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

NEXVIADYME® (avalglucosidase alfa)
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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. This RMP summary 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 the product 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 RMP summary.

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ABBREVIATIONS

6MWT: 6-Minute Walk Test
ADA: Anti-Drug Antibody
AE: Adverse Event
AESI: Adverse Event of Special Interest
AIMS: Alberta Infant Motor Scale
CRIM: Cross-Reactive Immunologic Material
DLP: Data Lock Point
EMA: European Medicines Agency
EPAR: European Public Assessment Report
ERT: Enzyme Replacement Therapy
ETP: Extended Treatment Period
FVC: Forced Vital Capacity
HCP: Healthcare Professional
Hex4: Hexose Tetrasaccharide
HHD: Hand-Held Dynamometry
HSAT: High and Sustained Antibody Titer
IAR: Infusion Associated Reaction
IgE: Immunoglobulin E
IgG: Immunoglobulin G
INN: International Nonproprietary Name
IOPD: Infantile-Onset Pompe Disease
LOPD: Late-Onset Pompe Disease
LVM-Z: Left Ventricular Mass-Z
MAH: Marketing Authorization Holder
MEP: Maximal Expiratory Pressure
MIP: Maximal Inspiratory Pressure
Nab: Neutralizing Antibody
PAP: Primary Analysis Period
PK: Pharmacokinetic
PL: Package Leaflet
PSUR: Periodic Safety Update Report
QMFT: Quick Motor Function Test
RMP: Risk Management Plan
SF-12: 12-Item Short Form Health Survey
SmPC: Summary of Product Characteristics

1. THE MEDICINE AND WHAT IT IS USED FOR

According to Swiss label

Nexviadyme (avalglucosidase alfa) is indicated for long-term enzyme replacement therapy for the treatment of patients with late-onset Pompe disease (acid α-glucosidase deficiency) (LOPD).

According to EU SmPC

NEXVIADYME is indicated for long-term enzyme replacement therapy for the treatment of patients with Pompe disease (acid α-glucosidase deficiency).

It contains avalglucosidase alfa as the active substance and it is given by intravenous infusion.

Further information about the evaluation of NEXVIADYME's benefits can be found in NEXVIADYME'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/nexviadyme

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

Important risks of NEXVIADYME, together with measures to minimize such risks and the proposed studies for learning more about NEXVIADYME'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 PL and SmPC addressed to patients and HCPs;
- 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 addition to these measures, information about adverse reactions is 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 NEXVIADYME 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 NEXVIADYME 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 NEXVIADYME. 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	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
Important potential risks	Immunogenicity leading to loss of response (High sustained IgG antibody titers and/or neutralizing antibodies)
	Medication error in home infusion setting
	Immune complex related reactions

Missing information	Use in pregnant and lactating women
	Use in patients with renal or hepatic insufficiency

IgE: Immunoglobulin E; IgG: Immunoglobulin G.

2.2. SUMMARY OF IMPORTANT RISKS

Table 2 – Important identified risk: "Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies" with corresponding risk minimization activities and additional pharmacovigilance activities

Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies	
Evidence for linking the risk to the medicine	To date, the clinical development program for avalglucosidase alfa includes the completed Phase 1/2 open-label, dose-escalation study (TDR12857), completed on 28-Jul-2015, an ongoing long-term safety, PK and exploratory efficacy extension study (LTS13769), a Phase 3 randomized, double-blinded efficacy and safety study (EFC14028) and a phase 2 open-label, ascending dose cohort, safety, PK and preliminary efficacy study (ACT14132). The PAP for EFC14028 and ACT14132 studies is completed. The ETP for these two studies are ongoing. Infusion associated reactions were observed in all 4 clinical studies. Anaphylaxis, a severe potentially fatal systemic allergic reaction that occurs suddenly after contact with an allergen was observed in 2 (1.4%) patients in the avalglucosidase alfa program. As described, the level of data and evidence is sufficient to demonstrate that avalglucosidase alfa can be associated with "IARs including hypersensitivity and anaphylactic reactions". This is a known risk associated with ERTs. The safety profile of avalglucosidase alfa is consistent with that of alglucosidase and possibly more favorable in the treatment of adult and pediatric patients with Pompe disease (LOPD and IOPD). IARs including hypersensitivity have been reported in avalglucosidase clinical trials. It was deemed that the data was sufficient to include as an identified risk. Considering the possible impact of this event on the benefit-risk balance, and the fact that this risk is planned to be mitigated notably through the labeling, the MAH has proposed to include it as an important identified risk in list of safety concerns.
Risk factors and risk groups	Pompe disease is classified into different phenotypes based on age at onset of symptoms, extent of organ involvement, and rate of progression to death. These phenotypes range from a rapidly progressive infantile-onset form to a more slowly progressive late-onset form, with considerable variability and overlap between these 2 extremes. Infantile-onset Pompe disease presents in the first months of life and is characterized by severe cardiomyopathy, hypotonia, respiratory failure, and without

Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies	
	treatment, leads to death within the first year. Patients with advanced Pompe disease or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their undergoing co-morbidity during infusions. In the EFC14028 study, the frequency of IARs and hypersensitivity in patients increased with higher ADA titers (≥12 800). Additionally, IgE ADA positive patients are at increased risk of developing anaphylactic reactions upon re-administering the drug.
Risk minimization measures	**Routine risk minimization measures** Labeled in sections 4.4 and 4.8 of SmPC. Labelled in section 2 of PL. Instructions for treatment administration, pretreatment, decision criteria to have a patient move to home infusion and instructions in case of adverse reactions are included in SmPC section 4.2. Instructions to mitigate the infusion associated reactions are included in SmPC section 4.4. How to detect signs and symptoms, the need to seek for immediate medical attention is labelled in PL section 4. Prescription only medicine. **Additional risk minimization measures** Educational materials (HCP guide for Immunosurveillance service and Home infusion guide).
Additional pharmacovigilance activities	Post-Authorization safety study Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET) and EFC14462.

ADA: Anti-Drug Antibody; ERT: Enzyme Replacement Therapy; ETP: Extended Treatment Period; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; IgE: Immunoglobulin; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; MAH: Marketing Authorization Holder; PAP: Primary Analysis Period; PK: Pharmacokinetic; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 3 – Important potential risk: "Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)" with corresponding risk minimization activities and additional pharmacovigilance activities

Immunogenicity leading to loss of response (High Sustained IgG Antibody Titers and/or neutralizing antibodies)	
Evidence for linking the risk to the medicine	To date, the clinical development program for avalglucosidase alfa includes the completed Phase 1/2 open label, dose escalation study (TDR12857), completed on 28-Jul-2015, an ongoing long-term safety, PK and exploratory efficacy extension study (LTS13769), a Phase 3 randomized, double blinded efficacy and safety study (EFC14028) and a phase 2 open-label, ascending dose cohort, safety, PK and preliminary efficacy study (ACT14132). The PAP for EFC14028 and ACT14132 studies is completed. The ETP for these two studies is ongoing. A small number of patients developed ADA peak titers ≥51 200 in the avalglucosidase alfa studies. Of the 61 treatment-naïve patients, there were 4 patients (3 in EFC14028 and 1 in TDR12857/ LTS13769) with ADA titers ≥51 200.
Risk factors and risk groups	The presence or absence of endogenous enzyme, reported as CRIM status, is a known risk factor. For patients with IOPD, the major risk group is CRIM-negative patients who do not produce any endogenous enzyme. If not given prophylactic immune tolerance induction, these patients develop high and sustained ADA titers, as well as NAb when treated with alglucosidase alfa, which contribute to poor clinical outcomes. A retrospective analysis by a lead Investigator of 32 IOPD patients receiving alglucosidase alfa showed median titers in CRIM-negative patients of 51 200 at 24 weeks and 153 600 at 52 weeks whereas median titers in CRIM-positive patients were 600 at 24 weeks and 200 at 52 weeks. Patients with LOPD produce low levels of endogenous enzyme and are considered CRIM-positive. These patients are generally not at risk for developing HSAT and very few make high ADA titers which then decrease over time. The effects of antibody development on the long-term safety and efficacy of avalglucosidase alfa continue under investigation in longer term studies.
Risk minimization measures	**Routine risk minimization measures** Labeled in sections 4.4 and 4.8 of SmPC. Recommendations and description of the testing to be considered for immunogenicity monitoring are labeled in Section 4.4 of SmPC. Prescription only medicine. **Additional risk minimization measures** Educational materials (HCP guide for Immunosurveillance service).
Additional pharmacovigilance activities	Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET) and EFC14462.

ADA: Anti-Drug Antibody; CRIM: Cross-Reactive Immunologic Material; ETP: Extended Treatment Period; HCP: Healthcare Professional;

HSAT: High and Sustained Antibody Titer; IgE: Immunoglobulin; IOPD: Infantile-Onset Pompe Disease; LOPD: Late-Onset Pompe Disease; Nab: Neutralizing Antibody; PAP: Primary Analysis Period; PK: Pharmacokinetic; SmPC: Summary of Product Characteristics.

Table 4 – Important potential risk: "Medication error in home infusion setting" with corresponding risk minimization activities and additional pharmacovigilance activities

Medication error in home infusion setting	
Evidence for linking the risk to the medicine	It is expected and understood that the HCP administering avalglucosidase alfa in the home setting are experienced in the management of the Pompe disease, as well as in the management of other ERTs. As of 31-May-2021, 15 patients have ever received home infusion in trials (LTS13769 [N = 2], EFC14028 [N = 11] and ACT14132 [N = 2]). Safety events occurred in 4 patients. One EFC14028 patient receiving avalglucosidase alfa in the home setting experienced an IAR. A 32-year-old female patient who began treatment with avalglucosidase alfa in Mar-2019, started to receive home infusions in Apr-2020 (first home infusion given at week 59 in the open-label period). During the first home infusion and two hours after infusion start, the patient had eyelid edema and flushing. Both events were assessed as a non-serious AESI and IAR of mild intensity. Therapy with avalglucosidase alfa was interrupted and the patient received methylprednisolone and dexchlorpheniramine as corrective treatments. The patient recovered from both events the same day. After this dose interruption the patient returned to the study site to receive infusions and was monitored for any recurring IARs before resuming home infusions again with no recurrence of IARs. Six unrelated non-serious AEs in 2 other patients in EFC14028 and 1 unrelated non-serious AE in 1 patient in LTS13769 were reported). No medication error occurred in the setting of home infusion. In the "Home infusion report" provided by the EMC expert center, where MYOZYME is routinely administered in home setting as standard practice, the data confirmed that few IARs were identified associated with the administration of MYOZYME, similarly to the hospital set-up. No severe IARs were reported in the home setting, the majority of IARs were mild in intensity and did not necessitate advanced clinical intervention. However, as for other ERTs for which the home infusion is possible, there is a possible risk of medication errors in the home infusion setting, linked to Insufficient understanding of the instructions for use of the product (eg, dose calculation, reconstitution, administration). Considering these facts, the MAH proposes to include "Medication errors in the home infusion setting" as an important potential risk in the RMP.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures** Labeled in sections 4.2 and 6.6 of SmPC. Labeled in sections 3 and 5 of PL. Decision criteria to have a patient move to home are included in SmPC section 4.2, as well as the description of home infusion infrastructure, resources, and procedures. The precautions for disposal, instructions for reconstitution and dilution as well as the description of infusion preparation and administration are included in SmPC section 6.6. Prescription only medicine. **Additional risk minimization measures**

Medication error in home infusion setting	
	Educational materials (Home infusion guide).
Additional pharmacovigilance activities	Post-authorization safety study Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET) and EFC14462.

AE: Adverse Event; AESI: Adverse Event of Special Interest; ERT: Enzyme Replacement Therapy; IAR: Infusion Associated Reaction; HCP: Healthcare Professional; MAH: Marketing Authorization Holder; PL: Package Leaflet; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

Table 5 – Important potential risk: "Immune complex related reactions" with corresponding risk minimization activities and additional pharmacovigilance activities

Immune complex related reactions	
Evidence for linking the risk to the medicine	Evidence of immune complexes was not observed in any tissue or organ in mice or monkeys. As for other ERTs, due to the biological mechanism of immune complex mediated reactions, this risk cannot be totally ruled out. Neither cases of potential immune-mediated reactions were identified in patients during the clinical studies, nor cases contained events consistent with immune mediated reactions. Considering this lack of cases and the biological plausibility, the MAH has proposed to include "Immune complex related reactions" as an important potential risk in the RMP.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures** Not applicable Prescription only medicine. **Additional risk minimization measures** None
Additional pharmacovigilance activities	Studies LTS13769, EFC14028 (COMET), ACT14132 (mini-COMET) and EFC14462.

ERT: Enzyme Replacement Therapy; MAH: Marketing Authorization Holder; RMP: Risk Management Plan.

Table 6 – Missing information: "Use in pregnant and lactating women" with corresponding risk minimization activities

Missing information: Use in pregnant or lactating women	
Risk minimization measures	**Routine risk minimization measures** Labeled in section 4.6 of SmPC. Prescription only medicine. **Additional risk minimization measure** None
Additional pharmacovigilance activities	AGLU03506 (Pompe Disease Pregnancy Sub-registry).

SmPC: Summary of Product Characteristics.

Table 7 – Missing information: "Use in patients with renal or hepatic insufficiency" with corresponding risk minimization activities

Missing information: Use in patients with renal or hepatic insufficiency	
Risk minimization measures	**Routine risk minimization measures** Labeled in sections 4.2 and 5.2 of SmPC. Prescription only medicine. **Additional risk minimization measure** None
Additional pharmacovigilance activities	DIREGC07005 (Pompe Disease Registry).

SmPC: Summary of Product Characteristics.

2.3. POST-AUTHORISATION DEVELOPMENT PLAN

2.3.1. Studies which are conditions of the marketing authorisation

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

2.3.2. Other studies in post-authorisation development plan

Table 8 - Other studies in post-authorization development plan

LTS13769 (Category 3)
Purpose of the study: Evaluate long-term safety (including infusion associated reactions and immunogenicity) and PK of repeated biweekly infusions of avalglucosidase alfa.
EFC14028 (COMET) (Category 3)
Purpose of the study: Primary objective is to determine the effect of avalglucosidase alfa treatment on respiratory muscle strength as measured by FVC% predicted in the upright position, as compared to alglucosidase alfa.
Secondary objectives are to determine the safety (including infusion associated reactions and immunogenicity) and effect ofavalglucosidase alfa treatment on functional endurance (6MWT), inspiratory muscle strength (MIP), expiratory muscle strength (MEP), lower extremity muscle strength (HHD), motor function (QMFT), and health-related quality of life (SF-12). The main purpose of this ongoing long-term ETP is to provide long-term safety up to 96 weeks, followed by an extended open-label long-term follow-up period up to 144 additional weeks. Adverse events, including adverse events of special interest and potential immune complex mediated reactions, are collected every 2 weeks. Anti-avalglucosidase alfa antibodies (ADAs) (with Nab in ADA-positive patients) are evaluated 1 week following the 1st infusion in ETP, then monthlythrough Week 73, then every 12 weeks up to the end of the follow-up.
ACT14132 (mini-COMET) (Category 3)
Purpose of the study: The primary objective of the study is to evaluate the safety profile, including infusion associated reactions and immunogenicity of avalglucosidase alfa in patients with IOPD previously treated with alglucosidase alfa.
EFC14462 (Category 3)
Purpose of the study: The primary objective is to determine the safety, tolerability, and effect of avalglucosidase alfa treatment on survival and invasive ventilator-free survival of IOPD patients less than or equal to 6 months of age after 52 weeks of treatment. Secondary objectives are to determine the effect of avalglucosidase alfa treatment on survival and invasive ventilator-freesurvival at 12 and 18 months of age, as well the change in LVM-Z score; AIMS score; body length, body weight, and headcircumference Z scores; and urinary Hex4 at Week 52; to determine the PK profile at week 12 and week 52; to determine safety, tolerability, and immunogenicity of avalglucosidase alfa.
DIREGC07005 (Pompe Disease Registry) (Category 3)
Purpose of the study:

The Pompe Registry collects and analyzes clinical data regularly collected by clinicians related to the onset, progression,and management of Pompe disease including patients treated with avalglucosidase alfa who also report renal and/or hepatic insufficiency.

AGLU03506 (Pompe Disease Pregnancy Sub-registry) (Category 3)

Purpose of the study:

The primary objective of this sub-registry is to track pregnancy outcomes, including complications and infant growth, in allwomen with Pompe disease during pregnancy, regardless of whether they receive disease-specific therapy, such as ERTwith alglucosidase alfa or avalglucosidase alfa.

This Sub-registry is a multicenter, international, longitudinal, observational, and voluntary program designed to track pregnancy outcomes for any pregnant woman enrolled in the Pompe Registry, regardless of whether she is receiving disease-specific therapy (such as ERT with alglucosidase alfa or avalglucosidase alfa) and irrespective of the commercial product with which she may be treated.

Post-Authorization Safety Study (Category 3)

Purpose of the study:

This study aims at gathering more comprehensive safety information on avalglucosidase alfa in a structured way to further characterize the important identified risk of infusion associated reactions, including hypersensitivity and anaphylactic reactions, and the important potential risk of medication error in the setting of clinical/ hospital and home infusion.

6MWT: 6-Minute Walk Test; ADA: Anti-Drug Antibody; AIMS: Alberta Infant Motor Scale; ETP: Extended Treatment Period; ERT: EnzymeReplacement Therapy; FVC: Forced Vital Capacity; Hex4: Hexose Tetrasaccharide; HHD: Hand-Held Dynamometry; IOPD: Infantile-Onset Pompe disease; LVM-Z: Left Ventricular Mass-Z; MEP: Maximal Expiratory Pressure; MIP: Maximal Inspiratory Pressure;Nab: Neutralizing Antibody; PK: Pharmacokinetic; QMFT: Quick Motor Function Test; SF-12: 12-Item Short Form Health Survey.

REFERENCES

None