EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Xenpozyme

Date: December 2024

Unit: Technical Assessment Unit

Assessment report

Xenpozyme

Administrative information:

Trade name of the medicinal product:	Xenpozyme
INN (or common name) of the active substance(s):	Olipudase Alfa 20 mg
Manufacturer of the finished product	Genzyme Ireland Limited, IDA Industrial Park Old Kilmeaden Road, Waterford-Ireland.
Marketing Authorization holder	Sanofi BV.,Paasheuvelweg 25, 1105 BP Amsterdam, The Netherlands - The Netherlands
Applied Indication(s):	Xenpozyme is indicated as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in pediatric and adult patients with type A/B or type B.
Pharmaceutical form(s) and strength(s):	Powder for concentrate for solution for infusion Strength: 20 mg/vial
Route of administration	intravenous (IV) administration
Approved pack	Carton box contains one clear colourless glass (type I) vial (single dose) closed with siliconized gray chlorobutyl elastomer lyophilization stopper with an outer

	FluroTec and B2-04 coating, an aluminium seal with a plastic Flip-off cap made of homopolymer polypropylene and insert leaflet.

List of abbreviations:

EMA	European medicines Agency
CTD	Common Technical Document
AI	Active ingredient
EU	European union
WFI	Water for injection
ASMD	Acid sphingomyelinase deficiency
NPD	Niemann-Pick disease
ASMKO	Acid sphingomyelinase knock out
ASM	Acid sphingomyelinase
S1P	Sphingosine-1- phosphate
SPH	Sphingosine
SM	Sphingomyelin
QT	Section on an electrocardiogram report that represents the time it takes the heart muscle to contract and then recover.
QTc	Interval reflects ventricular repolarization, and its prolongation can lead to fatal ventricular arrhythmias
IL	Interleukin
G-CSF	Granulocyte-colony stimulating factor
KC	keratinocyte chemoattractant
TK	Toxicokinetics
QOW	every other week
NOAEL	No observable adverse effect level
ADA	Antidrug antibody
BMI	Body mass index
CNS	Central Nervous System
QoL	quality of life

Dossier initial submission and evaluation process:

- The product was submitted for registration via reliance level I.
- The dossier evaluation by the registration administration units was started on 4.9.2023 after providing all the required documents (EMA detailed unredacted assessment report along with Full CTD for the product)

1. **General introduction about the product including brief description of the AI, its mode of action and indications**:

-The olipudase alfa drug product is a sterile lyophilized powder for solution for intravenous infusion.
-It is supplied in an aseptically filled single-use vial with nominal strength of 20 mg/vial. Prior to lyophilization, the nominal fill volume was 5.0 mL. The composition of formulation excipients prior to lyophilization is the same as the drug substance.
-The drug product is reconstituted with nominal 5.1 mL sterile water for injection (WFI).
-The drug product is filled in a 20 mL USP-NF /Ph. Eur. Type 1 colorless clear glass vial closed with 20 mm siliconized gray chlorobutyl elastomeric stopper. The stoppered vials are crimped with an aluminum seal with a Flip-Off ® button.

2. **Quality aspects:**

- **Manufacturer(s):**

  - **Drug substance:**

Active substance is manufactured at Patheon Biologics LLC - USA

  - **Drug product:**

Finished product is manufactured at Genzyme Ireland Limited, Waterford-Ireland.

- **Stability**

-Based on available stability data,

  - **Drug substance:**

➢ **Approved Storage Conditions of the active substance:**
Store at 5 ± 3°C.
➢ **Approved shelf life for the active substance:**
24 weeks

- **Drug product:**

➢ **Approved Storage Conditions of the finished product:**

-**Unopened vials:** Store in a refrigerator (2°C - 8°C).

-Reconstituted 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 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).

➢ **Approved shelf life for the finished product:**

Unopened vials: 60 months

3. Non-clinical and clinical aspects:

- Acid sphingomyelinase deficiency (ASMD), also named Niemann-Pick disease (NPD), occurs due to a genetic mutation in Asm gene. The disease is known to generate a spectrum of phenotypes, which have been classified as type A, type B, and type A/B.In ASMD, there is a lack of a functioning enzyme, acid sphingomyelinase, which is found in lysosomes and

is needed to break down certain fats, resulting in build-up of fats and changing the way cells work and causing them to die, affecting normal functioning of tissues and organs, including the liver, spleen, lungs, heart and brain.
- Acid sphingomyelinase deficiency (ASMD), type A is characterized as the early-onset and acute neuronopathic form of NPD and results in failure to thrive, hepatosplenomegaly, rapidly progressive neurological degeneration, and death usually before the age of 3 years.
-Type B is a much milder disease with no or little neurological involvement. One of the more common disease manifestations are hepatosplenomegaly and dyslipidemia, other more variable features include liver dysfunction, pulmonary disease, skeletal involvement, retinal stigmata, and growth retardation. Type B ASMD is usually diagnosed in childhood after organomegaly is observed, typically after the age of 2 years. The majority of patients diagnosed with Type B disease live into adulthood.
-As an autosomal recessive single-gene disease, ASMD generates a spectrum of phenotypes and cases have been classified that are intermediate between the A and B extremes. Patients with this intermediate form may develop neurologic symptoms during childhood and have a chronic neurodegenerative disease course.
- The active substance in Xenpozyme, olipudase alfa, is a recombinant human acid sphingomyelinase expressed in Chinese hamster ovary cells. It is expected to replace the patients' deficient enzyme and thereby reduce the build-up of fats within lysosomes and relieve some of the symptoms of the disease. It is not, however, expected to treat the central nervous system manifestations of the disease as the medicine is unable to cross the blood-brain barrier.

Non- clinical aspect:

pharmacology

-The applicant made use of a disease model for NPD, ASMKO mice. In this mouse model, the ASM enzyme is removed. In this model, characteristic foam cells were mainly observed in bone marrow and spleen. These animals show a significant neurological phenotype that resembles neuropathic ASMD. ASMKO mice also do not display the organomegaly that is characteristic of ASMD. Despite the phenotypic differences in these mice, this model is suitable to show proof of concept for the clinical use of olipudase alfa in NPD type B.
The applicant presented data on the activity of the enzyme at different pH. The enzyme is most active in the late endosome.
-In vivo, dose-dependent decreases of SM were observed in ASMKO mice treated with 1, 3 or 5 mg/kg olipudase.

- A single administration of olipudase alfa at 20 mg/kg results in a rapid increase in ceramide, sphingosine and sphingosine-1-phosphate in the serum of ASMKO mice. There appear to be two distinct phases to the generation of ceramide characterized by an early, rapid rise (2-45 min) followed by a second rise at 240 and 540 minutes post dose. SPH and S1P were significantly elevated at 240 minutes post dose and remained elevated at 540 minutes post dose. Sphingosine-1-phosphate levels returned to baseline at 540 minutes post dose.
- The 2 phases of degradation products may indicate separate SM breakdown events due to different sources of SM. The initial production of ceramide in ASMKO mice (5-45 min. post dose) is likely the result of olipudase alfa mediated hydrolysis of sphingomyelin that is not present in lysosomes, but rather in an "easy to access" pool. It is unknown where this pool may reside but may include sphingomyelin found in the outer leaflet of the plasma membrane or blood lipid particles. The early high peak of ceramide, following SM degradation by olipudase alfa in ASMKO mice, was apparently not observed in ASM patients. This is reassuring for the safety. The second and later peak of ceramide likely reflects SM degradation in the endolysosomal compartment.
- After a debulking regimen with olipudase (3 mg/kg QOD for four times), all ASMKO mice survived the final 20 mg/kg olipudase dose. The debulking regimen eliminated the toxic response to olipudase, and elevations of ceramide, SPH, and S1P seen with high doses of olipudase. In addition, plasma ceramide, SPH, and S1P levels were significantly lower than those seen in historical controls up to 540 minutes. The increased levels of ceramide (C16) observed after a single dose of 20 mg/kg olipudase to ASMKO mice that are correlated with increased lethality and poor clinical outcome are not observed in C57BL/6 mice and can be eliminated by applying a debulking regimen.

In ASMKO mice, high doses of olipudase result in bradycardia accompanied by a statistically significant QT prolongation. Also, QTc was significantly increased 5,6,7, and 8 hours after administration of 20 mg/kg olipudase alfa. This is possibly linked to the toxic effects of a single high dose of olipudase alfa. Patients will not receive such a high dose. In addition, no QTc prolongation has been observed in the clinical study.

When olipudase alfa was administered to monkeys, mice, and dogs, no toxicity was observed up to a dose of 30 mg/kg.

N.B. High doses of olipudase alfa ≥ 10 mg/kg administered to ASMKO mice resulted in unexpected toxicity characterized by cardiovascular shock, hepatic inflammation, adrenal hemorrhage, elevations in ceramide and cytokines (especially IL-6, G-CSF, and keratinocyte chemoattractant [KC]), and death. These toxicities are related to the sudden massive degradation of SM in the disease model, which does not occur in the wild-type animals as there is no SM accumulated.

- **Pharmacokinetics:**

-The non-clinical kinetics of olipudase alfa were investigated in the non-clinical species CD-1, C57BL/6, and acid sphingomyelinase knock-out (ASMKO) mice, Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs and Cynomolgus monkeys. 3 lots evaluated in ASMKO mice. While the reason for the observed differences in PK parameters between lots is unknown, it is important to note that these differences did not affect the pharmacodynamics of olipudase alfa. Depletion of sphingomyelin in target organs, such as the liver and spleen, were similar between these olipudase alfa lots in the ASMKO mice, suggesting that, the differences in olipudase alfa clearance and exposure do not affect efficacy.

- **Toxicology:**

-Overall, single administration of olipudase alfa was well tolerated in all species evaluated (doses up to 75 mg/kg) with the exception of the ASMKO mouse where acute toxicity was observed at single doses ≥10 mg/kg. The dose-related toxicity observed in ASMKO mice was likely due to the rate and amount of substrate degradation.
-Similarly, repeated administration of olipudase every other week for 26 weeks to healthy rats and monkeys did not result in adverse effects at the highest tested dose of 30 mg/kg. Moreover, in the disease model ASMKO mice, no significant adverse effects were seen following administration of 3 mg/kg olipudase every other week for 13 weeks (7 total doses).
Administration of the low debulking doses of 3 mg/kg could prevent the toxicity of the high doses (up to 30 mg/kg) of olipudase in this animal model. The olipudase administration decreased the number of foamy macrophages and the degree of cytoplasmic vacuolization in multiple organs and tissues of the ASMKO mice, consistent with sphingomyelin elimination; However, the process of accumulation resumed following the recovery period.
*Therefore, the results demonstrate that the toxicity of high doses of olipudase alfa can be ameliorated by controlled sphingomyelin degradation through dose escalation.
-Olipudase did not cause adverse effects on fertility, embryo-foetal and postnatal development in healthy animals when administered up to the highest dose of 30 mg/kg. It is however noted that clinical signs of toxicity (mortality in mice, reduced body weight and body weight gain in rabbits) were seen in both species at the low dose level of 3 mg/kg/dose, which appears to correlate with the highest incidence and/or titers of antidrug antibodies observed at this level.
-The result from TK analysis in single dose toxicity showed that in rats and dogs were linear with dose (3 to 30 mg/kg) as evaluated by the normalization of the exposure to the dose administered. Moreover, in repeated administration every other week (QOW) to animals

showed no accumulation, less than dose proportional increase in exposure over the dose range studied in toxicology studies. There was no consistent trend for sex differences in exposure, and a decrease in exposure with ADA was also observed.
** Based on above result the NOAEL will be considered 30 mg/kg which corresponding to the 10-fold MRHD. Additionally, the exposure ratios in the chronic toxicity studies in rats and monkeys (serum exposure at NOAEL in rats and monkeys / 3 mg/kg biweekly dose in adult ASMD patients) are 2.3 and 3.9-fold, respectively

Clinical aspect:

Clinical Pharmacology (PK & PD)

- The key biomarkers (chitotriosidase, CCL18, plasma lyso-sphingomyelin, plasma ceramide, ACE, and liver sphingomyelin) showed reductions for BL to week 52 in both adult and paediatric patients.
In general, it is observed that under olipudase alfa treatment up to week 26 marked reductions for these parameters are observed, thereafter reductions seem to plateau and remain at these low levels up to week 52 and beyond (data available up to week 232 for some adults). As expected from the MoA all PD parameters point in the same direction, suggestive for improvement. In addition, liver histopathology samples confirm that under olipudase alfa treatment, debulking of sphingomyelin occurs, confirming the MoA. Notably, consistent with the observations on these biomarkers, reductions in spleen volume (which is one of the two primary endpoints) and liver volume were observed in both the adults (pivotal study DFI12712) and paediatrics (Study DFI13803).
- Overall conclusion regarding pharmacokinetics: The proposed posology in patients with a BMI >30 kg/m2 is sufficiently substantiated. Further, **no studies have been carried out in patients with renal or hepatic impaired function, but the disposition of olipudase alfa is not expected to be impacted by renal or hepatic impairment**.
In addition, population pharmacokinetic analysis did not show a difference in olipudase alfa exposure due to renal or hepatic impairment (liver cirrhosis).

Clinical Efficacy :

-It is considered demonstrated that under continued olipudase alfa treatment, spleen and liver volume are reduced. These reductions are clinically meaningful. It is also considered demonstrated that DLco improves or stabilises under continued treatment. The observed improvements of DLco are also considered clinically relevant.

- Results in adults and paediatrics are comparable, and the extrapolation of adult data to paediatrics is sufficiently substantiated and justified. In addition to the observed improvements in organomegaly, improvements in pharmacodynamic parameters, other lung function parameters, improvement of dyspnoea and improvement in QoL were noted.
-The indication in type A/B and B ASMD patients is acceptable. As the youngest patients were diagnosed around birth and some patients treated in the first months of life, no age restriction has to be included in the indication.

- **Clinical Safety:**

-As it was a rare disease, the previous studies were conducted on low number of patients which is acceptable.Based on the evaluations during the clinical trials, the immunogenicity profile of olipudase alfa has been adequately characterized and the development of ADA does not pose a clinical risk in the majority of patients. Based on the clinical data no impact of ADAs was observed, from a safety perspective ADA's did not have an influence on the observed TEAEs.

*** The overall benefit/risk balance of Xenpozyme is favourable as an enzyme replacement therapy for the treatment of non-Central Nervous System (CNS) manifestations of Acid Sphingomyelinase Deficiency (ASMD) in pediatric and adult patients with type A/B or type B.*

For more information, please visit EMA published assessment report link:

https://www.ema.europa.eu/en/documents/assessment-report/xenpozyme-epar-public-assessment-report_en.pdf