Part VI Summary of risk management plan for Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid (Alpha$_1$-Proteinase Inhibitor (Human))

This is a summary of the risk management plan (RMP) for Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid. The RMP details important risks of Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid, how these risks can be minimised, and how more information will be obtained about Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid 's risks and uncertainties (missing information).

Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how the product should be used.

Important new concerns or changes to the current ones will be included in updates of Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid's RMP.

I. The medicine and what it is used for

Prolastin®, Plitalfa® and Prolasplan® are authorised for long-term augmentation therapy in subjects with documented severe alpha1-proteinase inhibitor deficiency (e.g. genotypes PiZZ, PiZ(null), Pi (null,null) and PiSZ). Patients are to be under optimal pharmacologic and non-pharmacologic treatment and show evidence of progressive lung disease (e.g. lower forced expiratory volume per second (FEV1) predicted, impaired walking capacity or increased number of exacerbations) as evaluated by a healthcare professional experienced in the treatment of alpha1-proteinase inhibitor deficiency.

Prolastin®-C and Prolastin®-C liquid are not authorized in any EEA country but their indications for use are essentially the same.

Prolastin® 1000 mg, Plitalfa® and Prolasplan® are available as a lyophilized powder in a single-use vial of approximately 1,000 mg of Alpha1-Proteinase Inhibitor (Human) to be reconstituted with Sterile Water for Injection, PhEur, provided in a separate 40 mL vial.

Prolastin® 4000 mg is available as a lyophilized powder in a single-use vial of 4,000 mg of Alpha1-Proteinase Inhibitor (Human) to be reconstituted with Sterile Water for Injection, PhEur, (160 ml) provided in a separate 250 mL vial.

Prolastin® 5000 mg is available as a lyophilized powder in a single-use vial of 5,000 mg of Alpha1-Proteinase Inhibitor (Human) to be reconstituted with Sterile Water for Injection, PhEur, (200 ml) provided in a separate 250 mL vial.

Prolastin®-C is available as a lyophilized powder in a single-use vial of approximately 1,000 mg of Alpha1-Proteinase Inhibitor (Human) to be reconstituted with Sterile Water for Injection, USP, provided in a separate 20 mL vial.

Prolastin®-C Liquid is a solution for injection containing approximately 1,000 mg of Alpha$_1$-Proteinase Inhibitor (Human) in a single-use vial of 20 mL.

Prolastin®-C Liquid: solution for injection containing approximately 500 mg of Alpha1-Proteinase Inhibitor (Human) in a single-use vial of 10 mL.

Prolastin®-C Liquid: solution for injection containing approximately 4,000 mg of Alpha1-Proteinase Inhibitor (Human) in a single-use vial of 100 mL (80 mL fill).

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

Important risks of Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid, together with measures to minimise such risks and the proposed studies for learning more about Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid '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 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.

In addition to these measures, information about adverse reactions is 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 Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid 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 Prolastin®, Plitalfa®, Prolasplan®, Prolastin®-C and Prolastin®-C Liquid. 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;

List of important risks and missing information	
Important identified risks	- Hypersensitivity including anaphylactic reactions
Important potential risks	- Theoretical risk of pathogen infection - Increased or unknown risks with home-treatment
Missing information	- Use in women who are pregnant or lactating - Use in children - Use in adults aged 65 years and older - Limited experience in patients with FEV1≤35 - Use in patients with lung transplantation or volume reduction surgery

II.B Summary of important risks

Important identified risk: Hypersensitivity including anaphylactic reactions	
Evidence for linking the risk to the medicine	Hypersensitivity reactions, including life-threatening anaphylactic reactions can occur even when a previous administration has been tolerated (including a negative test). Caution is therefore needed with every dose, even if previous tests have been made.
Risk factors and risk groups	All patients using any intravenous protein product are exposed to the risk. Risk factors associated with anaphylactic reactions are IgA deficiency and history of hypersensitivity reactions. Most often, hypersensitivity reactions are associated with first-time exposure as well as with rapid infusion rate.
Risk minimisation measures	Routine risk minimisation measures: Adequately addressed in the EU SmPC section 4.3, 4.4 and 4.8; US PI (specific for Prolastin®-C and Prolastin®-C Liquid) section 4, 5.1, 6.2 and 17.

Important potential risk: Theoretical risk of pathogen infection	
Evidence for linking the risk to the medicine	Because this product is made from human blood, it may carry a risk of transmitting infectious agents. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit infectious agent, e.g. viruses and, theoretically, the Creutzfeld-Jakob disease (CJD) agent. The possibility of transmitting

Important potential risk: Theoretical risk of pathogen infection	
	infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
Risk factors and risk groups	All patients receiving the infusion are exposed to the risk of theoretical risk of pathogen infection.
Risk minimisation measures	Routine risk minimisation measures: Adequately addressed in the EU SmPC section 4.4; US PI (specific for Prolastin®-C and Prolastin®-C Liquid) section 5(5.2), 11 and 17.

Important potential risk: Increased or unknown risks with home-treatment	
Evidence for linking the risk to the medicine	Potential risks associated with home-treatment is related to the handling and administration of the medicinal product as well as to the handling of adverse reactions, particularly hypersensitivity.
Risk factors and risk groups	All patients suitable for home-treatment are exposed to the risk.
Risk minimisation measures	Routine risk minimisation measures: Adequately addressed in the EU SmPC section 4.4. No text included in US PI (specific for Prolastin®-C and Prolastin®-C Liquid).

Missing information: Use in women who are pregnant or lactating	
Risk minimisation measures	Routine risk minimisation measures: Adequately addressed in the EU SmPC section 4.6; US PI (specific for Prolastin®-C and Prolastin®-C Liquid) section 8.1 and 8.2.

Missing information: Use in children	
Risk minimisation measures	Routine risk minimisation measures: Adequately addressed in the EU SmPC section 4.2; US PI (specific for Prolastin®-C and Prolastin®-C Liquid) section 8.4.

Missing information: Use in adults aged 65 years and older	
Risk minimisation measures	Routine risk minimisation measures: Adequately addressed in the EU SmPC section 4.2; US PI (specific for Prolastin®-C and Prolastin®-C Liquid) section 8.5.

Missing information: Limited experience in patients with FEV1≤35	
Risk minimisation measures	No risk minimization measures. No text included in EU SmPC neither in US PI.

Missing information: Use in patients with lung transplantation or volume reduction surgery	
Risk minimisation measures	No risk minimization measures. No text included in EU SmPC neither in US PI.

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of Alpha1-Proteinase Inhibitor (Human).

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

There are no studies required for Alpha1-Proteinase Inhibitor (Human).