เอกสารกำกับยาภาษาอังกฤษ

Xenpozyme

1. NAME OF THE MEDICINAL PRODUCT

Xenpozyme 20 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION.

Each vial contains 20 mg of olipudase alfa*.
After reconstitution, each vial contains 4 mg of olipudase alfa per mL. Each vial must be further diluted before use (see "Special precautions for disposal and other handling").

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

Excipient with known effect
Each vial contains 3.02 mg of sodium.
For the full list of excipients, see "List of excipients".

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).
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 or type B.

4.2 Posology and method of administration

Xenpozyme treatment should be supervised by a healthcare professional 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 such as serious systemic hypersensitivity reactions. Treatment with Xenpozyme should always be initiated via a dose escalation regimen followed by a maintenance dose. For missed doses see below.

In order to avoid dosing errors including overdose (see "Overdose"), all instructions for dosage and administration (see below), and for preparation and handling (see "Special precautions for disposal and other handling"), should be followed.

Posology

The rapid metabolism of accumulated sphingomyelin (SM) by olipudase alfa 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 "Preclinical safety data").

Xenpozyme dose is based on the actual body weight for patient with a body mass index (BMI) ≤ 30 or an optimal body weight for patient with a BMI > 30 (see section for patients with a BMI > 30).

Adults

Dose escalation phase

The recommended starting dose of Xenpozyme is 0.1 mg/kg* for adults administered (refer to 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*
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 dose of Xenpozyme is 3 mg/kg* every 2 weeks.

*Actual body weight will be used for patients with a BMI ≤ 30. For patients with a BMI > 30, an optimal body weight will be used as described below.

Pediatric patients

Dose escalation phase

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

Table 2: Dose escalation regimen in pediatric patients

Pediatric 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)

*Actual body weight will be used for patients with a BMI ≤ 30. For patients with a BMI > 30, an optimal body weight will be used as described below.

Maintenance phase

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

*Actual body weight will be used for patients with a BMI ≤ 30. For patients with a BMI > 30, an optimal body weight will be used as described below.

Patients with BMI> 30

In adult and paediatric patients with a body mass index (BMI) > 30, the body weight that is used to calculate the dose of Xenpozyme is estimated via the following method (for dose escalation and maintenance phases).

Body weight (kg) to be used for dose calculation = 30 × (actual height in m)^2

Example:
For a patient with:
BMI of 38
body weight of 110 kg
height of 1.7 m.
The dose to be administered will be calculated using a body weight of 30 × 1.72 = 86.7 kg.

Missed doses

A dose is considered missed when 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.

Table 3: Dosing recommendations for Xenpozyme missed doses*

Consecutive missed doses	During the dose escalation phase	During the maintenance phase:
If 1 infusion is missed:	Administer the last tolerated dose, before resuming dose escalation, according to the dose escalation regimen in adults (Table 1) or in pediatric patients (Table 2).	Administer the maintenance dose and adjust the treatment schedule accordingly.
If 2 consecutive infusions are missed:	Administer 1 dose below the last tolerated dose (using a minimal dose of 0.3 mg/kg), before resuming dose escalation according to Table 1 or Table 2.	Administer 1 dose below the maintenance dose (i.e. 2 mg/kg). Then for subsequent infusions, administer the maintenance dose (3 mg/kg) every 2 weeks.
If 3 or more consecutive infusions are missed:	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. 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.	Resume dose escalation at 0.3 mg/kg according to Table 1 or Table 2. For adult patients who have missed maintenance dosing for an extended period during which sphingomyelin could have reaccumulated, the treating physician should consider resuming dosing at 0.1 mg/kg and dose escalate according to Table 1. For paediatric patients who have missed maintenance dosing for an extended period during which sphingomyelin could have reaccumulated, the treating physician should 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, that dose should be administered twice as per Table 1 and Table 2.

Monitoring of transaminase level

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). 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 and Table 2 for adult and pediatric patients, respectively, and recommendations in case of missed doses (see "Missed doses").

Special populations

Elderly patients

No dose adjustment is recommended for patients over the age of 65 (see "Pharmacokinetics").

Hepatic impairment

No dose adjustment is recommended in patients with hepatic impairment (see "Pharmacokinetics").

Renal impairment

No dose adjustment is recommended in patients with renal impairment (see "Pharmacokinetics").

Method of administration

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

For instructions for the preparation of Xenpozyme before administration and volumes of administration, see "Special precautions for disposal and other handling".

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 "Special warnings and precautions for use"). The infusion rate and duration of infusion (+/- 5 min) for each step of infusion are detailed in Table 4 and Table 5:

Table 4: 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	NA	NA	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; NA: Not applicable

Table 5: 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	NA	NA	NA	18 min
0.1	0.1 mg/kg/hr for 20 min	0.3 mg/kg/hr onwards	NA	NA	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	NA	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; NA: Not applicable

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 “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 for injection using the same infusion rate as the one used for the last part of the infusion.

Home infusion during maintenance phase:

Home infusion under the supervision of a healthcare professional may be considered for patients on maintenance dose and who are tolerating their infusions well. The decision to have patients moved to home infusion should be made after evaluation and recommendation by the prescribing physician.

Appropriate medical support, including personnel trained in emergency measures, should be readily available when Xenpozyme is administered. If anaphylactic or other acute reactions occur, immediately discontinue the Xenpozyme infusion, initiate appropriate medical treatment and seek the attention of a physician. If severe hypersensitivity reactions occur, subsequent infusions should only occur in a setting where resuscitation measures are available. The dose and infusion rate used in the home settings should remain the same as

were used in the supervised clinical settings, and should not be changed without supervision of the prescribing physician. In case of missed doses or delayed infusion, the prescribing physician should be contacted as subsequent infusions may occur in a supervised clinical setting.

4.3 Contraindications

Life-threatening hypersensitivity (anaphylactic reaction) to olipudase alfa or to any of the excipients listed in "List of excipients" (see "Special warnings and precautions for use").

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered medicinal 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 "Undesirable effects"). The most frequent IARs were headache, urticaria, pyrexia, nausea, and vomiting (see "Undesirable effects"). IARs typically occurred between the time of infusion and up to 24 hours after infusion completion.

Hypersensitivity/anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in Xenpozyme-treated patients (see "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.

Mild to moderate hypersensitivity reactions reported in more than one adult patient included urticaria, erythema, pruritus, rash, and angioedema. In pediatric patients, mild to moderate hypersensitivity reactions reported in more than one patient included urticaria, erythema, rash, and pruritus.

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 desensitization regimen that enabled the patient to resume treatment with Xenpozyme. The risks and benefits of readministering Xenpozyme following anaphylaxis or severe hypersensitivity reaction should be considered. If considering re-administration of Xenpozyme following anaphylaxis, the prescribing physician should contact the local Sanofi Genzyme representative for advice. 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 pediatric patients, respectively (see "Posology and method of administration").

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

Transient transaminases 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 "Undesirable effects"). At the time of the next scheduled infusion, these elevated transaminase levels generally returned to the levels observed prior to the Xenpozyme infusion.

Transaminases (ALT and AST) levels should be obtained within 1 month prior to Xenpozyme treatment initiation (see "Immunogenicity"). During dose escalation or upon resuming treatment following missed doses, transaminases 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 "Immunogenicity").

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Women of childbearing potential

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

Pregnancy

There are limited data from the use of olipudase alfa in pregnant women. Studies in animals have shown reproductive toxicity (see "Reproductive and developmental toxicity"). 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 foetus.

Breast-feeding

It is unknown whether olipudase alfa is excreted in human milk. There is insufficient information on the excretion of olipudase alfa in animal milk. A risk to the newborns/infants 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.

Fertility

No human data are available on the effects of olipudase alfa on male and female fertility. Animal data do not indicate direct or indirect harmful effects with respect to fertility (see "Reproductive and developmental toxicity").

4.7 Effects on ability to drive and use machines

Because hypotension has been reported in clinical studies, Xenpozyme may have minor influence on the ability to drive and use machines (see "Undesirable effects").

4.8 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) were headache (31.7%), urticaria (26.7%), pyrexia (25%), nausea (20%), vomiting (16.7%), abdominal pain (16.7%), myalgia (13.3%), pruritus (13.3%), rash (11.7%), abdominal pain upper (10%), erythema (10%) and C-reactive protein increased (10%).

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 pediatric patients.

Adverse reactions reported in the pooled safety analysis of clinical studies are listed in Table 6 per System Organ Class, presented by frequency categories: very common (≥1/10), common (≥1/100 to<1/10), uncommon (≥1/1 000 to <1/100), rare (≥1/10 000 to <1/1 000), very rare (<1/10 000) and not known (cannot be estimated from the available data).

Table 6: Adverse drug reactions in patients treated with Xenpozyme in pooled safety 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
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%) pediatric patients. IAR symptoms reported in at least 3 adult patients (≥7.5%) were headache (25%), nausea (17.5%), urticaria (12.5%), 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 pediatric 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.

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

One pediatric 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. Anti-olipudase alfa IgE antibodies were detected in both pediatric patients.

In 2 adult and 3 pediatric 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.

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 by 46.9% and mean AST decreased by 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

As with all therapeutic proteins, there is a potential for immunogenicity to Xenpozyme.

Immunogenicity was evaluated in adult patients from 3 clinical studies (DFI13412, DFI12712/ASCEND, and LTS13632) and in pediatric patients from 2 clinical studies (DFI13803/ASCEND-Peds, and LTS13632).

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 titer ≤400) except for three patients with an intermediate ADA response (peak titers ranging 800 - 6400). The median ADA peak titer was 200. Eight out of these 19 adult patients had neutralizing 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 pediatric patients, 15 out of 20 (75%) pediatric patients treated with Xenpozyme developed treatment-emergent ADA. The median time to seroconversion from first Xenpozyme infusion was 12 weeks. The majority of pediatric patients had a low ADA response except for four patients with an intermediate ADA response. The median ADA peak titer was 200. Nine out of the 15 pediatric 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 pediatric patient experienced an anaphylactic reaction and developed IgE ADA, and IgG ADA with a peak titer of 1600.

IgE ADA testing may be considered for patients who experienced a severe hypersensitivity reaction to olipudase alfa (see “Pharmacodynamic properties”).

No effect of ADA was observed on pharmacokinetics and efficacy of Xenpozyme in adult and pediatric 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

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 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 linked to Xenpozyme, see “Special warnings and precautions for use” and “Undesirable effects”.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Enzymes, 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 efficacy and safety

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 multicenter, 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 intravenous 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 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 years). 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< .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 was noted at week 26 of treatment, the first post-dose endpoint assessment.

The results from the PAP at week 52 are detailed in Table 7.

Table 7 - Mean (SD) values for efficacy endpoints at baseline and 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	48.45 (10.77)	49.44 (10.99)	NA	NA
Percent change in % predicted DLco from baseline to Week 52	2.96 (3.38)	21.97 (3.34)	19.01 (4.76) [9.32, 28.70]	0.0004
Mean spleen volume (MN) at baseline	11.21 (3.84)	11.70 (4.92)	NA	NA
	0.48 (2.50)	-39.45 (2.43)	-39.93 (3.50)	<0.0001

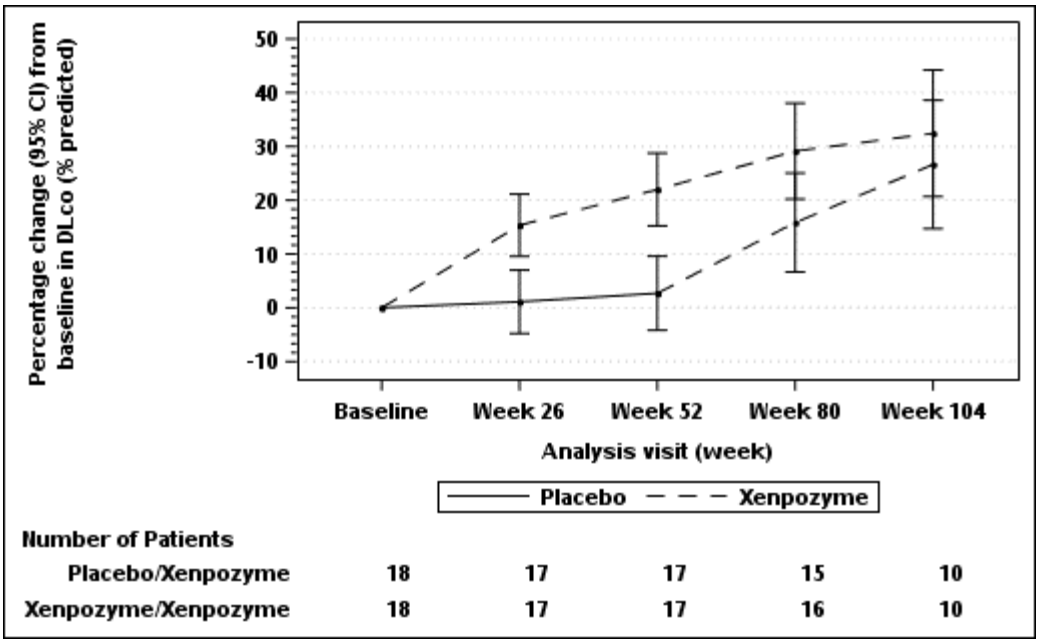
Percent change in Spleen volume from baseline to Week 52			[-47.05, -32.80]	
Secondary endpoints				
Mean liver volume (MN) at baseline	1.62 (0.50)	1.44 (0.32)	NA	NA
Percent change in Liver volume from baseline to Week 52	-1.47 (2.54)	-28.06 (2.49)	-26.60 (3.59) [-33.91, -19.28]	<0.0001
Mean platelet count (10^9/L) at baseline	115.58 (36.27)	107.18 (26.93)	NA	NA
Percent change in Platelet Count from baseline to Week 52	2.49 (4.19)	16.82 (3.96)	+14.33 (5.78) [2.56, 26.10]	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 Figures 1 and 2 and Table 8.

Figure 1: Plot of the LS means (95%CI) of the percentage change in DLco (% predicted) from baseline to Week 104 - mITT population

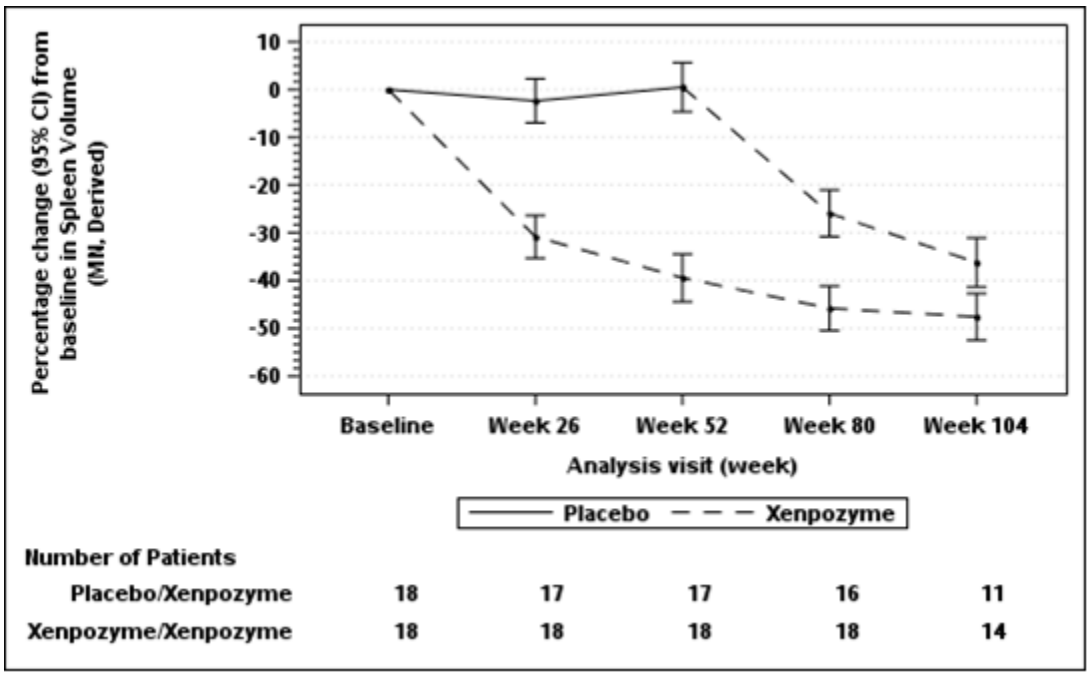


The vertical bars represent the 95% CIs for the LS means.

The LS means and 95% CIs are based on a mixed model for repeated measures approach, using data up to Week104.

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 - 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 Week104
Patients in placebo/Xenpozyme group received placebo by Week 52 and switched to Xenpozyme thereafter.

Table 8: 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 > 9 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 9).

Table 9: 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

Paediatric population

The ASCEND-Peds study (Phase 1/2 clinical study) is a multi-center, 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.

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 10).

Table 10: LS Mean percentage change (SE) or change (SD) from baseline to week 52 (all age cohort) of efficacy parameters

	Baseline value (n=20)	Week 52 (n=20)
Mean % predicted DLco (SD) Percent change in % predicted DLco* 95% CI	54.8 (14.2)	71.7 (14.8) 32.9 (8.3) 13.4, 52.5
Mean spleen volume (MN) (SD) Percent change in spleen volume (in MN) 95% CI	19.0 (8.8)	9.3 (3.9) -49.2 (2.0) -53.4, -45.0
Mean liver volume (MN) (SD) Percent change in liver volume (in MN) 95% CI	2.7 (0.7)	1.5 (0.3) -40.6 (1.7) -44.1, -37.1
Mean platelet count (10^9/L) (SD) Percent change in platelet count 95% CI	137.7 (62.3)	173.6 (60.5) 34.0 (7.6) 17.9, 50.1

Mean height Z-scores (SD) Change in height Z-scores* 95% CI	-2.1 (0.8)	-1.6 (0.8) 0.6 (0.4) (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.

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 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 > 8 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 11).

Table 11: Mean percentage change or change (SD) from baseline to month 48 (all age cohort) of efficacy parameters

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

N: number of patients

The European Medicines Agency has deferred the obligation to submit the results of studies with Xenpozyme in one or more subsets of the paediatric population in the treatment of Acid Sphingomyelinase Deficiency (see 4.2 for information on paediatric use).

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 (Cmax) and area under the concentration-time curve over a dosing interval (AUC0-**τ**) at steady state were 30.2 µg/mL (17%) and 607 µg.h/mL (20%), respectively.

Absorption

There is no absorption since Xenpozymeis administered intravenously.

Distribution

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

Biotransformation

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

Elimination

The mean (CV%) clearance of olipudase alfa is 0.331 L/h (22%). The mean terminal half-life (t1/2) 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)

There is limited information on olipudase alfa pharmacokinetics in elderly patients (only 2 patients between 65 and 75 years of age included in clinical studies with Xenpozyme).

Pediatric

The PK of olipudase alfa were assessed in 20 paediatric patients including 4 adolescent patients, 9 child patients and 7 child/infant patients (Table 12). 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 12 - 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 (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.
AUC0-**τ**: area under the plasma concentration versus time curve over a dosing interval; Cmax: 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

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, single dose toxicity and repeated dose toxicity conducted in wild type animals (mice, rats, rabbits, dogs and monkeys) at dose levels 10 times above the Maximum recommended human dose (MRHD). Studies to evaluate the mutagenic and carcinogenic potential of olipudase alfa have not been performed.

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 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.

An increased incidence of exencephaly was observed when pregnant mice were treated daily with olipudase alfa at exposure levels comparable to the human exposure 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 significantly exceeding the human exposure at the recommended maintenance therapeutic dose and frequency.

In mice administered 3 mg/kg olipudase alfa on postpartum day 7, olipudase alfa was detected in milk 2 days after administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-methionine
Sodium phosphate dibasic heptahydrate
Sodium phosphate monobasic 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

Unopened vials: 60 months.

Reconstituted medicinal product

After reconstitution with sterile water for injection, chemical, physical and microbiological in use stability has been demonstrated for up to 24 hours at 2 - 8°C or 12 hours at room temperature (up to 25°C).

From a microbiological point of view, the reconstituted medicinal product should be used immediately. If not used for dilution immediately, in use storage times and conditions prior to dilution are the responsibility of the user and should normally not be longer than 24 hours at 2°C - 8°C or 12 hours at room temperature (up to 25°C).

Diluted medicinal product

After dilution with sodium chloride 9 mg/mL (0.9%) solution for injection, chemical, physical and microbiological in use stability has been demonstrated between 0.1 mg/mL and 3.5 mg/mL for 24 hours at 2 8°C, and up to 12 hours (including infusion time) when stored at room temperature (up to 25°C).

From a microbiological point of view, the diluted medicinal product should be used immediately. If not used immediately after dilution, in use storage times and conditions are the responsibility of the user and should normally not be longer than 24 hours at 2°C to 8°C followed by 12 hours (including infusion time) at room temperature (up to 25°C).

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions after reconstitution and dilution of the medicinal product, see "Shelf-life".

6.5 Nature and contents of container

20 mg of powder for concentrate for solution for infusion in a vial (Type I glass) with a siliconized chlorobutyl-elastomer lyophilization stopper, and an aluminum seal with a plastic flip-off cap.

Each pack contains 1, 5, 10 or 25 vials. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Vials are for single use only.

Infusions should be administered in a stepwise manner preferably using an infusion pump.

Preparation of the dosing solution

The powder for concentrate for solution for infusion must be reconstituted with sterile water for injection, 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 conditions. Filtering devices should not be used at any time during the preparation of the infusion solution. Avoid foaming during reconstitution and dilution steps.

1) Determine the number of vials to be reconstituted based on the individual patient's weight and the prescribed dose.
   Patient weight (kg) × dose (mg/kg) = patient dose (in mg). Patient dose (in mg) divided by 20 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.
2) Remove the required number of vials from refrigeration and set aside for approximately 20 to 30 minutes to allow them to reach room temperature.

3) Reconstitute each vial by injecting 5.1 mL of sterile water for injection into the vial using a slow drop-wise addition technique to the inside wall of the vial.
4) Tilt and roll each vial gently. Each vial will yield a 4 mg/mL clear, colorless solution.
5) Visually inspect the reconstituted solution in the vials for particulate matter and discoloration. Xenpozyme solution should be clear and colorless. Any vials exhibiting opaque particles or discoloration should not be used.
6) 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 13 for the recommended total infusion volume based on patients age and/or weight).

Table 13: 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	NA
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 13):
    - Prepare an infusion solution at 0.1 mg/mL by adding 0.25 mL (1 mg) of the reconstituted solution prepared in step 3 and 9.75 mL of 0.9% sodium chloride for injection in 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 within 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 3) 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).

  ○ Prefilled 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 12.
    - Add slowly the required volume of the reconstituted solution from step 3) into the infusion bag (avoid foaming within the bag).

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) The diluted solution must be filtered through an in-line low protein-binding 0.2 μm filter during administration.
9) 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.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Sanofi-aventis (Thailand) Ltd.

8. MARKETING AUTHORISATION NUMBER(S)

1C 15020/67 (NBC)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3 April 2024

10. DATE OF REVISION OF THE TEXT

Olipudase alfa CCDS v7.0 (27 Jun 2024)