Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prolastin1000mg, powder and solvent for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial of powder contains:
1000 mg alpha$_1$-proteinase inhibitor, human.
1 ml of the reconstituted solution contains 25 mg alpha$_1$-proteinase inhibitor (human).

Produced from the plasma of human donors

Excipients with known effect:
Prolastin contains 2.76 mg sodium per ml of reconstituted solution (120 mmol/l).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for infusion
Powder: White to beige.
Solvent: Clear colourless solution.

The reconstituted solution appears clear to opalescent with colourless to slightly yellowish green colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Prolastin is indicated for long-term augmentation therapy in subjects with documented severe alpha$_1$-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 alpha$_1$-proteinase inhibitor deficiency.

4.2 Posology and method of administration

Physicians experienced with chronic obstructive lung diseases should initiate the treatment and supervise the first infusions. Subsequent infusions can be administered by a healthcare professional, see section 4.4.
The duration of treatment is at the discretion of the attending physician. A specific limit on the duration of treatment is not envisaged.

Posology

Adults, including elderly patients
Unless otherwise prescribed, a once-weekly dose of 60 mg active ingredient/kg body weight (equivalent to 180 ml reconstituted solution for infusion containing 25 mg/ml alpha$_1$-proteinase inhibitor (human) in the case of a patient weighing 75 kg) as a short-term infusion is usually sufficient to keep the serum alpha$_1$-proteinase inhibitor level constantly over 80 mg/dl which correlates with pulmonary levels of 1.3 microM. Theoretically this serum and epithelial-lining fluid levels are estimated protective levels against further worsening of the pulmonary emphysema.

Paediatric population
No experience is available on use of Prolastin in children and adolescents below the age of 18.

Method of administration

Prolastin should only be administered by intravenous infusion after reconstitution.

The dry powder must be dissolved with the solvent (40 ml water for injections) as described in section 6.6 and administered using a suitable infusion set (not included).
The prepared solution must be used within 3 hours of its preparation.
The infusion rate should not exceed 0.08 ml/kg body weight per minute (equivalent to 6 ml per minute in a patient weighing 75 kg). This infusion rate may be adjusted based upon patient tolerability.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Prolastin must not be used in patients with

- selective IgA deficiency who are known to have antibodies against IgA, as allergic reactions to the point of anaphylactic shock may occur in such cases,
- known hypersensitivity to alpha$_1$-proteinase inhibitors or to any of the excipients listed in section 6.1 (see also section 4.4).

4.4 Special warnings and precautions for use

The recommended infusion rate given under section 4.2 should be adhered. If any reaction takes place that might be related to the administration of Prolastin, the rate of infusion should be decreased, or the administration should be stopped, as required by the clinical condition of the patient.

Since Prolastin can cause a transient increase in blood volume, particular caution is necessary in patients with severe heart failure and patients at risk of circulatory overload.

Hypersensitivity
Rarely hypersensitivity reactions may occur, even in patients who have tolerated previous treatment with human alpha$_1$-proteinase inhibitor. In the event of a severe hypersensitivity reaction (with a fall in blood pressure to < 90 mmHg, dyspnoea or even anaphylactic shock), Prolastin should be discontinued immediately and suitable therapy, with treatment for shock as necessary, should be instituted.

Home-treatment
There are limited data regarding the use of Prolastin in home-treatment.
Potential risks associated with home-treatment are related to the handling and administration of the medicinal product as well as to the handling of adverse reactions. Patients should in any case be informed of signs of hypersensitivity reactions.

The decision of whether a patient is suitable for home-treatment is made by the attending physician, who should ensure appropriate training is provided (e.g. regarding reconstitution, use of Mix2Vial set, assembly of intravenous tubing, infusion techniques, maintenance of a treatment diary, identification of adverse reactions and measures to be taken in case such reactions occur) and the use is reviewed at regular intervals.

Transmissible agents
Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The measures taken may be of limited value against non-enveloped viruses such as hepatitis A and parvovirus B19.
Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular repeated receipt of human plasma-derived proteinase inhibitors.

Traceability

Every time that Prolastin is administered to the patient, the name and batch number should be clearly recorded in order to maintain a link between the patient and the batch of the product.

Smoking
Prolastin therapy cannot be denied to smokers. However, since the efficacy of Prolastin will be compromised by tobacco smoke in the lungs, cessation of smoking is strongly recommended.

Sodium content
This medicinal product contains 110.4 mg (4.8 mmol) sodium per vial. In case of a patient of 75 kg body weight this is equivalent to 24.84 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
This should be taken into account for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

There are no known interactions between Prolastin and other medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy
For Prolastin no clinical data on exposed pregnancies are available. Animal studies have not been conducted. Caution should be exercised when prescribing to pregnant women.

Lactation
It is unknown whether alpha$_1$-proteinase inhibitor is excreted in human breast milk. The excretion of alpha$_1$-proteinase inhibitor in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Prolastin should be made taking into account the benefit of breast-feeding to the child and the benefit of Prolastin therapy to the woman.

4.7 Effects on ability to drive and use machines

Prolastin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Treatment with Prolastin may result in known reactions as fever, flu-like symptoms, dyspnoea, urticaria, nausea, etc.
However, uncommon or rare immunological reactions may occur as with any protein treatment, even when the patient has shown no hypersensitivity or allergic reaction to previous administration. This would include allergic reactions such as urticaria or dyspnoea, very rarely anaphylaxis (see section 4.4).
Symptoms which are of possible immunological origin should be evaluated before patients are re-challenged with therapy.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).
Frequencies have been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

The following undesirable effects have been observed during treatment with Prolastin:

System organ class	Uncommon > 0.1% to <1%	Rare >0.01% to <0.1%	Very rare < 0.01%
Immune system disorders	Urticaria	Hypersensitivity reactions	Anaphylactic shock
Nervous system disorders	Dizziness / dazed state headache		
Cardiac disorders		Tachycardia	
Vascular disorders		Hypotension Hypertension	
Respiratory, thoracic and mediastinal disorders	Dyspnoea		
Skin and subcutaneous tissue disorders	Rash		
Gastrointestinal disorders	Nausea		
Musculoskeletal and connective tissue disorders	Joint pain / arthralgia	Back pain	
General disorders and administration site conditions	Chills, fever, flu-like symptoms, chest pain		

For information on viral safety, see section 4.4.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Consequences of overdose are not known.
In the event of overdose, the patient should be observed closely for the occurrence of undesirable effects and supportive measures should be available as necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: proteinase inhibitor
ATC code: B02AB02

Alpha$_1$-proteinase inhibitor is a normal constituent of human blood that inhibits the activity of neutrophil elastase, amongst other enzymes. Alpha$_1$-proteinase inhibitor has a molecular weight of 51kDa and belongs to the family of serine protease inhibitors.

It is currently assumed that the pathogenesis of emphysema in alpha$_1$-proteinase inhibitor deficiency is attributable to a chronic biochemical imbalance between elastase and alpha$_1$-proteinase inhibitor. Elastase, which is synthesised by pro-inflammatory cells in the lower respiratory tract, is capable of breaking down elastic tissue. One of the principal inhibitors

of elastase is alpha$_1$-proteinase inhibitor, which is lacking in hereditary alpha$_1$-proteinase inhibitor deficiency. As a result, the alveolar structures remain unprotected against the elastase that is released by the neutrophils in the lower respiratory tract and to which they are therefore chronically exposed.
This leads to progressive degradation of the elastic tissue and when serum alpha$_1$ antitrypsin levels decrease below 80 mg/dl, this is associated with an increased risk for development of emphysema.
In two controlled observational registries, the most significant slowing of reduction in the rate of FEV1 has been observed in patients with FEV1 35 to 60 % of predicted.

5.2 Pharmacokinetic properties

After intravenous administration, virtually 100% of the alpha$_1$-proteinase inhibitor dose is immediately available in the patient's bloodstream. The mean in vivo recovery rate is 4.2 mg/dl per kg body weight. The in vivo half life is approximately 4.5 days.

5.3 Preclinical safety data

The active ingredient of Prolastin, alpha$_1$-proteinase inhibitor, is obtained from human plasma and behaves like endogenous plasma constituents. Administration of a single dose of Prolastin to various animal species, as well as administration of daily doses during five consecutive days to rabbits, showed no indications of toxic effects. Additional preclinical studies with repeated dosing (chronic toxicity, carcinogenicity, reproduction toxicity) were not conducted. These studies cannot usefully be performed in conventional animal models, as antibodies are expected to be formed as a result of administration of heterologous human proteins.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder: Sodium chloride, Sodium dihydrogen phosphate
Solvent: Water for injections

6.2 Incompatibilities

In the absence of compatibility studies Prolastin must not be mixed with medicinal products or other solutions for infusion.

6.3 Shelf life

3years.
The reconstituted solution should always be used within 3 hours of its preparation.

6.4 Special precautions for storage

Do not store above 25 ˚C.
Do not freeze. Once prepared, the solution for infusion should not be stored in a refrigerator. Discard any unused solution according to local requirements.

6.5 Nature and contents of container

Powder:
Type I glass vial with chlorobutyl rubber stopper and aluminium cap.

Solvent:
Type I glass vial with chlorobutyl rubber stopper and aluminium cap.

Pack sizes:
Single pack Prolastin 1000 mg, powder and solvent for solution for infusion containing:
One powder vial (1000 mg alpha$_1$-proteinase inhibitor, human),
one solvent vial (40 ml water for injections),
one Mix2Vial transfer device for reconstitution.
Bundle pack containing:

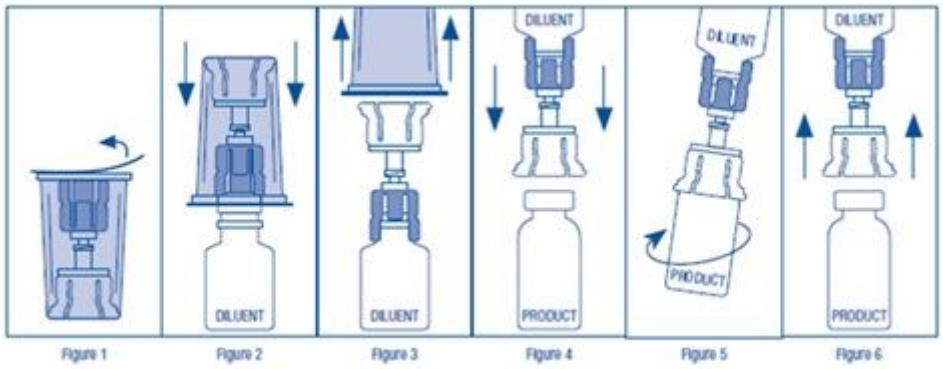
Four single packs of Prolastin 1000 mg, powder and solvent for solution for infusion.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The dry powder is to be brought into contact with and dissolved in the contents of one vial containing 40 ml water for injections, as described below. The reconstituted solution appears clear to opalescent and colourless to slightly yellowish green colour. Total reconstitution should be obtained within 5 minutes.

Preparation of the reconstituted solution for infusion

1. Use aseptic technique (clean and sanitized) in order to maintain sterility. Perform the reconstitution procedure on a flat work surface.
2. Ensure that the vials of Prolastin and the solvent (Sterile Water for Injections) are at room temperature (20-25ºC).
3. Remove the protective cap from the Prolastin vial and clean the top of the stopper with an alcohol swab. Allow the rubber stopper to dry.
4. Repeat this step with the vial of sterile water.
5. Open the sterile Mix2Vial package by peeling away the lid (**Figure 1**). Do not remove the device from the package.
6. Place the solvent vial upright on an even surface. Holding the solvent vial securely, push the blue end of the Mix2Vial straight down until the spike penetrates the stopper (**Figure 2**).
7. Remove the clear outer packaging from the Mix2Vial and discard it (**Figure 3**).
8. Place the Prolastin vial upright on a flat surface and invert the solvent vial with the Mix2Vial still attached.
9. While holding the Prolastin vial securely on a flat surface, push the clear end of the Mix2Vial straight down until the spike penetrates the stopper (**Figure 4**). The solvent will automatically transfer into the Prolastin vial by the vacuum contained within it. Note: If the Mix2Vial is connected at an angle, thevacuum may be released from the product vial and the solvent will not transferinto the product vial. If vacuum is lost, use a sterile syringe and needle toremove the sterile water from the solvent vial and inject it into the Prolastinvial, directing the stream of fluid against the wall of the vial.
10. With the solvent and Prolastin vials still attached to the Mix2Vial, gently swirl (**Figure 5**) until the powder is completely dissolved. Do not shake to avoid foaming. The reconstituted solution should be clear. Do not use if particulate matter or discoloration is observed.
11. As more than one vial of product will be needed to achieve the required dose, repeat instructions above using an additional package containing a new Mix2Vial. Do not reuse the Mix2Vial.
12. Remove the Mix2Vial (**Figure 6**) and proceed with the administration of the product by aseptic technique.



Only clear solutions should be used. The reconstituted solution must always be used within 3 hours of its preparation. Any unused medicinal product or waste material should be disposed of in accordance with legal requirements.

7 MARKETING AUTHORISATION HOLDER

Grifols Deutschland GmbH
Colmarer Strasse 22
60528 Frankfurt
Germany

8 MARKETING AUTHORISATION NUMBER

PA1405/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th January 2007
Date of latest renewal: 21st March 2021

10 DATE OF REVISION OF THE TEXT

November 2022