Summary of the Risk Management Plan (RMP) for XENPOZYME®

XENPOZYME® (OLIPUDASE ALFA)
Marketing Autorisation Holder : sanofi-aventis (suisse) sa
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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them. The RMP summary of XENPOZYME® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le medicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of XENPOZYME® in Switzerland is the "Arzneimittelinformation/ Information sur le medicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Sanofi-aventis (suisse) sa is fully responsible for the accuracy and correctness of the content of this published summary RMP of XENPOZYME®.

1. THE MEDICINE AND WHAT IT IS USED FOR

According to Swiss label

Xenpozyme is indicated as 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.

According to EU-SmPC

XENPOZYME is 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. It contains olipudase alfa as the active substance, a recombinant human acid sphingomyelinase produced in a Chinese hamster ovary (CHO) cell line by recombinant deoxyribonucleic acid (DNA) technology. XENPOZYME is given by intravenous (IV) infusion.

Further information about the evaluation of XENPOZYME's benefits can be found in XENPOZYME's EPAR, including in its plain-language summary, available on the European medicines agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/xenpozyme

2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of XENPOZYME, together with measures to minimize such risks and the studies for learning more about XENPOZYME's risks are outlined in the next sections.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals respectively;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of XENPOZYME, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections.

In addition to these measures, information about adverse reactions will be collected continuously and regularly analyzed, including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of XENPOZYME is not yet available, it is

listed under “missing information” outlined in the next section.

2.1. List of important risks and missing information

Important risks of XENPOZYME are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of XENPOZYME. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 1 - List of important risks and missing information

Important identified risk	Immunogenicity: • Infusion associated reactions (IARs), • Systemic hypersensitivity including anaphylactic reactions, • Anti-drug antibody (ADA) mediated hypersensitivity reactions
Important potential risks	Medication errors in home infusion setting Foetal toxicity
Missing information	Use in lactating women Long-term safety (beyond 2 years)

ADA: Anti-Drug Antibody; IAR: Infusion Associated Reaction.

2.2. Summary of important risks

Table 2 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Immunogenicity: Infusion associated reactions (IAR), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions

Immunogenicity: Infusion associated reactions (IAR), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions	
Evidence for linking the risk to the medicine	Clinical trial experience, class effects, scientific literature, other (eIND).
Risk factors and risk groups	Systemic hypersensitivity and IARs: • Patients with previous hypersensitivity/allergy to olipudase alfa and its excipients. • Available clinical data suggest children may have greater predisposition, compared to adults. Additional risk characterization has not been fully established. Anti-drug antibody mediated hypersensitivity reactions: The immunologic response to olipudase alfa in adult versus pediatric ASMD patients was relatively similar. Adults had a median ADA peak titer of 50 (range 50-3200) compared to pediatric patients with a median ADA peak titer of 200 (range 50-1600).

Immunogenicity: Infusion associated reactions (IAR), systemic hypersensitivity including anaphylactic reactions, Anti-Drug Antibody (ADA) mediated hypersensitivity reactions	
Risk minimization measures	**Routine risk minimization measures:** • Sections 4.2, 4.3, 4.4 and 4.8 of the SmPC. • Sections 2, 3 and 4 of the PL. • Legal Status: Restricted medical prescription. **Additional risk minimization measures:** • A HCP Guide for HCPs in home infusion setting including nurses. • A Patient Card for patients/caregivers.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Study LTS13632 • Study DFI12712 (ASCEND) See Section 2.3 of this summary for an overview of the post-authorization development plan.

ADA: Anti-Drug Antibody; ASMD: Acid Sphingomyelinase Deficiency; eIND: Emergency Investigational New Drug; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 3 - Important potential risk with corresponding risk minimization activities and additional pharmacovigilance activities: Medication errors in home infusion setting

Medication errors in home infusion setting	
Evidence for linking the risk to the medicine	Potential medication error is listed as an important potential risk in the RMP of other marketed ERTs for which home infusion setting is possible. Clinical trial experience: No medication errors have been identified by the time of data cutoff (15-Mar-2021).
Risk factors and risk groups	Patients receiving medication in home infusion setting.
Risk minimization measures	**Routine risk minimization measures:** Legal Status: Restricted medical prescription. **Additional risk minimization measures:** A HCP guide for HCPs in home infusion setting including nurses.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Study LTS13632 Study DFI12712 (ASCEND) See Section 2.3 of this summary for an overview of the post-authorization development plan.

ERT: Enzyme Replacement Therapy; HCP: Healthcare Professional; RMP: Risk Management Plan.

Table 4 - Important potential risk with corresponding risk minimization activities: Foetal toxicity

Foetal toxicity	
Evidence for linking the risk to the medicine	Non-clinical data
Risk factors and risk groups	Pregnant women and WOCBP.
Risk minimization measures	**Routine risk minimization measures:** • Sections 4.6 and 5.3 of the SmPC. • Section 2 of the PL. • Legal status: Restricted medical prescription. **Additional risk minimization measures:** A Patient Card for patients/caregivers.

PL: Package Leaflet; SmPC: Summary of Product Characteristics; WOCBP: Women of Childbearing Potential.

Table 5 - Missing information with corresponding risk minimization activities: Use in lactating women

Use in lactating women	
Risk minimization measures	**Routine risk minimization measures:** • Sections 4.6 and 5.3 of the SmPC. • Section 2 of the PL. • Legal status: Restricted medical prescription. **Additional risk minimization measures:** None

PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 6 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Long-term safety (beyond 2 years)

Long-term safety (beyond 2 years)	
Risk minimization measures	**Routine risk minimization measures:** • Section 4.8 of the SmPC. • Legal status: Restricted medical prescription. **Additional risk minimization measures:** None

Long-term safety (beyond 2 years)	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Study LTS13632 • Study DFI12712 (ASCEND)

SmPC: Summary of Product Characteristics.

2.3. Post-authorization development plan

2.3.1. Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of XENPOZYME.

2.3.2. Other studies in post-authorization development plan

Table 7 - Other studies in post-authorization development plan

LTS13632 - A long-term clinical trial (Cat. 3)

Purpose of the study:

To obtain data regarding the safety and efficacy of olipudase alfa in patients with ASMD who are exposed to long-term treatment with olipudase alfa.

Primary objective:

To assess the long-term safety of olipudase alfa in patients with ASMD.

Secondary objective:

To assess the maintenance of effect of olipudase alfa and to characterize the PDs and PKs following long-term administration.

DFI12712 ASCEND Adults Phase 2/3 clinical trial (Cat. 3)

Purpose of the study:

To evaluate the efficacy, safety, PDs and PKs of olipudase alfa in adult patients with ASMD.

Primary objectives:

To evaluate the efficacy of olipudase alfa (recombinant human acid sphingomyelinase) administered intravenously once every 2 weeks for 52 weeks in adult patients with ASMD by assessing changes in:

- Spleen volume as measured by abdominal MRI.
- Infiltrative lung disease as measured by the pulmonary function test, diffusing capacity of the lung for carbon monoxide.

Secondary objectives:

- To confirm the safety of olipudase alfa administered intravenously once every 2 weeks for 52 weeks.
- To characterize the effect of olipudase alfa on the patient perception related to spleen volume as measured by SRS

after 52 weeks of study drug administration.

- To characterize the effect of olipudase alfa on the following endpoints assessed sequentially:
  - The effect of olipudase alfa on liver volume after 52 weeks of study drug administration
  - The effect of olipudase alfa on platelet count after 52 weeks of study drug administration
  - The effect of olipudase alfa after 52 weeks of study drugs administration on fatigue
  - The effect of olipudase alfa after 52 weeks of study drug administration on pain
  - The effect of olipudase alfa after 52 weeks of study drug administration on dyspnea

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ASMD: Acid Sphingomyelinase Deficiency; MRI: Magnetic Resonance Imaging; PD: Pharmacodynamic; PK: Pharmacokinetic; SRS: Splenomegaly Related Score.