PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PROLASTIN®-C

Alpha$_1$-Proteinase Inhibitor (Human) Injection

Lyophilized Powder for Solution - For Intravenous use Only

1000 mg / vial

Alpha$_1$-Antitrypsin Replenisher

Manufactured by:
Grifols Therapeutics LLC
8368 U.S. 70 Bus. Hwy West
Clayton, North Carolina
27520
U.S.A.

Imported and Distributed by:
Grifols Canada Ltd.
5060 Spectrum Way
Suite 405
Mississauga, Ontario
L4W 5N5

Date of Initial Authorization:
September 19, 1988

Date of Revision:
October 29, 2024

Submission Control Number: 287098

RECENT MAJOR LABEL CHANGES

Not Applicable

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PROLASTIN-C (alpha$_1$-proteinase inhibitor [human] injection) is indicated for:

- chronic replacement therapy of individuals having congenital deficiency of alpha$_1$-PI (alpha$_1$-antitrypsin deficiency), related to genotypes PiZZ, PiZ(null), Pi (null)(null), PiSZ or other deficiency causing alleles, and with clinically demonstrable emphysema.

Clinical and biochemical studies have demonstrated that with such therapy, it is possible to increase plasma levels of alpha$_1$-PI, and that levels of functionally active alpha$_1$-PI in the lung epithelial lining fluid are increased proportionately. As some individuals with alpha$_1$-antitrypsin deficiency will not go on to develop emphysema, only those with evidence of such disease should be considered for chronic replacement therapy with Alpha$_1$-Proteinase Inhibitor (Human). Subjects with the PiMZ or PiMS phenotypes of alpha$_1$-antitrypsin deficiency should not be considered for such treatment as they appear to be at small risk for emphysema. Clinical data are not available as to the long-term effects derived from chronic replacement therapy of individuals with alpha$_1$-antitrypsin deficiency with Alpha$_1$-Proteinase Inhibitor (Human). Only adult subjects have received Alpha$_1$-Proteinase Inhibitor (Human) to date.

1.1 Pediatrics

Pediatrics (<18 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Prolastin-C in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years): Of 32 subjects randomized in a pharmacokinetic/safety study supporting a Liquid formulation of Prolastin-C, 17 were ≥65 years of age. While the data was limited, no overall differences for Prolastin-C have been observed between patients 65 years of age and older and younger patients (See Section 7.1.4).

2 CONTRAINDICATIONS

Prolastin-C is contraindicated in:

- patients who are hypersensitive to Alpha$_1$-Proteinase Inhibitor (Human) or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section.
- individuals with selective immunoglobulin A (IgA) deficiencies, since these patients may experience severe reactions, including anaphylaxis, to IgA which may be present.
- individuals with a history of anaphylaxis or other severe systemic reaction to alpha$_1$-proteinase inhibitor (human) products.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The "threshold" level of alpha$_1$-PI in the serum believed to provide adequate anti-elastase activity in the lung of individuals with alpha$_1$-antitrypsin deficiency is 80 mg/dL (based on commercial standards for alpha$_1$-PI immunologic assay). However, assays of alpha$_1$-PI based on commercial standards measure antigenic activity of alpha$_1$-PI, whereas the labeled potency value of alpha$_1$-PI is expressed as actual functional activity, i.e., actual capacity to neutralize porcine pancreatic elastase. As functional activity may be less than antigenic activity, serum levels of alpha$_1$-PI determined using commercial immunologic assays may not accurately reflect actual functional alpha$_1$-PI levels.

Therefore, although it may be helpful to monitor serum levels of alpha$_1$-PI in individuals receiving Prolastin-C, using currently available commercial assays of antigenic activity, results of these assays should not be used to determine the required therapeutic dosage.

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of Prolastin-C is 60 mg/kg body weight administered once weekly by intravenous infusion. This dose is intended to increase and maintain a level of functional alpha$_1$-PI in the epithelial lining of the lower respiratory tract, providing adequate anti-elastase activity in the lung of individuals with alpha$_1$-antitrypsin deficiency.

4.3 Reconstitution

Prolastin-C should be reconstituted with Sterile Water for Injection, USP (see Table 1). Prolastin-C and diluent should be brought to room temperature prior to reconstitution. Prolastin-C should be filtered through a sterile filter needle as supplied in the package prior to use.

Table 1 - Reconstitution

Approximate Alpha$_1$-PI Functional Activity	Volume of Diluent to be Added to Prolastin-C Vial	Approximate Available Volume	Concentration per mL
1000mg*	20mL	20.2 to 21.6 mL	≥ 40 mg/mL

* Each vial of Prolastin-C (Alpha$_1$ Proteinase Inhibitor [Human]), has the functional activity, as determined by inhibition of porcine pancreatic elastase, stated on the label of the vial.

Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.

Vacuum Transfer

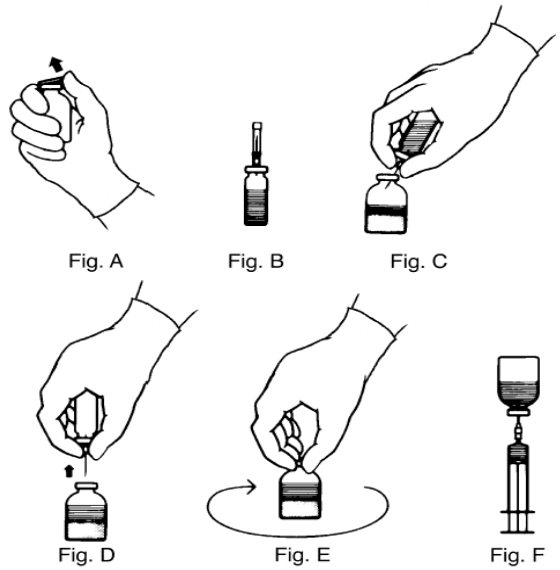
Aseptic technique should be followed.

1. Warm the Prolastin-C (Product) and sterile water (diluent) to room temperature (25°C) before reconstitution.
2. Remove the plastic flip-top caps from each vial (Figure 1: A). Swab the exposed stopper surfaces with alcohol and allow surface to dry.
3. Carefully remove the plastic sheath from the short end of the transfer needle. Insert the exposed needle into the center of the stopper in the diluent vial (Figure 1: B).

4. Carefully grip the sheath of the other end of the transfer needle and twist to remove it.
5. Invert the diluent vial and insert the attached needle into the Prolastin-C vial at a 45° angle (Figure 1: C). This will direct the stream of diluent against the wall of the Product vial and minimize foaming. The vacuum will draw the diluent into the Product vial. Because the vial of Prolastin-C is under vacuum, the stopper must only be pierced one time by the needle, to ensure complete transfer of diluent.
6. Remove the diluent vial and transfer needle (Figure 1: D).
7. Immediately after adding the diluent, swirl vigorously for 10–15 seconds to thoroughly break-up cake then swirl continuously until the powder is completely dissolved (Figure 1: E). Some foaming will occur, but this does not affect the quality of the product. The vial should then be visually inspected for particulate matter and discoloration prior to administration.
8. Attach the filter needle (from the package) to sterile syringe. Withdraw the Prolastin-C solution into the syringe through the filter needle (Figure 1: F).
9. Remove the filter needle from the syringe and replace with an appropriate injection needle for administration. Discard filter needle into a puncture-proof container.
10. The contents of more than one vial of Prolastin-C may be drawn into the same syringe before administration. If more than one vial of Prolastin-C is used, withdraw contents from vial using aseptic technique. Place contents into a sterile I.V. administration container (plastic or glass) using a syringe. Avoid pushing a large I.V. spike into the product container stopper as this has been known to force the stopper into the vial, with a resulting loss of sterility.

Described above is one acceptable method of reconstitution. The product may also be reconstituted with other appropriate transfer devices according to the manufacturer's accepted procedure.

Figure 1 – Steps in the Reconstitution of Prolastin-C



4.4 Administration

FOR INTRAVENOUS USE ONLY.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution is clear or slightly opalescent, and colourless or pale yellow or pale green or pale brown. Do not use if the product is discoloured or cloudy.

Reconstituted Prolastin-C should be given alone, without mixing with other agents or diluting solutions.

Prolastin-C may be given at a rate of 0.08 mL/kg/min or greater and must be administered intravenously. The recommended dosage of 60 mg/kg takes approximately 15 minutes to infuse.

Record brand name, Drug Identification Number (DIN) and the batch/lot number of the product for each patient (see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).

Following administration, discard open vials, administration equipment and unused solution per local requirements.

5 OVERDOSAGE

To date, there have been no reported cases of overdose for Prolastin-C or other Alpha$_1$ Proteinase Inhibitor (Human) manufactured by Grifols. No data are available in regard to overdosage in humans.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous injection	Lyophilized powder for reconstitution and injection 1000 mg/20 mL vial Human Alpha$_1$ proteinase inhibitor	Sodium chloride, Sodium phosphate

Prolastin-C is supplied as a sterile, white to beige, lyophilized powder in single use vials with

the total alpha$_1$-PI functional activity, in milligrams, stated on the label of each vial (Approximate functional activity of 1000 mg per vial; see Table 1).

A suitable volume of Sterile Water for Injection, USP (20 mL), a sterile double-ended transfer needle and a sterile filter needle are provided.

Description

Prolastin-C (Alpha$_1$-Proteinase Inhibitor [Human]) is a sterile, stable, lyophilized preparation of highly purified human Alpha$_1$-Proteinase Inhibitor (alpha$_1$-PI), also known as alpha$_1$-antitrypsin. Alpha$_1$-Proteinase Inhibitor (Human) is intended for use in therapy of congenital alpha$_1$-antitrypsin deficiency.

Prolastin-C is prepared from pooled human plasma of normal donors by modification and refinements of the cold ethanol method of Cohn. See WARNINGS AND PRECAUTIONS. Prolastin-C is produced through a modification of the Prolastin manufacturing process that results in improved product purity and a higher concentration of the same active substance, alpha$_1$-PI, in the reconstituted product.

7 WARNINGS AND PRECAUTIONS

General

Prolastin-C is made from human plasma and may carry a risk of transmitting infectious agents, e.g. such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite steps designed to reduce this risk. Prolastin-C is purified from human plasma obtained from healthy donors. When medicinal biological products are administered, infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by: (1) epidemiological controls on the population and selection of individual donors by a medical interview; (2) screening of individual donations and plasma pools for viral infection markers; and (3) manufacturing procedures with demonstrated capacity to inactivate/remove pathogens.

ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Canada Ltd. [1-866-482-5226].

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering to the patient.

Administer only by the intravenous route.

As with any colloid solution, there will be an increase in plasma volume following intravenous administration of Alpha$_1$-Proteinase Inhibitor (Human). Caution should therefore be used in patients at risk for circulatory overload.

Product administration and handling of the needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious virus including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

Carcinogenesis and Mutagenesis

Long-term studies in animals to evaluate carcinogenesis and mutagenesis have not been

conducted.

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, may occur. Monitor vital signs and observe the patient carefully throughout the infusion. Early signs and symptoms of hypersensitivity reactions may include pruritus; generalized urticaria; flushing; swollen lips, tongue, or uvula; wheezing; tightness of the chest; dyspnea; hypotension; and syncope. If hypersensitivity symptoms occur, promptly stop Prolastin-C infusion and begin appropriate therapy. Have epinephrine and other appropriate therapy available for the treatment of any acute anaphylactic or anaphylactoid reaction.

Prolastin-C may contain trace amounts of IgA. Patients with known antibodies to IgA, which can be present in patients with selective or severe IgA deficiency, have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions.

Sexual Function/Reproduction

Long-term studies in animals to evaluate impairment of fertility have not been conducted.

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproduction studies have not been conducted with Prolastin-C. It is also not known whether Prolastin-C can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Prolastin-C should be given to a pregnant woman only if clearly needed.

7.1.2 Breast-feeding

It is not known whether Alpha$_1$-PI is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Prolastin-C is administered to a nursing woman.

7.1.3 Pediatrics

Safety and effectiveness in the pediatric population have not been established.

7.1.4 Geriatrics

A clinical pharmacokinetic/safety study randomized 32 patients to a cross-over design for treatment with both Prolastin-C and a liquid formulation of human alpha$_1$-proteinase inhibitor. Among the 32 patients, 17 were aged 65 years or older (range: 65 to 71 years).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Therapeutic administration of Prolastin-C 60 mg/kg weekly, has been demonstrated to be well-tolerated. There have been very rare cases of anaphylactic/anaphylactoid reactions reported in post-marketing use of alpha$_1$-proteinase inhibitor (Human) products.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Two separate clinical studies were conducted with Prolastin-C: Study 11815, a 20 week, open-label, safety study in 38 subjects, and Study 11816, a 16 week, randomized, double-blind, cross-over pharmacokinetic comparability study vs. Prolastin® (original product) in 24 subjects, followed by an 8 week open label treatment with Prolastin-C.

Table 3: Adverse Event Frequency as a % of all infusions (> 0.5%) *Irrespective of Causality*

	Prolastin-C No. of infusions: 1132	**Prolastin** No. of infusions: 192
Adverse Event	No. of AE (percentage of all infusions)	No. of AE (percentage of all infusions)
Upper respiratory tract infection	9 (0.8%)	1 (0.5%)
Urinary tract infection	8 (0.7%)	0
Nausea	7 (0.6%)	0
Headache	4 (0.4%)	3 (1.6%)
Arthralgia	2 (0.2%)	2 (1.0%)

Source: studies 11815 and 11816

Table 4: Adverse Reactions Occurring during the First 8 Weeks of Each Double-Blinded Treatment

	Prolastin-C (N=24)	**Prolastin®** (N=24)
Adverse Reaction*,†	No. of Subjects with Adverse Reaction (percentage of all subjects)	No. of Subjects with Adverse Reaction (percentage of all subjects)
Pruritus	1 (4)	0

* An adverse reaction is defined as any treatment-emergent adverse event that was considered drug "potentially related" to the investigational product.

† Source: 11816 study.

Table 5: Adverse Reaction Frequency as a Percent of All Infusions during the First 8 Weeks of Each Double-Blinded Treatment

Adverse Reaction*,†	**Prolastin-C** No. of infusions: 188 No. of Adverse Reaction (percentage of all infusions)	**Prolastin** No. of infusions: 192 No. of Adverse Reaction (percentage of all infusions)
Pruritus	1 (0.5)	0

* An adverse reaction is defined as any treatment-emergent adverse event that was considered drug "potentially related" to the investigational product.

† Source: 11816 study.

Table 6: Adverse Reactions Occurring in Two or More Subjects (>5%) during the 20 Week Single-Arm Open-Label Trial

Adverse Reaction*,†	**Prolastin-C** (N=38) No. of Subjects with Adverse Reaction (percentage of all subjects)
Chills	2 (5)

* An adverse reaction is defined as any treatment-emergent adverse event that was considered drug "potentially related" to the investigational product.

† Source: 11815 study.

The most common drug related adverse event was chills, which occurred in 3.2% of Prolastin-C patients across both studies (n=2). The following drug related adverse events were reported in 1.6% of patients (one subject each) treated with Prolastin-C: malaise, headache, rash (severe), hot flush, and pruritus.

In clinical studies with the original product, Prolastin®, six reactions were observed with 517 infusions, or 1.16%. None of the reactions was severe. The adverse reactions reported included delayed fever (maximum temperature rise was 38.9°C, resolving spontaneously over 24 hours) occurring up to 12 hours following treatment (0.77%), light-headedness (0.19%), and dizziness (0.19%). Mild transient leukocytosis and dilutional anemia several hours after infusion have also been noted.

8.5 Post-Market Adverse Reactions

Additionally, since market entry of Alpha$_1$-Proteinase Inhibitor (Human), occasional reports of the following events have been received: flu-like symptoms, allergic-like reactions, dyspnea, tachycardia, shortness of breath, bronchospasm, wheezing, urticaria, back pain, clamminess, sweating, diarrhea, and fatigue.

Less frequently, the following have also been reported: hypotension, anxiety, cyanosis, swelling of hands and feet, angio-, facial and lip edema, nasal congestion, sinusitis, abdominal pains or cramps, pallor, and weakness.

Rare cases of hypersensitivity reactions, transient increase in blood pressure or hypertension and chest pain have also been reported.

Very rare cases of anaphylactic/anaphylactoid reactions have also been reported.

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Alpha$_1$-antitrypsin deficiency is a chronic, hereditary, usually fatal, autosomal co-dominant disorder in which a low concentration of alpha$_1$-PI (alpha$_1$-antitrypsin)[1] is associated with slowly progressive severe emphysema that most often manifests itself in the third to fourth decades of life. The emphysema is typically worse in the lower lung zones. The pathogenesis of development of emphysema in alpha$_1$-antitrypsin deficiency is not well understood at this time. It is believed, however, to be due to a chronic biochemical imbalance between elastase (an enzyme capable of degrading elastin tissues, released by inflammatory cells, primarily neutrophils, in the lower respiratory tract) and alpha$_1$-PI (the principal inhibitor of neutrophil elastase), which is deficient in alpha$_1$-antitrypsin disease. As a result, it is believed that alveolar structures are unprotected from chronic exposure to elastase released from a chronic, low-level burden of neutrophils in the lower respiratory tract, resulting in progressive degradation of elastin tissues. The eventual outcome is the development of emphysema. Neonatal hepatitis with cholestatic jaundice appears in approximately 10% of newborns with alpha$_1$-antitrypsin deficiency. In some adults, alpha$_1$-antitrypsin deficiency is complicated by cirrhosis. Since severe alpha$_1$-antitrypsin deficiency is one of the most common serious genetic conditions, it is

[1] Although the terms "Alpha$_1$-Proteinase Inhibitor" and "alpha$_1$-antitrypsin" are used interchangeably in the scientific literature, the hereditary disorder associated with a reduction in the serum level of alpha$_1$-PI is conventionally referred to as "alpha$_1$-antitrypsin deficiency" while the deficient protein is referred to as “Alpha$_1$-Proteinase Inhibitor”.

recommended that families of index cases also be screened for deficiency of the alpha$_1$-PI protein.

A large number of phenotypic variants of alpha$_1$-antitrypsin deficiency exists. The most severely affected individuals are those with the PiZZ variant, typically characterized by alpha$_1$-PI serum levels <35% normal. Epidemiologic studies of individuals with various phenotypes of alpha$_1$-antitrypsin deficiency have demonstrated that individuals with endogenous serum levels of alpha$_1$-PI ≤50 mg/dL (based on commercial standards) have a risk of >80% of developing emphysema over a lifetime. However, individuals with endogenous alpha$_1$-PI levels >80 mg/dL, in general, do not manifest an increased risk for development of emphysema above the general population background risk. From these observations, it is believed that the “threshold” level of alpha$_1$-PI in the serum required to provide adequate anti-elastase activity in the lung of individuals with alpha$_1$-antitrypsin deficiency is about 80 mg/dL (11 µM), based on commercial standards for immunologic assay of alpha$_1$-PI. The maintenance of blood serum levels of alpha$_1$-PI above 80 mg/dL (11 µM) is historically thought to provide therapeutically relevant anti-neutrophil elastase protection.

10.2 Pharmacodynamics

In clinical studies, patients received Alpha$_1$-Proteinase Inhibitor (Human) replacement therapy, 60 mg/kg body weight, once weekly for up to 26 weeks (average 24 weeks of therapy). With this schedule of replacement therapy, blood levels of alpha$_1$-PI were maintained above 80 mg/dL (based on the commercial standards for alpha$_1$-PI immunologic assay).

No drug attributable pharmacodynamic changes were observed in any of the clinical studies to date. Increased anti-neutrophil elastase activity is achieved in both serum and ELF following intravenous administration. Development of antibodies directed against alpha$_1$-PI has not been reported in any of the studies. Similarly, transmission of viral disease has not been seen.

10.3 Pharmacokinetics

In clinical studies, the mean *in vivo* recovery of alpha$_1$-PI was 4.2 mg (immunologic)/dL per mg (functional)/kg body weight administered. The half-life of alpha$_1$-PI *in vivo* was approximately 6 days.

In another study, several individuals with the PiZ phenotype of alpha$_1$-antitrypsin deficiency were treated with a partially purified preparation of alpha$_1$-PI. Using this material, five adults with severe serum alpha$_1$-antitrypsin deficiency (PiZ phenotype) and advanced emphysema received 4 grams of Alpha$_1$-Proteinase Inhibitor (Human), intravenously, at weekly intervals for four doses. During this period of weekly replacement therapy alpha$_1$-PI serum levels were maintained at ≥70 mg/dL, the level likely required for effective anti-elastase protection of the lung.

In a subsequent study, nineteen subjects with alpha$_1$-antitrypsin deficiency received Prolastin (the original formulation), intravenously 60 mg/kg body weight, once weekly for up to 26 weeks (average 24 weeks of therapy). With this schedule of replacement therapy, blood levels of alpha$_1$-PI were maintained above 80 mg/dL (see CLINICAL TRIALS).

A further study evaluated an intravenous dosage of 250 mg/kg of alpha$_1$-PI (Prolastin) administered every 28 days in an attempt to assess whether the intervals between dosing could be increased beyond one week, while still retaining protective anti-neutrophil elastase alpha$_1$-PI levels in the serum and the epithelial lining fluid (ELF). Nine subjects were included. Analysis of the repeated dosage data indicated that overall, the serum alpha$_1$-PI levels fell to below 80 mg/dL at about 18-21 days after the administration of the 250 mg/kg Prolastin

dosage, reaching a nadir of about 50 mg/dL at 28 days. A serum level of 70 to 80 mg alpha$_1$-PI/dL equates to a pulmonary alveolar ELF level of 1.2 µmol. This is the ELF level which is considered protective against elastase activity in the normal subject.

11 STORAGE, STABILITY AND DISPOSAL

Prolastin-C should be stored at temperatures not to exceed 25°C. Freezing should be avoided as breakage of the diluent vial might occur. Administer within 3 hours after reconstitution.

12 SPECIAL HANDLING INSTRUCTIONS

None

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Alpha$_1$-Proteinase Inhibitor (Human)

Chemical name: α1-antitrypsin [CAS 9041-92-3]

Molecular formula: 394 amino acid sequence (see below)

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1    EDPQGDAAQKTDTSHHDQDHPTFNKITPNLAEFAFSLYRQLAHQSNSTNI
51   FFSPVSIATAFAMLSLGTKADTHDEILEGLNFNLTEIPEAQIHEGFQELL
101  RTLNQPDSQLQLTTGNGLFLSEGLKLVDKFLEDVKKLYHSEAFTVNFGDT
151  EEAKKQINDYVEKGTQGKIVDLVKELDRDTVFALVNYIFFKGKWERPFEV
201  KDTEEEDFHVDQVTTVKVPMMKRLGMFNIQHCKKLSSWVLLMKYLGNATA
251  IFFLPDEGKLQHLENELTHDIITKFLENEDRRSASLHLPKLSITGTYDLK
301  SVLGQLGITKVFSNGADLSGVTEEAPLKLSKAVHKAVLTIDEKGTEAAGA
351  MFLEAIPMSIPPEVKFNKPFVFLMIEQNTKSPLFMG KVVNPTQK
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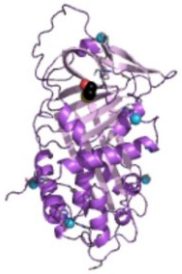
Molecular mass: 51 000 Daltons

Structural formula: 3D Structure of uncleaved Alpha$_1$ Protease Inhibitor (Alpha$_1$-PI)



Physicochemical properties: isoelectric point of 4.4 to 4.8; functions by forming a tight complex with target proteases; glycoprotein (12% carbohydrate) with 3 N-asparagine linked chains which are externally exposed and cover the surface of the protein

Product Characteristics:

Prolastin-C is prepared from pooled human plasma of normal donors by modification and refinements of the cold ethanol plasma fractionation method first described by Cohn. Alpha$_1$-proteinase inhibitor (Human) is obtained from Fraction IV-1 paste, which undergoes several purification steps, including the viral inactivation steps discussed below. The specific activity of Prolastin-C is ≥0.7 mg functional alpha$_1$-PI per mg total protein, and when reconstituted as directed, the concentration of alpha$_1$-PI is ≥ 40 mg/mL. When reconstituted, Prolastin-C has a pH of 6.6-7.4, a sodium content of 100-210 mM, a chloride content of 60-180 mM, and a sodium phosphate content of 15-25 mM.

Each vial of Prolastin-C contains the labelled amount of functionally active alpha$_1$-PI in milligrams per vial (mg/vial), as determined by capacity to neutralize porcine pancreatic elastase. Prolastin-C contains no preservative and must be administered by the intravenous route.

Viral Inactivation

When medicinal biological products are administered, infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by epidemiological surveillance of the donor population and selection of individual donors by medical interview; testing of individual donations and plasma pools; and the presence in the manufacturing processes of steps with demonstrated capacity to inactivate/remove pathogens.

In the manufacturing process of Prolastin-C, there are several steps with the capacity for virus inactivation or removal. The main steps of the manufacturing process that contribute to the virus clearance capacity are as follows:

- Cold ethanol fractionation
- PEG precipitation
- Depth filtration
- Solvent Detergent treatment
- 15 nm Nanofiltration

Cold Ethanol Fractionation, PEG Precipitation, and Depth Filtration are important steps for purifying alpha$_1$-PI and they have a very high pathogen removal capacity. Two additional steps, Solvent/Detergent Treatment and 15 nm Nanofiltration, are included in the process as dedicated steps with pathogen clearance capacity. The Solvent/Detergent Treatment step can effectively inactivate enveloped viruses. The 15 nm Nanofiltration step has been implemented because of its high capacity to remove enveloped and non-enveloped viruses as small as 18 nm.

To provide additional assurance of the pathogen safety of the final product, the capacity of the Prolastin-C manufacturing process to remove and/or inactivate viruses has been demonstrated by laboratory spiking studies on a scaled down process model using a wide range of viruses with diverse physicochemical properties.

The combination of all of the above-mentioned measures provides the final product with a high margin of safety from the potential risk of transmission of infectious viruses.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the variant Creutzfeldt-Jakob disease (vCJD) and Creutzfeldt-Jakob disease (CJD) agents. These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed by the manufacturing process.

14 CLINICAL TRIALS

Studies described in this section have been conducted with either Prolastin or Prolastin-C. The original Alpha$_1$-Proteinase Inhibitor (Human), approved and marketed in Canada was Prolastin. This was replaced with Prolastin-C, which is produced through a modification of the Prolastin manufacturing process that results in improved product purity, a higher concentration of the same active substance, and a greater demonstrated margin of safety from the risk of transmission of infectious pathogens.

14.1 Trial Design and Study Demographics

Prolastin-C Studies

Prolastin-C has been studied in 62 individual subjects in 2 separate clinical trials. The first study was a randomized, double-blind, crossover trial comparing Prolastin-C to Prolastin (Study 11816). A total of 24 adult subjects with severe Alpha$_1$-antitrypsin deficiency were enrolled in the study, with 12 subjects randomized to each treatment sequence. All but one subject had the PiZZ genotype and the remaining subject had PiSZ. All subjects had received prior alpha$_1$-PI therapy Prolastin for at least 1 month. The primary pharmacokinetic endpoint was the $AUC_{0\text{-}7days}$ following 8 weeks of treatment with Prolastin-C or Prolastin.

Study subjects were randomly assigned to receive either 60 mg/kg body weight of functional Prolastin-C or Prolastin weekly by IV infusion during the first 8-week treatment period. Following the last dose in the first 8-week treatment period, subjects underwent PK serial sampling blood draws and then crossed over to the alternate treatment for the second 8-week treatment period. Following the last treatment in the second 8-week treatment period, subjects underwent serial PK blood sampling. In addition, blood samples were drawn for trough levels before infusion at Weeks, 6, 7, and 8, as well as before infusion at Weeks, 14, 15, and 16. In the 8-week open-label treatment phase that followed the crossover period, all subjects received 60 mg/kg body weight of functional Prolastin-C.

The second clinical trial was a multi-center, open-label safety study was conducted to evaluate the safety and tolerability of Prolastin-C (study 11815). In this study, 38 subjects were treated with weekly IV infusions of 60 mg/kg body weight of Prolastin-C for 20 weeks. Half the subjects were naïve to previous alpha$_1$-PI augmentation prior to study entry and the other half were receiving augmentation with Prolastin prior to entering the study. A diagnosis of severe Alpha$_1$-antitrypsin deficiency was confirmed by the demonstration of the PiZZ genotype in 32 of 38 (84.2%) subjects, and 6 of 38 (15.8%) subjects presented with other alleles known to result in severe Alpha$_1$-antitrypsin deficiency. These groups were distributed evenly between the naïve and non-naïve cohorts.

Prolastin Studies

In earlier clinical studies conducted with Prolastin (Alpha$_1$-Proteinase Inhibitor (Human)), 23 subjects with the PiZZ variant of congenital alpha$_1$-antitrypsin deficiency and documented destructive lung disease participated in a study of acute and/or chronic replacement therapy with Alpha$_1$-Proteinase Inhibitor (Human).

14.2 Study Results

Prolastin-C Studies

Results from the multi-center, open-label safety study conducted to evaluate the safety and tolerability of Prolastin-C (Study 11815) indicate that Prolastin-C is safe and well-tolerated.

Prolastin Studies

In 23 subjects with the PiZZ variant of congenital alpha$_1$-antitrypsin deficiency and documented destructive lung disease, the mean *in vivo* recovery of alpha$_1$-PI was 4.2 mg (immunologic)/dL per mg (functional)/kg body weight administered. The half-life of alpha$_1$-PI *in vivo* was approximately 4.5 days. Based on these observations, a program of chronic replacement therapy was developed. Nineteen of the subjects in these studies received Prolastin® replacement therapy, 60 mg/kg body weight, once weekly for up to 26 weeks (average 24 weeks of therapy). With this schedule of replacement therapy, blood levels of alpha$_1$-PI were maintained above 80 mg/dL (based on the commercial standards for alpha$_1$-PI immunologic assay). Within a few weeks of commencing this program, bronchoalveolar lavage studies demonstrated significantly increased levels of alpha$_1$-PI and functional antineutrophil elastase capacity in the epithelial lining fluid of the lower respiratory tract of the lung, as compared to levels prior to commencing the program of chronic replacement therapy with Alpha$_1$-Proteinase Inhibitor (Human).

All 23 individuals who participated in the investigations were immunized with Hepatitis B Vaccine and received a single dose of Hepatitis B Immune Globulin (Human) on entry into the investigation. Although no other steps were taken to prevent hepatitis, neither hepatitis B nor non-A, non-B hepatitis occurred in any of the subjects. All subjects remained seronegative for HIV antibody. None of the subjects developed any detectable antibody to alpha$_1$-PI or other serum protein.

Long-term controlled clinical trials to evaluate the effect of chronic replacement therapy with Alpha$_1$-Proteinase Inhibitor (Human) on the development of or progression of emphysema in patients with congenital alpha$_1$-antitrypsin deficiency have not been performed. Estimates of the sample size required of this rare disorder and the slow, progressive nature of the clinical course have been considered impediments in the ability to conduct such a trial. Studies to monitor the long-term effects have continued since the approval of Prolastin. Open-label assessments of patient registries, using untreated patients as controls, have evaluated the effects of long-term (up to 7 years) treatment with Alpha$_1$-Proteinase Inhibitor (Human) on patients with alpha$_1$ antitrypsin deficiency. The results of these assessments, while not as definitive as randomized, controlled trials, indicate that patients treated with Alpha$_1$-Proteinase

Inhibitor (Human) have significantly reduced mortality and significantly slowed decline in FEV1 compared to untreated patients with alpha1-antitrypsin deficiency.

14.3 Comparative Bioavailability Studies

In study 11816, the key pharmacokinetic parameters of alpha$_1$-PI in plasma, based on potency assays, showed comparability between Prolastin-C and Prolastin treatments, as shown in Table 7.

Table 7: Pharmacokinetic parameters of Alpha$_1$-PI in plasma (Study 11816)

Treatment	$AUC_{0\text{-}7days}$ (hr*mg/mL) Mean (%CV)	C_{max} (mg/mL) Mean (%CV)	t_{max} or Adj t_{max} (hr) Median (Range)	$t_{1/2}$ (hr) Mean (%CV)
Prolastin-C (n=22 or 23)	155.9 (17%)	1.797 (10%)	0.673 (0.23-2.59)	146.3 (16%)
Prolastin (n=22 or 23)	152.4 (16%)	1.848 (15%)	0.820 (0.25-2.90)	139.3 (18%)

The geometric least-squares mean ratio for Prolastin-C vs. Prolastin was 1.03, with a 90% confidence interval of 0.97-1.09. A ratio so close to 1.0 indicates a high degree of concordance between treatments. Figure 2 shows the concentration vs. time curves of alpha$_1$-PI after intravenous administration of Prolastin-C and Prolastin.

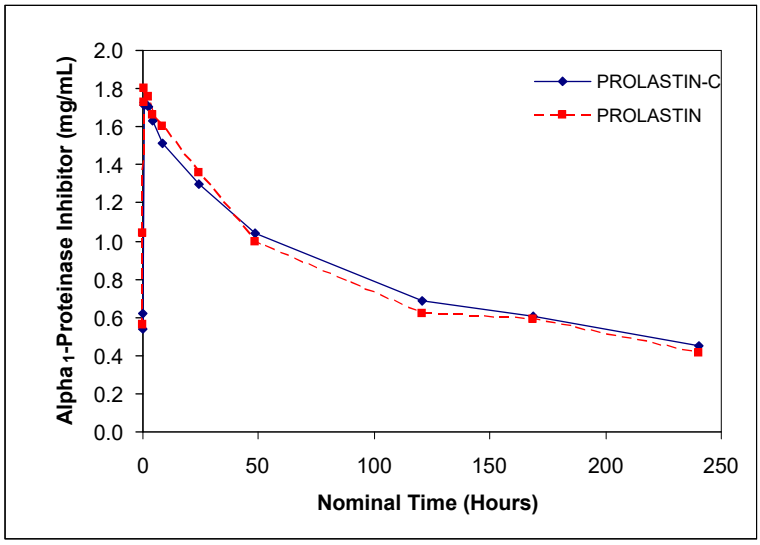


Figure 2: Mean Plasma Alpha$_1$-PI Concentration vs. Time Curves Following Treatment with Prolastin-C or Prolastin (study 11816)

Trough levels measured during the pharmacokinetic study via a content assay showed Prolastin-C treatment resulted in a mean trough of 16.9 µM with a coefficient of variation of 14%. All subjects (100%) maintained alpha$_1$-PI plasma levels above 11 µM with both Prolastin-C and Prolastin.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Single-doseToxicity

The acute toxicity of alpha$_1$-PI administered intravenously, was determined in mice, rats, and rabbits and compared to the acute toxicity of the excipient control substance. At an infusion rate of 3 mL/min, the LD_{50} of alpha$_1$-PI in mice was 3,750 mg/kg bw (150±6 mL/kg) and that of the control was >156 mL/kg. In rabbits, there was no indication of any toxicity at the highest dose of alpha$_1$-PI tested, 517 mg/kg bw (20.7 mL/kg), which was infused at a rate of 6 mL/min although one of three rabbits each in the groups receiving 172 mg/kg bw and 517 mg/kg bw, respectively, of alpha$_1$-PI died during the observation period. These two deaths were not related to administration of alpha$_1$-PI. An additional three rabbits were administered alpha$_1$-PI at a dose of 517 mg/kg bw without any sign of adverse effect throughout the 14-day observation period.

Repeat-dose Toxicity

A series of rabbits also received alpha$_1$-PI or excipient control substance, 227 mg/kg bw (9.1 mL/kg)), administered intravenously at a rate of 6 mL/min, daily on five successive days. All rabbits in the study gained weight and there were no significant differences in weight gain on the 6th day or 33rd day of the study between animals receiving alpha$_1$-PI compared to those receiving control substance. No significant hematologic abnormalities were noted on the 6th or 33rd days of the study following five consecutive days of administration of alpha$_1$-PI. An unexplained decrease in the cholesterol level of animals receiving alpha$_1$-PI was seen on day six in one series of animals but was not seen when repeated in another group. Two rabbits died during the course of the study, both of which were receiving alpha$_1$-PI. One rabbit died on day 4, with diarrhea present, and its death was felt to be related to infection. The other rabbit died on day 27 (three weeks after the infusion period) and histopathology revealed no probable cause of death. Overall, no effects directly ascribable to administration of alpha$_1$-PI were detected in animals undergoing necropsy and histopathologic analysis on days 6 or 33 of the study.

No studies were performed regarding subchronic or chronic toxicity.

Genotoxicity: No studies were performed regarding genotoxicity

Reproductive and Developmental Toxicology:

No studies were performed regarding reproductive toxicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PROLASTIN®-C

(Alpha$_1$-Proteinase Inhibitor (Human))

Read this carefully before you start taking Prolastin-C and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Prolastin-C.

What is Prolastin-C used for?

Alpha$_1$ Antitrypsin Deficiency, also known as Alpha$_1$, is an inherited disorder that causes significant reduction in the naturally occurring protein alpha$_1$ antitrypsin (AAT).

Scientists also call this protein Alpha$_1$-Proteinase Inhibitor (alpha$_1$-PI) because it inhibits not only trypsin but also other enzymes called proteinases.

It is believed that Alpha$_1$ affects as many as 100,000 people in the United States and similar numbers in Europe. Alpha$_1$ is most common among Caucasians of Northern European and Iberian descent. It is the most common cause of genetic liver disease in children and genetic emphysema in adults.

Lung disease (emphysema) is the most common problem associated with a deficiency of AAT. AAT is produced by the liver and shields the body from damage caused by neutrophil elastase. Neutrophil elastase is an enzyme produced by white blood cells.

Under normal conditions, neutrophil elastase helps fight bacteria that cause infection. However, if not neutralized by AAT, neutrophil elastase can destroy healthy lung tissue.

Alveoli are tiny air sacs in the lungs, which are responsible for taking in oxygen and releasing carbon dioxide. When adequate levels of AAT are not present, the enzymatic activity of neutrophil elastase is not blocked and the fine elastic tissue supporting the alveoli is destroyed. Over time, enough alveoli are destroyed to cause the lungs to lose much of their elasticity, resulting in emphysema. Therefore, people with a deficiency of AAT are at high risk for developing emphysema.

There are many components to treating AAT. The goal is to maintain better lung function. This can be done through smoking cessation, asthma medications (if necessary), infection control, good nutrition, environment modifications, exercise, and stress management.

Prolastin-C is a treatment that helps restore the natural balance of enzymes in the lungs and protects them from the damage caused by neutrophil elastase.

How does Prolastin-C work?

Prolastin-C, made from human plasma, is a concentrated form of AAT. Given as prescribed, Prolastin-C raises the blood and lung levels of AAT. This may help lessen damage to the lungs caused by the enzymatic activity of neutrophil elastase. Because Prolastin-C therapy augments or replaces AAT, it is known as "augmentation" or "replacement" therapy.

What are the ingredients in Prolastin-C?

Medicinal ingredients: Human alpha$_1$-proteinase inhibitor

Non-medicinal ingredients: sodium, chloride, and sodium phosphate

Prolastin-C comes in the following dosage forms:

single use vials with a functional activity of 1000 mg. An appropriate amount of Sterile Water for Injection, USP is also provided to dilute Prolastin-C.

Do not use Prolastin-C if:

- you are allergic to alpha$_1$-proteinase inhibitor or to any ingredient in the formulation or component of the container.
- your body does not make enough immunoglobulin A (IgA), which could cause you to have an allergic reaction to blood products that contain IgA.
- you have previously had an allergic reaction to any alpha$_1$-proteinase inhibitor product.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Prolastin-C. Talk about any health conditions or problems you may have, including if you:

- are pregnant or breastfeeding
- have had an allergic reaction to alpha$_1$-proteinase inhibitor or any of the other ingredients in the medicine

Other warnings you should know about:

Prolastin-C like other products made from human plasma, part of our blood, may contain viruses or other agents that can cause infection and illness. However, the processes used to make Prolastin-C are specifically designed with the ability to destroy or remove these agents if they are present. You should discuss the risks and benefits of this product with your healthcare professional.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Prolastin-C:

A doctor, nurse or other caregiver trained to give injections will give your treatment. If you are receiving Prolastin-C infusions at home, rather than a hospital or clinic, be sure to closely follow all instructions from your doctor.

Usual dose:

Your doctor will determine the amount of Prolastin-C that is right for you and when your treatments should be given.

Overdose:

There have been no reported cases of overdose for Prolastin-C or other Alpha$_1$ Proteinase Inhibitor (Human) products manufactured by Grifols. The effects of an overdose are not known.

If you think you, or a person you are caring for, have taken too much Prolastin-C, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

It is important that you receive Prolastin-C as instructed by your healthcare professional. You should consult him/her if a treatment is missed.

What are possible side effects from using Prolastin-C?

These are not all the possible side effects you may have when taking Prolastin-C. If you experience any side effects not listed here, tell your healthcare professional.

Prolastin-C is well tolerated, but side effects are occasionally reported. The most common side effects were diarrhea and fatigue, each of which occurred in 6% of subjects enrolled in clinical studies. Talk with your healthcare provider if you have the following side effects following treatment: fever, light-headedness, dizziness, flu-like symptoms, allergic-like reactions, chills, trouble breathing, rash, abnormal heartbeat, changes in blood pressure, or chest pain.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Severe allergic reaction (e.g. rash, hives, itching, difficulty breathing or swallowing, swelling of hands, face or mouth)		√	√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Prolastin-C should be stored at temperatures not to exceed 25°C. It should not be frozen. Administer within 3 hours after reconstitution.

Keep out of reach and sight of children.

If you want more information about Prolastin-C:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling 1-866-482-5226.

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