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

MYOZYME® (ALGLUCOSIDASE 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 MYOZYME® 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 MYOZYME® 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 MYOZYME®.

1. THE MEDICINE AND WHAT IT IS USED FOR

According to Swiss label

MYOZYME is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of Pompe disease (acid α glucosidase deficiency).

In patients with the late form of the disease, data on efficacy are limited.

According to EU-SmPC

MYOZYME is authorized for long term ERT in patients with a confirmed diagnosis of Pompe disease (acid α glucosidase deficiency). MYOZYME is indicated in adults and pediatric patients of all ages (see SmPC for the full indication). It contains alglucosidase alfa as the active substance and it is given by IV infusion.

Further information about the evaluation of MYOZYME's benefits can be found in MYOZYME's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

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

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

Important risks of MYOZYME, together with measures to minimize such risks and the proposed studies for learning more about MYOZYME'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 (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 the case of MYOZYME, 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 MYOZYME 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 MYOZYME 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. Some of the risks are related to the biological nature of the product. Identified risks are concerns for which there is sufficient proof of a link with the use of MYOZYME. 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 risks	Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies
	Immune mediated reactions
	Immunogenicity leading to loss of response (High sustained IgG antibody titres and/or neutralizing antibodies)
Important potential risk	None
Missing information	Use of MYOZYME in pregnant or lactating women
	Use of MYOZYME in elderly patients
	Use of MYOZYME in patients with renal or hepatic insufficiency
	Long-term safety information

IgE: Immunoglobulin E; IgG: Immunoglobulin G.

2.2. Summary of important risks

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

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	Clinical trial, postmarketing surveillance, literature
Risk factors and risk groups	Infantile-onset patients who develop high antibody titres appear to be at higher risk for developing more frequent IARs and hypersensitivity. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody titres. Patients with an acute illness (eg, acute febrile illness, such as pneumonia or sepsis, or wheezing/bronchospasm) at the time of alglucosidase alfa infusion appear to be at greater risk for IARs. Patients with advanced Pompe disease or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their cardiac or respiratory compromise during infusions. Patients treated with higher doses of alglucosidase alfa (>20 mg/kg) tended to develop a more robust IgG antibody response and experience more IARs. Patients who have experienced infusion reactions may be at increased risk of IARs when alglucosidase alfa is readministered. Additionally, IgE positive patients are at increased risk of developing IARs upon readministering the drug. In the LO study, there was no apparent association between higher IgG antibody titres and occurrence of IARs. It is recommended that patients be monitored for IgG antibody formation periodically. Baseline serum sample collection prior to the first infusion is encouraged. For IOPD patients, regular monitoring during first year of treatment (example: every 3 months) is suggested and subsequent monitoring dependent on clinical outcomes and antibody titre levels. For LOPD patients, antibody development should be assessed within 6 months and subsequent monitoring as clinically warranted based on safety and efficacy considerations. The probability of developing high sustained antibody titres and poor outcome appears higher among CRIM-negative patients (patients in whom no endogenous GAA protein was detected by Western blot analysis) than among CRIM-positive patients (patients in whom endogenous GAA protein was detected by western blot analysis). However, high and sustained antibody titres also occur in some CRIM-positive patients. The cause of a poor clinical outcome in some of these patients is thought to be multifactorial. It is unknown who will develop immediate hypersensitivity reactions (IgE positive) to alglucosidase alfa.

Infusion associated reactions including hypersensitivity and anaphylactic reactions, with or without development of IgG and IgE antibodies	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in sections 4.2, 4.3, 4.4, 4.7 and 4.8 • PL: Labelled in section 2 and 4 • Prescription only medicine **Additional risk minimization measures:** • Safety Information Packet

CRIM: Cross-Reactive Immunologic Material; GAA: Acid Alfa-Glucosidase; HCP: Healthcare Professional; IAR: Infusion Associated Reaction; IgG: Immunoglobulin G; IOPD: Infantile-Onset Pompe Disease; LO: Late-Onset; LOPD: Late-Onset Pompe Disease; PL: Package Leaflet SmPC: Summary of Product Characteristics.

Table 3 - Important identified risk with corresponding risk minimization activities: Immune mediated reactions

Immune mediated reactions	
Evidence for linking the risk to the medicine	Nonclinical trials, clinical trial, postmarketing surveillance, literature.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in sections 4.4 and 4.8 • PL: Labelled in sections 2 and 4 • Prescription only medicine **Additional risk minimization measures:** Safety Information Packet

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

Table 4 - Important identified risk with corresponding risk minimization activities: Immunogenicity leading to loss of response (High sustained IgG antibody titres and/or neutralizing antibodies)

Immunogenicity leading to loss of response (High sustained IgG antibody titres and/or neutralizing antibodies)	
Evidence for linking the risk to the medicine	Clinical trial, postmarketing surveillance, literature.
Risk factors and risk groups	Patients with positive uptake inhibition generally had higher IgG antibody titres than patients who remained negative for uptake inhibition in IO and LO studies. 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 titres, as well as neutralizing antibodies when treated with alglucosidase alfa, which contribute to poor clinical outcomes. 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 titres which then decrease over time.
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in section 4.4 • PL: Not mentioned • Prescription only medicine **Additional risk minimization measures:** Safety Information Packet

IgG: Immunoglobulin G; IO: Infantile Onset; LO: Late-Onset; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 5 – Missing Information with corresponding risk minimization activities and additional pharmacovigilance activities: Use of MYOZYME in pregnant or lactating women

Use of MYOZYME in pregnant or lactating women	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in section 4.6. • PL: Labelled in section 2 • Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in pregnant patients. • Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in breastfeeding patients.

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

Table 6 – Missing Information with corresponding risk minimization activities and additional pharmacovigilance activities: Use of MYZOZYME in elderly patients

Use of MYOZYME in elderly patients	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in section 4.2. • PL: Not mentioned • Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Pompe Registry to collect long term data in patients of all ages treated with alglucosidase alfa (including elderly patients).

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

Table 7 – Missing Information with corresponding risk minimization activities and additional pharmacovigilance activities: Use of MYOZYME in patients with renal or hepatic insufficiency

Use of MYOZYME in patients with renal or hepatic insufficiency	
Risk minimization measures	**Routine risk minimization measures:** • SmPC: Labelled in section 4.2. • PL: Not mentioned • Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Pompe Registry to collect long-term data in patients with hepatic and renal insufficiency treated with alglucosidase alfa.

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

Table 8 – Missing Information with corresponding risk minimization activities and additional pharmacovigilance activities: Long-term safety information

Long-term safety information	
Risk minimization measures	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Pompe Registry to collect long-term data in patients treated with alglucosidase alfa.

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 MYOZYME.

2.3.2. Other studies in post-authorization development plan

Table 9 - Other studies in post-authorization development plan

Pompe Registry to collect long term data in patients of all ages treated with alglucosidase alfa (including elderly patients) (Cat. 3)
Purpose of the study: To obtain additional information about the use of alglucosidase alfa in patients of all ages.
Pompe Registry to collect long term data in patients with hepatic and renal insufficiency treated with alglucosidase alfa (Cat. 3)
Purpose of the study: To obtain additional information about the use of alglucosidase alfa in patients with renal or hepatic insufficiency.
Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in pregnant patients (NCT00567073) (commitment to US FDA) (Cat. 3)
Purpose of the study: To track pregnancy outcomes in women with Pompe disease and to follow infants born to women with Pompe disease (commitment to US FDA).
Sub-registry study within the Pompe Registry to collect additional data on the use of alglucosidase alfa in breastfeeding patients (AGLU03406, NCT00566878) (commitment to US FDA) (Cat. 3)
Purpose of the study: To determine if alglucosidase alfa is present in breast milk from mothers with Pompe Disease being treated with alglucosidase alfa and to measure breast milk production and composition in women with Pompe Disease who receive alglucosidase alfa (commitment to US FDA).

FDA: Food and Drug Administration; US: United States.