Part VI-Summary of activities in the risk management plan

This is a summary of the risk management plan (RMP) for velmanase alfa (CHF-LMZYMAA1).

The RMP details important risks of velmanase alfa (CHF-LMZYMAA1), how these risks can be minimised, and how more information will be obtained velmanase alfa (CHF-LMZYMAA1)'s risks and uncertainties (missing information).
Velmanase alfa (CHF-LMZYMAA1)'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how velmanase alfa (CHF-LMZYMAA1) should be used.

I. The medicine and what it is used for?

Velmanase alfa (CHF-LMZYMAA1) is an enzyme replacement therapy for the treatment of non-neurological manifestations in patients with mild to moderate alpha-mannosidosis.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of velmanase alfa (CHF-LMZYMAA1), together with measures to minimise such risks and the proposed studies for learning more about velmanase alfa (CHF-LMZYMAA1)' risks, are outlined below.

Measures to minimise 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;
• Important advice on the medicine's packaging;
• The authorised 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of velmanase alfa (CHF-LMZYMAA1) is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of velmanase alfa (CHF-LMZYMAA1) are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 velmanase alfa (CHF-LMZYMAA1). 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 (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Infusion-related reactions Immunogenicity Hypersensitivity
Important potential risks	Loss of consciousness Acute renal failure Medication errors
Missing information	Safety in patients < 6 years of age Long term safety. Safety in non-Caucasian patients. Safety in pregnant or lactating women. Safety in patients with hepatic or renal insufficiency. Safety in patients not capable of performing endurance test. Administration of home infusion.

II.B Summary of important risks

Important identified risk: *Infusion related reactions*	
Evidence for linking the risk to the medicine	Clinical trials (rhLAMAN-02, rhLAMAN-03, rhLAMAN-04, rhLAMAN-05, rhLAMAN-10).
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: -Statement in sections 4.2 4.4, 4.8 and 6.6 of SmPC -Warnings and precautions in section 2 of PIL -Administration in section 3 of PIL -Listed as possible side effects in section 4 of PIL

Important identified risk: *Immunogenicity*	
Evidence for linking the risk to the medicine	Clinical trials (rhLAMAN-02, rhLAMAN-03, rhLAMAN-04, rhLAMAN-05, rhLAMAN-10).
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: -Special warnings and precautions related to immunogenicity in section 4.4 of SmPC -Listed in section 4.8 of SmPC -Warnings and precautions in section 2 of PIL

Important identified risk: *Hypersensitivity*	
Evidence for linking the risk to the medicine	Clinical trials (rhLAMAN-02, rhLAMAN-03, rhLAMAN-04, rhLAMAN-05, rhLAMAN-10).
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: -Special warnings and precautions related to hypersensitivity in section 4.4 of SmPC -Listed in section 4.8 of SmPC -Warnings and precautions in section 2 of PIL -Possible side effects in section 4 of PIL

Important potential risk: *Loss of consciousness*	
Evidence for linking the risk to the medicine	Clinical trials (rhLAMAN-02, rhLAMAN-03, rhLAMAN-04, rhLAMAN-05, rhLAMAN-10)
Risk factors and risk groups	None identified.
Risk minimisation measures	Routine risk minimisation measures: -Listed in section 4.8 of SmPC -Possible side effects in section 4 of PIL

Important potential risk: *Acute renal failure*	
Evidence for linking the risk to the medicine	Clinical trials (rhLAMAN-02, rhLAMAN-03, rhLAMAN-04, rhLAMAN-05, rhLAMAN-10)
Risk factors and risk groups	Arthrosis is a common co-morbidity in patients and may require the use of medications that may affect the kidney. Anti-inflammatory and anti-rheumatic products were used in 33.3% of subjects in clinical trials.
Risk minimisation measures	-Routine risk minimisation measures: -Listed in section 4.8 of SmPC -Possible side effects in section 4 of PIL

Important potential risk: *Medication errors*	
Evidence for linking the risk to the medicine	Clinical trials (rhLAMAN-02, rhLAMAN-03, rhLAMAN-04, rhLAMAN-05, rhLAMAN-10)
Risk factors and risk groups	Most errors in a UK-based prospective study occurred when giving bolus doses or making up drugs that require multiple step preparations (Taxis et al 2003)**Error!**

	Reference source not found.. In an Australian study, four error types, (wrong intravenous rate, mixture, volume and drug incompatibility) accounted for 91.7% of errors (Westbrook 2011)Error! Reference source not found.. A significant proportion of errors suggest skill and knowledge deficiencies, with errors and severity reducing with increasing clinical experience (Westbrook 2011)Error! Reference source not found..
Risk minimisation measures	Routine risk minimisation measures: Posology and administration instructions in section 4.2 of SmPC Pharmaceutical particulars, incompatibilities, storage, disposal, reconstitution and administration instructions in section 6 of SmPC. How to use in section 3 of PIL. How to store in section 5 of PIL.

Missing information: *Safety in patients < 6 years of age*	
Risk minimisation measures	Routine risk minimisation measures: Statement in sections 4.2 and 4.4 of SmPC regarding the lack of data on safety and efficacy in patients < 6 years of age. Warning in section 3 of PIL.

Missing information: *Long term safety*	
Risk minimisation measures	Not Applicable.

Missing information: *Safety in non-Caucasian patients*	
Risk minimisation measures	Not Applicable.

Missing information: *Safety in pregnant or lactating women*	
Risk minimisation measures	Routine risk minimisation measures: Warnings and precautions with regards to use in pregnancy, lactation and impact on fertility in section 4.6 of SmPC. Preclinical data on reproduction and development in section 5.3 of SmPC. Pregnancy and breast feeding listed in warnings and precaution section, section 2 of PIL.

Missing information: *Safety in patients with hepatic or renal insufficiency*	
Risk minimisation measures	Routine risk minimisation measures: Statement regarding no dose recommendations for use in hepatic or renal insufficiency in section 4.2 of SmPC. Description of pharmacokinetic properties in section 5.2 of SmPC.

Missing information: *Safety in patients not capable of performing endurance test.*	
Risk minimisation measures	Not Applicable

Missing information: *Administration of home infusion*	
Risk minimisation measures	Not Applicable

II. C. Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

Study (type and study number)	**Objectives**	**Efficacy uncertainties addressed**	**Status (planned, started)**	**Date for submission of interim or final reports**
rhLAMAN-8 Open label 24month study in patients from birth to < 6 years	Pharmacokinetics, safety and efficacy in patients from birth to < 6 years	Efficacy in patients from birth to < 6 years	Started	Final CSR February 2021
The Alpha-Mannosidosis Registry: Long term effectiveness and safety of Lamzede therapy in European patients with alpha-mannosidosis	To evaluate the long-term effectiveness and safety profile of treatment with Lamzede® under conditions of routine clinical care. To characterize the entire alpha-mannosidosis population, including variability of clinical manifestation, progression and natural history	Long-term effectiveness	Started	Annual reports to be submitted as part of the annual re-assessment

II.C.2 Other studies in post-authorisation development plan

Study (type and study number)	**Objectives**	**Efficacy uncertainties addressed**	**Status (planned, started)**	**Date for submission of interim or final reports**
rhLAMAN-7 Open label in patients previously enrolled in rhLAMAN-02 or rhLAMAN-05	Long term safety and efficacy including quality of life (QoL)	Long term efficacy including quality of life (QoL)	Started	Final CSR June 2023
rhLAMAN-9 Open label in patients previously enrolled in rhLAMAN-02 or rhLAMAN-05	Long term safety and efficacy including quality of life (QoL)	Long term efficacy including quality of life (QoL)	Started	Final CSR June 2023