Hepatic Impairment

Olipudase alfa is a recombinant protein and is expected to be eliminated by proteolytic degradation. Therefore, impaired liver function is not expected to affect the pharmacokinetics of olipudase alfa.

Renal Impairment

Four patients (11.1%) with mild renal impairment (60 mL/min ≤ creatinine clearance < 90 mL/min) were included in the ASCEND study. There were no clinically relevant differences in olipudase alfa pharmacokinetics in patients with mild renal impairment. The impact of moderate to severe renal impairment on the pharmacokinetics of olipudase alfa is not known. Olipudase alfa is not expected to be eliminated through renal excretion. Therefore, renal impairment is not expected to affect the pharmacokinetics of olipudase alfa.

5.3 PRECLINICAL SAFETY DATA

In acid sphingomyelinase knockout (ASMKO) mice (a disease model for ASMD), mortality was observed following an administration of single doses of olipudase alfa ≥ 3.3 times higher than maximum recommended human dose (MRHD) as an intravenous bolus injection. However, repeat dose studies show that administration of olipudase alfa via a dose escalation regimen did not result in compound-related mortality and reduced the severity of other toxicity findings up to the highest tested dose of 10 times the MRHD.

Genotoxicity

No studies were conducted to evaluate the genotoxicity of olipudase alfa.

Carcinogenicity

No studies were conducted to evaluate the carcinogenicity of olipudase alfa.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Dibasic sodium phosphate heptahydrate
Methionine
Monobasic sodium phosphate monohydrate
Sucrose

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Reconstituted medicinal product

From a microbiological point of view, the reconstituted medicinal product should be used immediately.

If not used for dilution immediately, after reconstitution with sterile water for injections, chemical, physical and microbiological in use stability has been demonstrated for up to 24 hours at 2°C to 8°C or 6 hours at room temperature (up to 25°C).

Diluted medicinal product

From a microbiological point of view, the diluted medicinal product should be used immediately.

If not used immediately after dilution, chemical, physical and microbiological in use stability has been demonstrated for up to 24 hours at 2°C to 8°C followed by 12 hours (including infusion time) at room temperature (up to 25°C).

Xenpozyme is for single use in one patient only. Discard any residue.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials

Store between 2ºC to 8ºC (Refrigerate).

For storage conditions after reconstitution and dilution see section 6.3 Shelf Life.

6.5 NATURE AND CONTENTS OF CONTAINER

Xenpozyme is supplied in type 1 glass vials with a siliconised chlorobutyl-elastomer lyophilisation stopper and an aluminium seal with plastic flip-off cap. Each vial contains 20mg olipudase alfa.

Each pack contains: 1, 5, 10 or 25 vials.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number: 927883-84-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

sanofi-aventis australia pty ltd

International Tower 3, Level 23

300 Barangaroo Avenue

Sydney NSW 2000

Freecall: 1800 818 806

Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

24 August 2023

10 DATE OF REVISION

02 June 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Dot point numbering updated
4.8	Adverse reactions reporting statement updated
8	Sponsor details updated