Part VI: Summary of the risk management plan

Summary of risk management plan for Rymphysia (alpha1-proteinase inhibitor (Human))

This is a summary of the risk management plan (RMP) for Rymphysia. The RMP details important risks of Rymphysia, how these risks can be minimised, and how more information will be obtained about alpha1-proteinase inhibitor (human)'s risks and uncertainties (missing information).

Rymphysia 's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Rymphysia should be used.

Important new concerns or changes to the current ones will be included in updates of Rymphysia's RMP.

I. The medicine and what it is used for

Rymphysia is indicated for maintenance treatment to slow the progression of emphysema in adults with documented severe alpha1-proteinase inhibitor deficiency (see SmPC for the full indication). It contains alpha1-proteinase inhibitor (human) (A1-PI) as the active substance and it is administered intravenously after reconstitution.

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

Important risks of Rymphysia, together with measures to minimise such risks and the proposed studies for learning more about Rymphysia 's 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 PL 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.

In addition to these measures, information about adverse reactions are collected continuously and regularly analysed including 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 Rymphysia is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Rymphysia are risks that need special risk management activities to further investigate or minimise 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 Rymphysia. 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	• Hypersensitivity reaction

List of important risks and missing information	
Important potential risks	• Transmission of infectious agent • Increased or unknown risks with home treatment / self-administration
Missing information	• Long term safety • Long term Immunogenicity • Use in pregnant and lactating women • Geriatric Use • Limited experience in patients who have undergone lung transplantation or volume reduction surgery • Limited experience in patients with FEV1≤35%

II.B Summary of important risks

Important identified risk: Hypersensitivity	
Evidence for linking the risk to the medicine	Preclinical studies and Clinical trials.
Risk factors and risk groups	Patients with known antibodies to IgA; patients with selective or severe IgA deficiency.
Risk minimisation measures	**Routine risk minimisation measures** SmPC section 4.3 states the use of product contraindicated in case of hypersensitivity reactions. SmPC section 4.4 where it is recommended to discontinue therapy in case of sign / symptoms of severe hypersensitivity reaction/anaphylactic reactions. SmPC section 4.8. where health care professionals are informed of hypersensitivity reaction after administration of product. How to detect signs and symptoms of allergic reaction is available in PL sections 2 and 4. Rymphysia is a prescription only medicine. **Additional risk minimisation measures** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** TAK-883-4002.

Important potential risk: Transmission of infectious agent	
Evidence for linking the risk to the	Scientific literature.

Important potential risk: Transmission of infectious agent	
medicine	
Risk factors and risk groups	Any patient who is administered a blood- or plasma-derived medicinal product is potentially at risk for transmission of infectious agents.
Risk minimisation measures	**Routine risk minimisation measures** SmPC section 4.4 and PL section 2 where information on measures taken for inactivation / removal of viruses (enveloped viruses - human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and non-enveloped viruses - hepatitis A and parvovirus B19 viruses) is provided. Recommendation on appropriate vaccination (hepatitis A and B) in case of regular / repeated administration of product. **Additional risk minimisation measures** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Important potential risk: Increased or unknown risks with home treatment / self-administration	
Evidence for linking the risk to the medicine	Medical Literature.
Risk factors and risk groups	Patients with known antibodies to IgA; patients with selective or severe IgA deficiency.
Risk minimisation measures	**Routine risk minimisation measures** SmPC section 4.2 where it is mentioned that first infusions of the drug should be administered under the supervision of a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency. SmPC section 4.4 where it is recommended to discontinue therapy in case of sign / symptoms of severe hypersensitivity reaction/anaphylactic reactions. SmPC section 4.4 where health care professionals are informed of potential risks associated with home treatment / self-administration. SmPC section 4.4 where health care professionals are advised to ensure appropriate training and on-going supervision. SmPC section 4.8 where health care professionals are informed of hypersensitivity reaction after administration of

Important potential risk: Increased or unknown risks with home treatment / self-administration	
	product. How to detect signs and symptoms of allergic reaction is available in PL sections 2 and 4. The need for adequate training, on-going supervision and aseptic technique is available in PL section 3. Rymphysia is a prescription only medicine. **Additional risk minimisation measures** Healthcare Professional and Patient/Caregiver Guide for home treatment and self-administration of Rymphysia.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** TAK-883-4002; A qualitative survey.

Missing information: Long term safety	
Risk minimisation measures	**Routine risk minimisation measures** In SmPC section 5.1 it is stated that long term safety data are not available for product. Rymphysia is prescription only medicine. **Additional risk minimisation measures** No additional risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: TAK-883-4002.

Missing information: Long term immunogenicity	
Risk minimisation measures	**Routine risk minimisation measures** SmPC section 4.8 it is stated that long term immunogenicity data are not available. Rymphysia is prescription only medicine. **Additional risk minimisation measures** No additional risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Missing information: Use in pregnant and lactating woman	
Risk minimisation measures	**Routine risk minimisation measures** In SmPC section 4.6 and PL section 2 it is stated that the safety and efficacy data are not available for product during the pregnancy exposure and in breast-feeding woman. Rymphysia is prescription only medicine. **Additional risk minimisation measures** No additional risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None.

Missing information: Geriatric use	
Risk minimisation measures	**Routine risk minimisation measures** SmPC section 4.2 and section 4.8 where it is stated safety and efficacy have not been established in elderly population. Rymphysia is prescription only medicine. **Additional risk minimisation measures** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** TAK-883-4002.

Missing information: Limited experience in patients who have undergone lung transplantation or volume reduction surgery	
Risk minimisation measures	**Routine risk minimisation measures** None. **Additional risk minimisation measures** No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Missing information: Limited experience in patients with FEV1≤35%	
Risk minimisation measures	**Routine risk minimisation measures** None.

Missing information: Limited experience in patients with FEV1≤35%	
	Additional risk minimisation measures No additional risk minimisation measures.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** TAK-883-4002.

II.C. Post-authorisation development plan

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

Not applicable.

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

Protocol number: TAK-883-4002 (Randomized, Open-label, Parallel-group, Multicenter, Non-inferiority and Dose-response Study to Evaluate the Efficacy and Safety of ARALAST NP (RYMPHYSIA) for Alpha1-Proteinase Inhibitor (A1PI) Augmentation Therapy in Subjects with A1PI Deficiency and Chronic Obstructive Pulmonary Disease Emphysema).

Protocol number: A qualitative survey to determine the effectiveness of the aRMM.