ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Xenpozyme 4 mg powder for concentrate for solution for infusion
Xenpozyme 20 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Xenpozyme 4 mg powder for concentrate for solution for infusion
Each vial contains 4 mg of olipudase alfa*.

Excipient with known effect

Each vial contains 0.60 mg of sodium.

Xenpozyme 20 mg powder for concentrate for solution for infusion
Each vial contains 20 mg of olipudase alfa*.

Excipient with known effect

Each vial contains 3.02 mg of sodium.

After reconstitution, each vial contains 4 mg of olipudase alfa per mL. Each vial must be further diluted before use (see section 6.6).

*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.

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.

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.

Treatment with Xenpozyme must always be initiated via a dose escalation regimen (see below) to minimise the risk of infusion-associated reactions, including acute phase reactions, and increases in liver transaminases. All instructions for dosage and administration (see below), and for preparation and handling (see section 6.6), should be followed to avoid the risk of overdose (see section 4.9). Please note that the dose escalation for paediatric patients differs from the one for adults. In addition to the dose escalation regimen, each dose must be administered using a staggered infusion rate (see Tables 3 and 4).
For missed doses see also below. Home infusion for patients should only be considered after the dose escalation phase.

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 (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*
Sixth dose (Week 10)	1 mg/kg*
Seventh dose (Week 12)	2 mg/kg*
Eighth dose (Week 14)	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 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.

Paediatric population

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 2A: 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)

*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 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.

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 × 1.7^2 = 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, the next dose should be administered as described below as soon as possible. Thereafter, administrations should be scheduled every 2 weeks from the date of the last administration. The dose escalation regimen for administration of Xenpozyme prevents a rapid release of catabolites, which can result in serious toxicity such as hepatic inflammation/transaminase elevations, serious and life-threatening infusion associated reactions or even death (see section 4.4, 4.8 and 4.9). A patient who has not been largely debulked or has suspected re-accumulation, due to missed doses, should resume treatment at a lower dose.

Table 2B: Xenpozyme dosing recommendations for adult and paediatric patients after one or several missed dose(s).

Consecutive missed doses	**Dose escalation phase**	**Maintenance phase**
If 1 infusion is missed*:	The last tolerated dose should be administered, before resuming dose escalation according to the regimen in adults (Table 1) or in paediatric patients (Table 2A).	The maintenance dose should be administered and the treatment schedule adjusted accordingly.

If 2 consecutive infusions are missed*:	1 dose level lower than the last tolerated dose (using a minimal dose of 0.3 mg/kg) should be administered, before resuming dose escalation according to Table 1 or Table 2A.	1 dose below the maintenance dose (i.e. 2 mg/kg) should be administered. Then for subsequent infusions, the maintenance dose (3 mg/kg) every 2 weeks should be administered.
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 first escalation dose described in Table 1. For paediatric patients who have not completed the dose escalation regimen, re-initiate the dose escalation regimen starting at at the first escalation dose described in Table 2A.	For adult patients who have missed maintenance dosing for 3 or more consecutive doses during which sphingomyelin could have reaccumulated, the treating physician is advised to re-initiate the dose escalation regimen starting at the first escalation dose described in Table 1. For paediatric patients who have missed maintenance dosing for 3 or more consecutive doses during which sphingomyelin could have reaccumulated, the treating physician is advised to re-initiate the dose escalation regimen starting at the first escalation dose described in Table 2A.

* In case the next scheduled infusion after a missed dose is a dose of 0.3 or 0.6 mg/kg, that dose should be administered twice as per Table 1 and Table 2A.

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 2A for adult and paediatric patients, respectively, and recommendations in case of missed doses (see missed doses section).

Special populations

Elderly patients
No dose adjustment is recommended for patients over the age of 65 (see section 5.2).

Hepatic impairment
No dose adjustment is recommended in patients with hepatic impairment (see section 5.2).

Renal impairment
No dose adjustment is recommended in patients with renal impairment (see section 5.2).

Method of administration

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

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

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.). The infusion rate and duration of infusion (+/- 5 min) for each step of infusion are detailed in Table 3 and Table 4.

When determining the infusion rate in Tables 3 and 4, use the dose level from the dose escalation regimen, found in either Table 1 (adult) or Table 2A (paediatric patients).

Table 3: 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
*Dose level from the dose escalation regimen in Table 1

Table 4: 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
*Dose level from the dose escalation regimen in Table 2A

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).

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 section 6.1 (see section 4.4).

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 section 4.8). The most frequent IARs were headache, urticaria, pyrexia, nausea and vomiting (see section 4.8). IARs typically occurred between the time of infusion and up to 24 hours after infusion completion.

Serious adverse reactions, including death, have occurred following overdose during the dose escalation phase (see sections 4.2 and 4.9).

Hypersensitivity/anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in Xenpozyme-treated patients (see section 4.8). In clinical studies, hypersensitivity reactions occurred in 9 (22.5%) adult and 9 (45%) paediatric patients including one paediatric patient who experienced anaphylaxis.

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 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 the local Sanofi representative 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 2A for adult and paediatric patients, respectively (see section 4.2).

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). 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 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 section 4.8). 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 section 4.2). 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 section 4.2). 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 0.60 mg sodium per 4 mg vial or 3.02 mg sodium per 20 mg vial, equivalent to 0.03 and 0.15%, respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult or an adolescent, and ≤0.08% and ≤0.38%, respectively, 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 section 5.3). 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. Olipudase alfa was detected in the milk of lactating mice (see section 5.3). 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 section 5.3).

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 section 4.8).

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%), 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.

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 (≥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 5: Adverse drug reactions in patients treated with Xenpozyme in pooled analysis of 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 57.5% of adult and 65% of paediatric patients. IAR symptoms reported most frequently in adult patients 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 most frequently in paediatric patients 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 30% patients, 22.5% adult and 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%).

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

In 2 adults 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.

Transaminase elevations

Transient transaminase (ALT or AST) elevations within 24 to 48 hours after an 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. In adult patients, all 16 patients with an elevated baseline ALT had an ALT within the normal range and 10 of 12 patients with an elevated baseline AST had an AST within the normal range.

Immunogenicity

Overall, 19 out of 40 (47.5%) adult patients and 15 out of 20 (75%) paediatric patients treated with Xenpozyme developed treatment-emergent anti-drug antibodies (ADA). The median time to seroconversion from first Xenpozyme infusion was approximately 52 weeks in adults and 12 weeks in paediatric patients. The majority of ADA-positive patients (16 out of 19 adult and 10 out of 15 paediatric patients) had a low ADA response (peak titer ≤ 400) or reverted to ADA-negative. Three adult ADA-positive patients and 4 paediatric ADA-positive patients developed intermediate ADA responses (peak titer ranged 800-6400). Eight out of the 19 adult ADA-positive patients and 9 out of the 15 paediatric ADA-positive patients had Neutralizing Antibodies (NAb) that inhibited the olipudase alfa activity. Only 2 adult patients and 3 paediatric patients had NAb at more than one timepoint. One paediatric patient experienced an anaphylactic reaction and developed IgE ADA, and IgG ADA with a peak titer 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%).

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

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. 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

Cases of overdose of Xenpozyme have been reported in paediatric patients during dose escalation. Some of these patients experienced serious adverse reactions 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 sections 4.4 and 4.8.

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 olipudase alfa 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 olipudase alfa 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 6.

Table 6: Mean (SD) values for efficacy endpoints at baseline and least squares (LS) mean percentage change (SE) from baseline to week 52

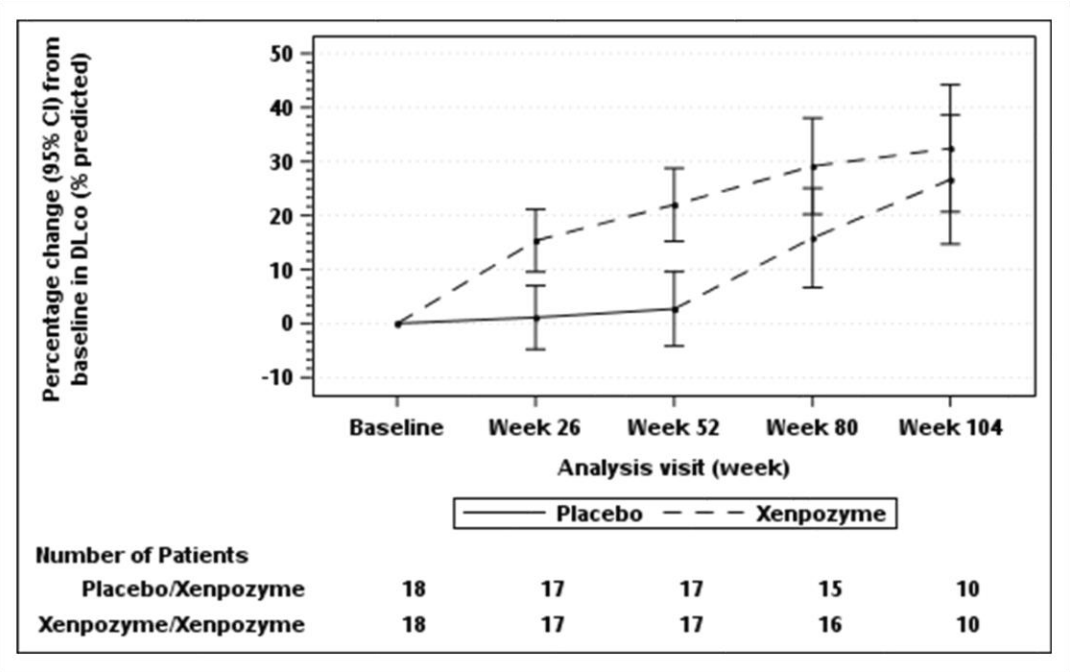
	Placebo (n=18)	Xenpozyme (n=18)	Difference [95% CI]	p value*
Primary endpoints				
Mean % predicted DLco at baseline	48.5 (10.8)	49.4 (11.0)	NA	NA
Percent change in % predicted DLco from baseline to week 52	3 (3.4)	22 (3.3)	19 (4.8) [9.3, 28.7]	0.0004
Mean spleen volume (MN) at baseline	11.2 (3.8)	11.7 (4.9)	NA	NA
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)	NA	NA
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)	NA	NA
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).

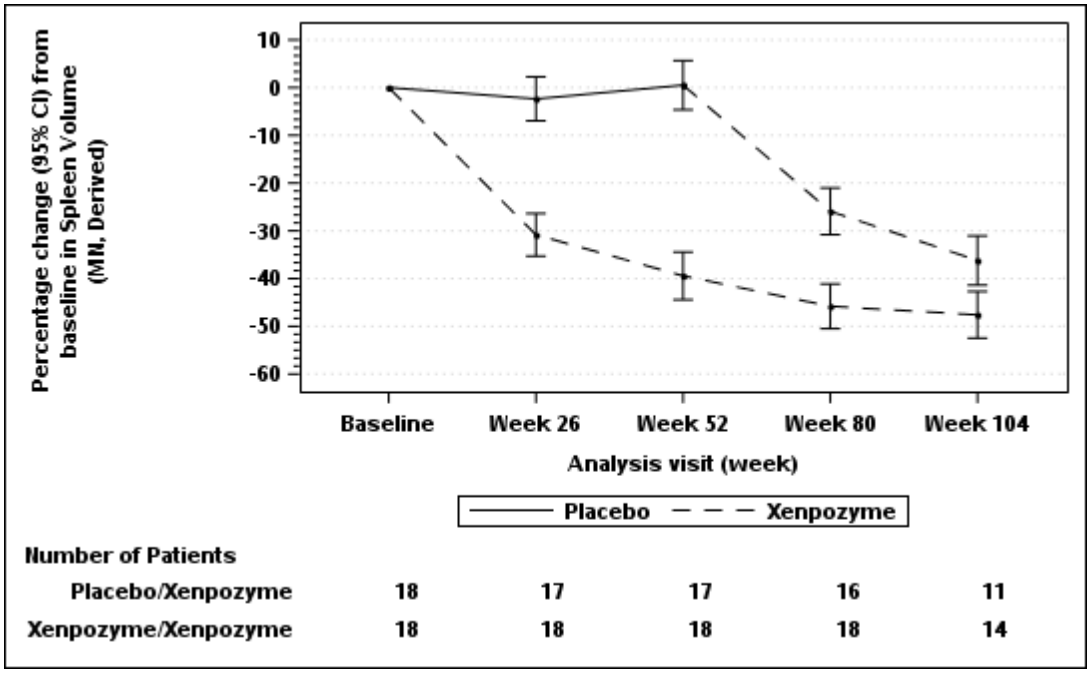
Seventeen of 18 patients previously receiving placebo and 18 of 18 patients previously treated with olipudase alfa for 52 weeks (PAP) started or continued treatment with olipudase alfa, respectively, for up to 4 years. Sustained effects of olipudase alfa on efficacy endpoints up to week 104 are presented in Figures 1 and 2 and Table 7.

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 week 104.
Patients in placebo/Xenpozyme group received placebo up to week 52 and switched to olipudase alfa 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 week 104.
Patients in placebo/Xenpozyme group received placebo up to week 52 and switched to olipudase alfa thereafter.

Table 7: LS mean percentage change (SE) from baseline to week 104 for liver volume (MN) and platelet count (10^9/L) in patients treated with olipudase alfa for 104 weeks

	Previous olipudase alfa group	
	week 52 (ETP start)	week 104
N Percent change in liver volume (SD)	17 -27.8 (2.5)	14 -33.4 (2.2)
N Percent change in platelet count (SD)	18 16.6 (4.0)	13 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 olipudase alfa 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 8).

Table 8: 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 olipudase alfa 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 olipudase alfa 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 olipudase alfa 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 9).

Table 9: 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 olipudase alfa 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 olipudase alfa 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 10).

Table 10: 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

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.

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%).

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 ($t_{1/2}$) ranged from 31.9 to 37.6 hours.

Linearity/non-linearity

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.

Special populations

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

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 PK of olipudase alfa were assessed in 20 paediatric patients including 4 adolescent patients, 9 child patients and 7 child/infant patients (Table 11). 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 11: 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.
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 less than 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 foetal 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 6 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 would normally not be longer than 24 hours at 2°C - 8°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 section 6.3.

6.5 Nature and contents of container

Xenpozyme 4 mg powder for concentrate for solution for infusion

4 mg of powder for concentrate for solution for infusion in a 5 mL 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 or 10 vials. Not all pack sizes may be marketed.

Xenpozyme 20 mg powder for concentrate for solution for infusion

20 mg of powder for concentrate for solution for infusion in a 20 mL 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). For example, when using 20 mg vials, 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:
   1.1 mL of sterile water for injection into the 4 mg vial
   5.1 mL of sterile water for injection into the 20 mg 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 12 for the recommended total infusion volume based on patients age and/or weight).

Table 12: 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 12):

  - 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 sodium chloride 9 mg/mL (0.9%) solution 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).
  - 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 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 B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1659/001
EU/1/22/1659/002
EU/1/22/1659/003
EU/1/22/1659/004
EU/1/22/1659/005
EU/1/22/1659/006
EU/1/22/1659/007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24 June 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Patheon Biologics
4766 LaGuardia Drive
Saint Louis
Missouri
63134
United States

Name and address of the manufacturer responsible for batch release

Genzyme Ireland Limited
IDA Industrial Park
Old Kilmeaden Road
Waterford
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Xenpozyme in each Member State the Marketing Authorization Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.
The educational programme is aimed at minimizing specific safety concerns.

The MAH shall ensure that in each member state where Xenpozyme is marketed, all healthcare professionals (HCPs) and patients/caregivers who are expected to prescribe, dispense, use Xenpozyme have access to/are provided with the following educational message to be disseminated through professional bodies:

- HCP educational materials
- Patient/caregiver educational materials

1. HCP educational materials:

1.1. HCP Guide for HCPs in home infusion setting including nurses:
The HCP guide includes the following key elements:

- On the front page, contact information of the prescribing/treating physician/centre that can be reached at any time,
- Reminder to read the summary of product characteristics (SmPC) prior to initiating treatment.
- To ensure awareness about the risk of immunogenicity, its monitoring and management, the guide includes the following:
    - Requirements that the home infusion HCPs/nurses should be trained for emergency measures and should have resuscitative equipment ready prior to initiating care.
    - Information on signs and symptoms of infusion-associated reactions (IARs), severe hypersensitivity or anaphylaxis and recommended actions for the management of adverse drug reactions (ADRs) if they occur.
    - Reminder to apply only maintenance dose (mg/kg) as prescribed by the treating/prescribing physician.
- Instruction to contact the prescribing/treating physician if the patient experienced signs/ symptoms of IARs, hypersensitivity, anaphylaxis or if one or more infusions are missed or delayed.
- Medical evaluation of the patient prior to administration of the infusion at home.
- Requirements and organization of the home infusion including equipment, pre-treatment and emergency treatments.
- Details and instructions on the preparation, reconstitution, dilution and administration of the product to prevent the risk of medication errors. A calculation template to prepare the infusion solution based on prescribed maintenance dose and patient's body weight with instructions to record the calculation and infusion date.
- The calculation template can be used as a basis for recording infusion details in the patient's medical record.

- Reminder to check if additional supplies are required.
- Reminder for reporting ADR and events of medication errors, pregnancy and breastfeeding.

2. Patient educational materials:

2.1 Patient Card for patients/caregivers
The patient card includes the following elements:

- Instruction to the patients/caregivers to seek urgent medical attention if any signs and symptoms of IARs, severe hypersensitivity or anaphylaxis listed in the card appear or worsen during and after infusion and to report the event to the treating/prescribing physician.

- Contact information of the prescribing/treating physician/centre that can be reached at any time.
- Reminder to the women of childbearing potential (WOCBP) to discuss with the prescribing/treating physician the need for effective contraceptive measures during treatment and for 14 days after the last dose if Xenpozyme is discontinued.

- Reminder to the WOCBP to contact their prescribing/treating physician if they suspect they might be pregnant or plan pregnancy and breastfeeding.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xenpozyme 4 mg powder for concentrate for solution for infusion
olipudase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 4 mg of olipudase alfa.

3. LIST OF EXCIPIENTS

Also contains:
L-methionine
Sodium phosphate dibasic heptahydrate
Sodium phosphate monobasic monohydrate
Sucrose
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 vial
5 vials
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous use after reconstitution and dilution.

For more information, scan QR code or visit www.xenpozyme.info.sanofi

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use immediately after dilution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1659/005 1 vial
EU/1/22/1659/006 5 vials
EU/1/22/1659/007 10 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xenpozyme 4 mg powder for concentrate
olipudase alfa
IV use after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 mg

6. OTHER

Sanofi B.V.-NL

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xenpozyme 20 mg powder for concentrate for solution for infusion
olipudase alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 20 mg of olipudase alfa.

3. LIST OF EXCIPIENTS

Also contains:
L-methionine
Sodium phosphate dibasic heptahydrate
Sodium phosphate monobasic monohydrate
Sucrose
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 vial
5 vials
10 vials
25 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous use after reconstitution and dilution.

For more information, scan QR code or visit www.xenpozyme.info.sanofi

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use immediately after dilution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Sanofi B.V.
Paasheuvelweg 25
1105 BP Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1659/001 1 vial
EU/1/22/1659/002 5 vials
EU/1/22/1659/003 10 vials
EU/1/22/1659/004 25 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Xenpozyme 20 mg powder for concentrate
olipudase alfa
IV use after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

20 mg

6. OTHER

Sanofi B.V.-NL

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Xenpozyme 4 mg powder for concentrate for solution for infusion
Xenpozyme 20 mg powder for concentrate for solution for infusion
olipudase alfa

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xenpozyme is and what it is used for

What Xenpozyme is
Xenpozyme contains an enzyme called olipudase alfa.

What Xenpozyme is used for
Xenpozyme is used to treat an inherited disorder called acid sphingomyelinase deficiency (ASMD). It is used in children and adults with ASMD types A/B or B to treat the signs and symptoms of ASMD not related to the brain.

How Xenpozyme works
Patients with ASMD lack a properly working version of the enzyme acid sphingomyelinase. This results in build-up of a substance called sphingomyelin, which damages organs such as spleen, liver, heart, lungs and blood. Olipudase alfa acts in the same way as the natural enzyme would, and so acts as a replacement, reducing the build-up of sphingomyelin in the organs and treating the signs and symptoms.

2. What you need to know before you are given Xenpozyme

You must not be given Xenpozyme
- If you have experienced life-threatening allergic (anaphylactic) reactions to olipudase alfa (see section ‘Warnings and precautions’ below) or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
You may have side effects called infusion-associated reactions (IARs) that may be caused by the infusion (drip) of the medicine. They may occur while you are being given Xenpozyme or within 24 hours after the infusion.

They may include allergic reactions (see section 4) and symptoms such as headache, a raised, itchy rash (hives), fever, nausea, vomiting and itchy skin.

If you think you are having an IAR, **tell your doctor straight away.**
If you have a severe allergic reaction during your infusion your doctor will stop your infusion and provide appropriate medical treatment. Your doctor will make a judgement about the risks and benefits of giving you further doses Xenpozyme.

If you have a mild or moderate IAR, your doctor or nurse may temporarily stop the infusion, lower the infusion rate, and/or reduce the dose.

Your doctor may also give (or have given) you other medicines to prevent or manage allergic reactions.
Your doctor will order blood tests to check how well your liver is working (by measuring levels of your liver enzymes) before starting the treatment, and then at regular intervals as the doses are adjusted (see section 3).

Other medicines and Xenpozyme
Tell your doctor or nurse if you are using, have recently used, or might use any other medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant, or are planning to have a baby, ask your doctor or nurse for advice before using this medicine.

There is limited experience with the use of Xenpozyme in pregnant women. Xenpozyme may be harmful to unborn children when taken by a woman during pregnancy. Xenpozyme should only be used during pregnancy if clearly necessary. Women who are able to become pregnant should use effective contraception during treatment and for 14 days after the last dose if Xenpozyme is discontinued.

It is not known whether Xenpozyme passes into human breast milk. Xenpozyme was detected in animal milk. Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding, or whether to stop taking Xenpozyme, considering the benefit of breast-feeding the baby and the benefit of Xenpozyme to the mother.

Driving and using machines
Xenpozyme may have a minor influence on the ability to drive and use machines because you may experience low blood pressure (which may make you feel faint).

Xenpozyme contains sodium
This medicine contains 0.60 mg sodium (main component of cooking/table salt) per 4 mg vial or 3.02 mg sodium per 20 mg vial. This is equivalent to 0.03% and 0.15%, respectively, of the recommended maximum daily dietary intake of sodium for an adult or an adolescent and ≤0.08% and ≤ 0.38%, respectively, of the maximum acceptable daily intake of sodium for children below 16 years of age.

3. How Xenpozyme is given

Xenpozyme will be given to you as a drip (infusion) under the supervision of a healthcare professional who is experienced in the treatment of ASMD or other metabolic diseases.

The dose you receive is based on your body weight and will be given to you every two weeks.
Treatment starts with a low dose of the medicine, which is gradually increased.
Infusion usually lasts around 3 to 4 hours but may be shorter or longer based on your doctor's judgement, and may be shorter during the period whilst your dose is being increased.

Adult patients
The recommended starting dose of Xenpozyme is 0.1 mg for each kg of body weight. This is increased in a planned way with each subsequent dose, until the recommended dose of 3 mg for each kg of body weight every 2 weeks is reached. It typically takes up to 14 weeks to reach the recommended dose but may be longer based on your doctor's judgement.

Children
The recommended starting dose of Xenpozyme is 0.03 mg for each kg of body weight. The subsequent doses should be increased in a planned way up to the recommended dose of 3 mg for each kg of body weight every 2 weeks. It typically takes up to 16 weeks to reach the recommended dose but may be longer based on your doctor's judgement.

Home infusion
Your doctor may consider home infusion of Xenpozyme if you are on stable dose and tolerating your infusions well. This decision to move to home infusion should be made after evaluation and recommendation by your doctor. If you get a side effect during an infusion of Xenpozyme, the person giving your home infusion may stop the infusion and start appropriate medical treatment.

Instructions for proper use
Xenpozyme is given by intravenous infusion (a drip into a vein). It is supplied as a powder that will be mixed with sterile water before it is given.

If you are given more Xenpozyme than you should
Tell your doctor immediately, if you suspect a change from your routine infusion.

If you miss a Xenpozyme infusion
It is important to have your infusion every 2 weeks. An infusion is considered missed if not given within 3 days from the scheduled infusion. Depending on the number of missed doses, your doctor may have to restart from a lower dose.

If you have missed an infusion or are unable to attend a scheduled appointment, please contact your doctor right away.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Infusion-associated reactions (IARs) have been seen while patients were being given the medicine or within 24 hours after the infusion.

The most serious side effects may include sudden severe allergic reactions, raised, itchy rash (hives), rash, increased liver enzymes and irregular heartbeat.

You must tell your doctor immediately if you get an IAR or an allergic reaction.
If you have an infusion reaction you may be given additional medicines to treat or help prevent future reactions. If the infusion reaction is severe, your doctor may stop the infusion of Xenpozyme and start giving appropriate medical treatment.

Very common (may affect more than 1 in 10 people):
- Headache
- Raised, itchy rash (hives)
- Fever – body temperature increased
- Nausea
- Abdominal (belly) pain
- Vomiting

- Itchy skin
- Muscles aches
- Rash
- Increased blood test for inflammation
- Pain in upper belly
- Reddening of the skin

Common (may affect up to 1 in 10 people):
- Itchy or red eyes
- Joint pain
- Fatigue
- Abnormal blood test for liver function
- Diarrhoea
- Low blood pressure
- Difficulty breathing
- Abdominal discomfort
- Rash (different types of rash sometimes with itch)
- Back pain
- Pain
- Chills
- Feeling very warm
- Wheezing
- Throat and voice box irritation
- Liver pain
- Skin lesions (such as solid elevated or red flat lesions)
- Bone pain
- Weakness
- Severe allergic reactions
- Eye discomfort
- Fast heartbeat
- Forceful heartbeat that may be rapid or irregular
- Throat tightness and swelling
- Stomach pain
- Rapid swelling under the skin in areas such as the face, throat, arms and legs which can be life threatening if throat swelling blocks the airway
- Catheter site-related reactions including pain, itching, or swelling
- Abnormal blood test for inflammation

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xenpozyme

Keep this medicine out of the sight and reach of children.

Do not use Xenpozyme after the expiry date stated on the label and the carton. The expiry date refers to the last day of the month.

Store in refrigerator between 2°C to 8°C.

After dilution, immediate use is recommended.

If not used immediately, the reconstituted solution may be stored for up to 24 hours at 2°C to 8°.

After dilution, the solution can be stored for up to 24 hours at 2-8°C followed by 12 hours (including infusion time) at room temperature.

Do not throw away any medicines via wastewater or household waste. Ask your doctor or nurse how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Xenpozyme contains
- The active substance is olipudase alfa. One vial contains 4 mg or 20 mg of olipudase alfa.
- Other ingredients are
  - L-methionine
  - Sodium phosphate dibasic heptahydrate
  - Sodium phosphate monobasic monohydrate
  - Sucrose

  see section 2 Xenpozyme contains sodium

What Xenpozyme looks like and contents of the pack
Xenpozyme is a powder for concentrate for solution for infusion in a vial (4 or 20 mg/vial).
The powder is white to off-white lyophilised powder.
After mixing with sterile water, it is a clear, colorless solution. The solution must be further diluted before infusion.

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Manufacturer
Genzyme Ireland Limited, IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website and on the website: www.xenpozyme.info.sanofi, or by scanning the QR code below (also included on the outer carton) with a smartphone.

<placeholder for QR code>

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The following information is intended for healthcare professionals only:

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). For example, when using 20 mg vials, 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:
   1.1 mL of sterile water for injection into the 4 mg vial
   5.1 mL of sterile water for injection into the 20 mg 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 1 for the recommended total infusion volume based on patients age and/or weight).

Table 1: 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
1.0	20	50	100	100
2.0	50	75	200	100
3.0	50	100	250	100

- For variable final volumes of infusion based on body weight in paediatric patients (see Table 1):

  - 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 sodium chloride 9 mg/mL (0.9%) solution 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 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 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).
  - 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 1.
    - 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.