swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Xenpozyme

International non-proprietary name: olipudase alfa
Pharmaceutical form: powder for concentrate for solution for infusion
Dosage strength(s): 4 mg, 20 mg
Route(s) of administration: intravenous use
Marketing authorisation holder: Sanofi-Aventis (Suisse) SA
Marketing authorisation no.: 67287
Decision and decision date: approved on 19.12.2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for olipudase alfa in the above-mentioned medicinal product.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 1 of the TPA. Orphan drug status was granted on 28 January 2019.

2.2 Indication and dosage

2.2.1 Requested indication

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.

2.2.2 Approved indication

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

2.2.3 Requested dosage

Summary of the requested standard dosage:
The Xenpozyme dose is based on actual body weight for patients with a body mass index (BMI) ≤ 30 or adjusted body weight for patients with a BMI > 30. The recommended starting dose of Xenpozyme is 0.1 mg/kg every 2 weeks for adults and 0.03 mg/kg every 2 weeks for paediatric patients. The dose should be subsequently increased according to the dose escalation regimens until the maintenance dose is reached. The recommended maintenance dose is 3 mg/kg of actual or adjusted body weight every 2 weeks for adult and paediatric patients.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	3 April 2023
Formal control completed	4 April 2023
List of Questions (LoQ)	13 June 2023
Response to LoQ	4 September 2023
Preliminary decision	20 October 2023
Response to preliminary decision	30 November 2023
Final decision	19 December 2023
Decision	approval

3 Medical context

Acid sphingomyelinase deficiency (ASMD) is a rare autosomal recessive lysosomal storage disease. It is due to deficiency of the lysosomal enzyme acid sphingomyelinase (ASM) caused by mutations of both alleles of the sphingomyelin phosphodiesterase 1 gene (SMPD1), encoding ASM. Transmission is therefore autosomal-recessive. There is a large number of known specific mutations with various impacts on enzyme dysfunction; therefore the spectrum and severity of the disease can be variable. The disease is very rare and estimated to have an incidence at birth of approx. 0.4 to 0.6 per 100,000 births.

ASMD type A (also called infantile neurovisceral ASMD) has its onset during infancy with severe multiorgan manifestations and neurodegeneration, rapid progression, and is uniformly fatal in early childhood, typically by 3 years of age. Most patients have massive hepatosplenomegaly, an atherogenic lipid profile, interstitial lung disease with progressive impairment of pulmonary function, and haematologic abnormalities, including reduced platelet counts. ASMD type B (also called chronic visceral ASMD) has a later onset and a variable progression rate and prognosis. Patients may live into later adulthood but may be burdened in principle with the same morbidities, except that they usually have little or no CNS involvement. ASMD type A/B is an intermediate type of the above, although the presentation is a continuum.

Current standard treatment options target the above manifestations of the disease. There is no disease-specific causative or disease-modifying treatment available for ASMD.

4 Quality aspects

4.1 Drug substance

Olipudase alfa (Xenpozyme®) is a recombinant human acid sphingomyelinase with a molecular weight of approximately 76 kDa. Olipudase alfa is expressed in a genetically modified Chinese hamster ovary (CHO) cell line. Olipudase alfa is manufactured using a perfusion production process in a bioreactor. The cell broth is harvested and olipudase alfa is subsequently purified in several chromatographic steps. The purification process also includes dedicated viral inactivation and clearance steps. After purification, the product is formulated in an aqueous buffered solution at pH 6.5, containing sodium phosphate, sucrose, and methionine. All excipients comply with the European Pharmacopoeia.
The process validation demonstrated a consistent manufacturing process that effectively reduces process-related impurities. The characterisation of the physicochemical and biological properties of the drug substance and its impurities was performed using state-of-the-art methods.
The specifications for release include relevant tests and limits, e.g. for identity, purity and impurities, quantity, safety, and potency. Batch analysis data of development, clinical, and process validation batches were provided. All batch release data comply with the drug substance specifications valid at the time of batch release. All the analytical methods are described and non-compendial methods were validated in accordance with ICH guidelines.
No significant changes were observed during storage of olipudase alfa drug substance under the proposed storage conditions.

4.2 Drug product

The finished product is a sterile lyophilised powder for intravenous infusion upon reconstitution with sterile water for injection and further dilution in 0.9% saline. The finished product is supplied in an aseptically filled single-use vial with a nominal strength of 20 mg/vial or 4 mg/vial.
The manufacture of olipudase alfa finished product consists of sterile filtration, aseptic filling/stoppering, lyophilisation, sealing, inspection, and labeling steps. Process validation studies were executed at commercial scale using 4x 20 mg/vial and 3x 4 mg/vial validation batches. The drug product specifications comply with current compendial or regulatory guidelines and include relevant tests and limits, e.g. for identity, purity, impurities, quantity, potency, safety, and general compendial tests. All analytical methods are validated. Batch analysis data for several batches from the commercial site are provided. All batch release data comply with the drug product specifications valid at the time of batch release.
The container closure system of the finished product consists of a Type I colourless glass vial with a chlorobutyl rubber stopper and an aluminium crimping cap. All components coming into contact with the finished product comply with Ph. Eur. requirements.
The drug product is stored at 2-8°C. The stability data support a shelf life of 60 months.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated. Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

5 Nonclinical aspects

Regarding the marketing authorisation application for Xenpozyme, the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the EMA assessment report (dated 19.05.2022) provided by the applicant.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Xenpozyme in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

There is no safety concern regarding impurities and excipients.

Based on the ERA, olipudase alfa does not represent a risk for the environment.

6 Clinical aspects

The evaluation of the clinical data of this application has been carried out in reliance on previous regulatory decisions by the EMA and FDA. The available assessment reports and respective product information texts from these authorities were used as a basis for the clinical evaluation.

For further details concerning clinical pharmacology, dosing recommendations, efficacy, and safety, see section 8 Appendix of this report.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Xenpozyme was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.