

PRODUCT MONOGRAPH

PROLASTIN[®]-C

Alpha₁-Proteinase Inhibitor (Human), Highly Purified

IV Injection, 1000 mg/vial

Alpha₁-Antitrypsin Replenisher

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PROLASTIN[®]-C

Alpha₁-Proteinase Inhibitor (Human), Highly Purified

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Table 1 – Product Information Summary

| Route of Administration | Dosage Form, Strength | Clinically Relevant Nonmedicinal Ingredients |
|--------------------------------|---|--|
| intravenous injection | lyophilized powder for reconstitution and injection 1000 mg/vial | <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i> |

DESCRIPTION

PROLASTIN[®]-C (Alpha₁-Proteinase Inhibitor [Human]) is a sterile, stable, lyophilized preparation of highly purified human Alpha₁-Proteinase Inhibitor (alpha₁-PI), also known as alpha₁-antitrypsin. Alpha₁-Proteinase Inhibitor (Human) is intended for use in therapy of congenital alpha₁-antitrypsin deficiency.

PROLASTIN[®]-C is prepared from pooled human plasma of normal donors by modification and refinements of the cold ethanol method of Cohn (1). 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, alpha₁-PI, in the reconstituted product.

INDICATIONS AND CLINICAL USE

Congenital Alpha₁-Antitrypsin Deficiency

PROLASTIN[®]-C is indicated for chronic replacement therapy of individuals having congenital deficiency of alpha₁-PI (alpha₁-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 alpha₁-PI, and that levels of functionally active alpha₁-PI in the lung epithelial lining fluid are increased proportionately (2-4). As some individuals with alpha₁-antitrypsin deficiency will not go on to develop emphysema, only those with evidence of such disease should be considered for chronic replacement therapy with Alpha₁-Proteinase Inhibitor (Human) (5). Subjects with the PiMZ or PiMS phenotypes of alpha₁-antitrypsin deficiency should not be considered for such treatment as they appear to be at small risk for

emphysema (5). Clinical data are not available as to the long-term effects derived from chronic replacement therapy of individuals with alpha₁-antitrypsin deficiency with Alpha₁-Proteinase Inhibitor (Human). Only adult subjects have received Alpha₁-Proteinase Inhibitor (Human) to date.

CONTRAINDICATIONS

- PROLASTIN[®]-C should not be given to patients who are hypersensitive to Alpha₁-Proteinase Inhibitor (Human) or to any ingredient in the formulation or component of the container. For a complete listing, see the [DOSAGE FORMS, COMPOSITION AND PACKAGING](#) section.
- PROLASTIN[®]-C should not be given to individuals with selective immunoglobulin A (IgA) deficiencies, since these patients may experience severe reactions, including anaphylaxis, to IgA which may be present.

WARNINGS AND PRECAUTIONS

General

Because this product is made from human blood, it may carry the risk of transmitting infectious agents, e.g. viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent or Creutzfeldt-Jakob Disease variant (vCJD) 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 disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. 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 Alpha₁-Proteinase Inhibitor (Human) (2). 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.

Place needles in sharps container after single use. Discard all equipment including any reconstituted PROLASTIN[®]-C product in accordance with biohazard procedures.

Carcinogenesis and Mutagenesis

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

Sexual Function/Reproduction

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

Special Populations

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.

Nursing Mothers

It is not known whether Alpha₁-Proteinase Inhibitor (Human) 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.

Pediatrics

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Therapeutic administration of PROLASTIN[®]-C 60 mg/kg weekly, has been demonstrated to be well-tolerated.

Clinical Trial Adverse Drug 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. Thus, 62 subjects were exposed to PROLASTIN[®]-C in clinical trials, receiving a total of 1132 infusions.

**Table 2: 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

The most common drug related adverse event was chills, which occurred in 3.2% of PROLASTIN[®]-C patients (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 Prolastin[®], six reactions were observed with 517 infusions of Alpha₁-Proteinase Inhibitor (Human), 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.

Post-Market Adverse Drug 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 transient increase in blood pressure or hypertension and chest pain have also been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

No drug-drug interactions are known.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

Each vial of PROLASTIN[®]-C (Alpha₁ Proteinase Inhibitor [Human]), has the functional activity, as determined by inhibition of porcine pancreatic elastase (1), stated on the label of the vial.

The “threshold” level of alpha₁-PI in the serum believed to provide adequate anti-elastase activity in the lung of individuals with alpha₁-antitrypsin deficiency is 80 mg/dL (based on commercial standards for alpha₁-PI immunologic assay) (6-8). However, assays of alpha₁-PI based on commercial standards measure antigenic activity of alpha₁-PI, whereas the labeled potency value of alpha₁-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 alpha₁-PI determined using commercial immunologic assays may not accurately reflect actual functional alpha₁-PI levels.

Therefore, although it may be helpful to monitor serum levels of alpha₁-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.

The recommended dosage of PROLASTIN[®]-C is 60 mg/kg body weight administered once weekly. This dose is intended to increase and maintain a level of functional alpha₁-PI in the epithelial lining of the lower respiratory tract, providing adequate anti-elastase activity in the lung of individuals with alpha₁-antitrypsin deficiency.

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.

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.

Reconstituted PROLASTIN[®]-C should be given alone, without mixing with other agents or diluting solutions.

Reconstitution

PROLASTIN[®]-C should be reconstituted with Sterile Water for Injection, USP (see [Table 3](#)). 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 3 – Reconstitution of PROLASTIN[®]-C

| Approximate Alpha ₁ -PI Functional Activity | Volume of Diluent Provided (To be Added to Vial) |
|--|---|
| 1000 mg | 20 mL |

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

Vacuum Transfer

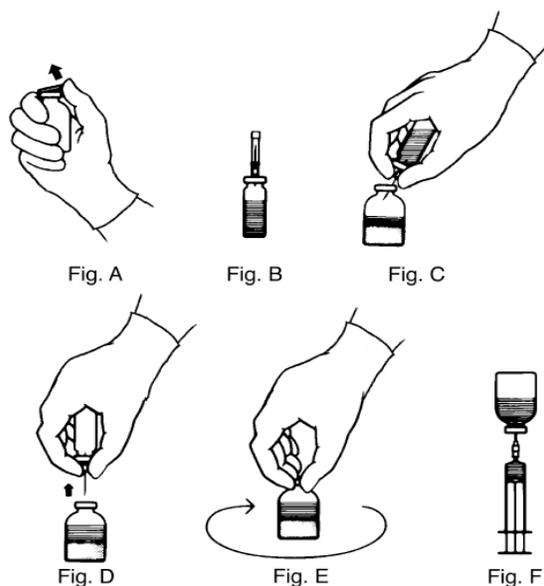
Aseptic technique should be followed.

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



OVERDOSAGE

To date, there have been no reported cases of overdose for PROLASTIN®-C or other Alpha₁ Proteinase Inhibitor (Human) manufactured by Grifols. No data are available in regard to overdose in humans.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Alpha₁-antitrypsin deficiency is a chronic, hereditary, usually fatal, autosomal co-dominant disorder in which a low concentration of alpha₁-PI (alpha₁-antitrypsin)^{*} is associated with slowly progressive severe emphysema that most often manifests itself in the third to fourth decades of

^{*} Although the terms "Alpha₁-Proteinase Inhibitor" and "alpha₁-antitrypsin" are used interchangeably in the scientific literature, the hereditary disorder associated with a reduction in the serum level of alpha₁-PI is conventionally referred to as "alpha₁-antitrypsin deficiency" while the deficient protein is referred to as "Alpha₁-Proteinase Inhibitor" (9).

life (10-17). The emphysema is typically worse in the lower lung zones (12,14,17). The pathogenesis of development of emphysema in alpha₁-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 alpha₁-PI (the principal inhibitor of neutrophil elastase), which is deficient in alpha₁-antitrypsin disease (7,18-21, 28). 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 (7,18-21). The eventual outcome is the development of emphysema. Neonatal hepatitis with cholestatic jaundice appears in approximately 10% of newborns with alpha₁-antitrypsin deficiency (19). In some adults, alpha₁-antitrypsin deficiency is complicated by cirrhosis (19). Since severe alpha₁-PI deficiency is one of the most common serious genetic conditions (26), it is recommended that families of index cases also be screened for alpha₁-PI deficiency (27).

A large number of phenotypic variants of alpha₁-antitrypsin deficiency exists (19). The most severely affected individuals are those with the PiZZ variant, typically characterized by alpha₁-PI serum levels <35% normal (19). Epidemiologic studies of individuals with various phenotypes of alpha₁-antitrypsin deficiency have demonstrated that individuals with endogenous serum levels of alpha₁-PI ≤50 mg/dL (based on commercial standards) have a risk of >80% of developing emphysema over a lifetime (11-14,16,17,22). However, individuals with endogenous alpha₁-PI levels >80 mg/dL, in general, do not manifest an increased risk for development of emphysema above the general population background risk (6,13). From these observations, it is believed that the “threshold” level of alpha₁-PI in the serum required to provide adequate anti-elastase activity in the lung of individuals with alpha₁-antitrypsin deficiency is about 80 mg/dL (11 μM), based on commercial standards for immunologic assay of alpha₁-PI (6-8). The maintenance of blood serum levels of alpha₁-PI above 80 mg/dL (11 μM) is historically thought to provide therapeutically relevant anti-neutrophil elastase protection (25, 27).

Pharmacokinetics

In clinical studies, the mean in vivo recovery of alpha₁-PI was 4.2 mg (immunologic)/dL per mg (functional)/kg body weight administered (4). The half-life of alpha₁-PI in vivo was approximately 6 days (See [ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics](#)).

Pharmacodynamics

In clinical studies, patients received Alpha₁-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 alpha₁-PI were maintained above 80 mg/dL (based on the commercial standards for alpha₁-PI immunologic assay) (3,4).

Duration of Effect

See [ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics](#).

STORAGE AND STABILITY

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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PROLASTIN[®]-C is supplied as a sterile, white to beige, lyophilized powder in single use vials with the total alpha₁-PI functional activity, in milligrams, stated on the label of each vial (Approximate functional activity of 1000 mg per vial; see [Table 3](#)).

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Brand name: PROLASTIN[®]-C
Proper name: Alpha₁-Proteinase Inhibitor (Human)

Product Characteristics

The specific activity of Alpha₁-Proteinase Inhibitor (Human) is ≥ 0.7 mg functional alpha₁-PI per mg total protein. and when reconstituted as directed, the concentration of alpha₁-PI is ≥ 40 mg/mL. When reconstituted, Alpha₁-Proteinase Inhibitor (Human) 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 alpha₁-PI in milligrams per vial (mg/vial), as determined by capacity to neutralize porcine pancreatic elastase (1). Alpha₁-Proteinase Inhibitor (Human) contains no preservative and must be administered by the intravenous route.

Viral Inactivation / Removal

In order to reduce the potential risk of transmission of infectious agents, PROLASTIN[®]-C is manufactured using a number of viral inactivation and removal steps. Although no procedure has been found to be totally effective in removing viral infectivity from plasma fractionation products, there has never been a confirmed case of viral transmission with PROLASTIN[®]-C or its predecessor, Prolastin[®].

The PROLASTIN[®]-C manufacturing process has several steps (Cold Ethanol Fractionation, PEG Precipitation, and Depth Filtration) that are important for purifying alpha₁-PI as well as removing potential virus contaminants. Two additional steps, Solvent/Detergent Treatment and 15 nm Virus Removal Nanofiltration, are included in the process as dedicated pathogen reduction steps. The Solvent/Detergent Treatment step effectively inactivates enveloped viruses (such as HIV-1, VSV, HBV, and HCV). The 15 nm Virus Removal Nanofiltration step has been implemented to reduce the risk of transmission of enveloped and non-enveloped viruses as small as 18 nm. The table below presents the virus reduction capacity of each process step and the accumulated virus reduction for the process as determined using in vitro viral validation studies in which virus was deliberately added to a process model in order to study virus reduction. In addition, the Solvent/Detergent Treatment step inactivates $\geq 5.4 \log_{10}$ of West Nile virus, a

clinically relevant enveloped virus. Studies have demonstrated that each step provides robust virus reduction across the production range for key operating parameters (see Table 4).

Table 4: Virus reduction (Log₁₀) for the Prolastin[®]-C manufacturing process

| Process Step | Enveloped Viruses | | | | Non-enveloped Viruses | | |
|------------------------------------|-------------------|--------|--------|-----------------|-----------------------|--------|--------|
| | HIV-1 | BVDV | PRV | VSV | Reo3 | HAV | PPV |
| Cold Ethanol Fractionation | 3.4 | 3.5 | 3.9 | ND [†] | ≥ 2.1 | 1.4 | 1.0 |
| PEG Precipitation | 4.3 | 2.8 | 3.3 | ND | 3.3 | 3.0 | 3.2 |
| Depth Filtration | ≥ 4.7 | 4.0 | ≥ 4.8 | ND | ≥ 4.0 | ≥ 2.8 | ≥ 4.4 |
| Solvent/Detergent Treatment | ≥ 6.2 | ≥ 4.6 | ≥ 4.3 | 5.1 | NA ^{††} | NA | NA |
| 15 nm Virus Removal Nanofiltration | ≥ 6.9 | ≥ 4.7 | ≥ 5.2 | ≥ 5.1 | ≥ 4.3 | ≥ 5.5 | 4.2 |
| Accumulated Virus Reduction | ≥ 25.5 | ≥ 19.6 | ≥ 21.5 | ≥ 10.2 | ≥ 13.7 | ≥ 12.7 | ≥ 12.8 |

[†] Not determined. VSV inactivation and/or removal was only determined for the Solvent/Detergent Treatment and 15 nm Virus Removal Nanofiltration steps.

^{††} Not applicable. This step is only effective against enveloped viruses.

HIV-1= Human Immunodeficiency Virus, type I; BVDV= Bovine Viral Diarrhea Virus; PRV= Pseudorabies Virus; VSV= Vesicular Stomatitis Virus; Reo3= Reovirus type 3; HAV= Human Hepatitis A Virus; PPV= Porcine Parvovirus

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. Studies of the PROLASTIN[®]-C manufacturing process demonstrate that a minimum of 6 log₁₀ reduction of TSE infectivity is achieved. These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

CLINICAL TRIALS

Studies described in this section have been conducted with either Prolastin[®] or Prolastin[®]-C. The original Alpha₁-Proteinase Inhibitor (Human), approved and marketed in Canada was Prolastin[®]. This has now been 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.

Study 11816: Pharmacokinetic Study

This pharmacokinetic study was a randomized, double-blind, crossover trial comparing PROLASTIN[®]-C to Prolastin[®]. A total of 24 adult subjects with severe AAT 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 alpha1-PI therapy Prolastin[®] for at least 1 month

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 key pharmacokinetic parameters of alpha₁-PI in plasma, based on potency assays, showed comparability between PROLASTIN[®]-C and Prolastin[®] treatments, as shown in Table 5.

Table 5: Pharmacokinetic parameters of Alpha₁-PI in plasma

| Treatment | AUC _{0-7days} | C _{max} | t _{max} or Adj t _{max} | t _{1/2} |
|---|--------------------------|-----------------------|--|--------------------|
| | (hr*mg/mL) Mean (%CV) | (mg/mL) Mean (%CV) | (hr) Median (Range) | (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 primary pharmacokinetic endpoint was the AUC_{0-7days} following 8 weeks of treatment with PROLASTIN[®]-C or Prolastin[®]. 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 1 shows the concentration vs. time curves of alpha1-PI after intravenous administration of PROLASTIN[®]-C and Prolastin[®].

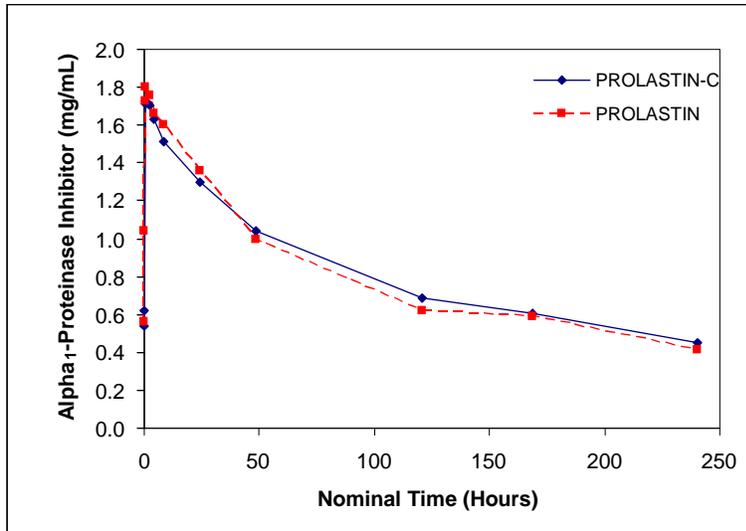


Figure 1: Mean Plasma Alpha1-PI Concentration vs. Time Curves Following Treatment with PROLASTIN[®]-C or Prolastin[®]

Trough levels measured during the pharmacokinetic study via a content assay showed PROLASTIN[®]-C treatment resulted in a mean trough of 16.9 μ M with a coefficient of variation of 14%. All subjects (100%) maintained alpha₁-PI plasma levels above 11 μ M with both PROLASTIN[®]-C and Prolastin[®].

Study 11815: Safety Study

This multi-center, open-label safety study was conducted to evaluate the safety and tolerability of PROLASTIN[®]-C. 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 alpha₁-PI augmentation prior to study entry and the other half were receiving augmentation with Prolastin[®] prior to entering the study. A diagnosis of severe AAT 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 AAT deficiency. These groups were distributed evenly between the naïve and non-naïve cohorts. Results from the study indicate that PROLASTIN[®]-C is safe and well-tolerated.

Prolastin[®] Studies

In earlier clinical studies conducted with Prolastin[®] (Alpha₁-Proteinase Inhibitor (Human)), 23 subjects with the PiZZ variant of congenital deficiency of alpha₁-antitrypsin deficiency and documented destructive lung disease participated in a study of acute and/or chronic replacement therapy with Alpha₁-Proteinase Inhibitor (Human). The mean in vivo recovery of alpha₁-PI was 4.2 mg (immunologic)/dL per mg (functional)/kg body weight administered (4). The half-life of alpha₁-PI in vivo was approximately 4.5 days (4). 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 alpha₁-PI were maintained above 80 mg/dL (based on the commercial standards for alpha₁-PI immunologic assay) (3,4). Within a few weeks of commencing this program, bronchoalveolar lavage studies demonstrated significantly increased levels of alpha₁-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 Alpha₁-Proteinase Inhibitor (Human) (3,4).

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 (4). All subjects remained seronegative for HIV antibody. None of the subjects developed any detectable antibody to alpha₁-PI or other serum protein.

Long-term controlled clinical trials to evaluate the effect of chronic replacement therapy with Alpha₁-Proteinase Inhibitor (Human) on the development of or progression of emphysema in patients with congenital alpha₁-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 (23). 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 Alpha₁-Proteinase Inhibitor (Human) on patients with alpha₁ antitrypsin deficiency. The results of these assessments, while not as definitive as randomized, controlled trials, indicate that patients treated with Alpha₁-Proteinase Inhibitor (Human) have significantly reduced mortality (29) and significantly slowed decline in FEV₁ (29, 30, 31) compared to untreated patients with alpha₁-antitrypsin deficiency.

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacokinetics

The half-life of alpha₁-PI administered intravenously in rabbits was determined to be 20.1 hours.

Pharmacodynamics

A series of studies was conducted in rats and rabbits to determine the effect of a single intravenous dose of alpha₁-PI, 100 mg/kg, infused rapidly, 8 mL (168 mg)/min in rats and 6 mL (126 mg)/min in rabbits, on a number of clinical and biochemical parameters. Rats were studied

both with and without an inhibitor of kininase II/angiotensin converting enzyme in order to potentiate any peptide-mediated cardiovascular effects which might be present. In rats, no significant cardiovascular or hematologic effects were observed, but a slight fall in fibrinogen 30 minutes following infusion of the alpha₁-PI was noted. In rabbits, a marginal fall in leukocytes was observed, but this proved to be not statistically significant. No significant hematologic changes were detected.

Human Pharmacology

Pharmacokinetics

Gadek et al have treated several individuals with the PiZ phenotype of alpha₁-antitrypsin deficiency with a partially purified preparation of alpha₁-PI (8). Using this material, five adults with severe serum alpha₁-antitrypsin deficiency (PiZ phenotype) and advanced emphysema received 4 grams of alpha₁-PI, intravenously, at weekly intervals for four doses. During this period of weekly replacement therapy alpha₁-PI serum levels were maintained at ≥70 mg/dL, the level likely required for effective antielastase protection of the lung (6,8,19).

In a subsequent study, nineteen subjects with alpha₁-antitrypsin deficiency received Prolastin[®], intravenously 60 mg/kg body weight, once weekly for up to 26 weeks (average 24 weeks of therapy) (4). With this schedule of replacement therapy, blood levels of alpha₁-PI were maintained above 80 mg/dL (see [CLINICAL TRIALS](#)).

A further study evaluated an intravenous dosage of 250 mg/kg of alpha₁-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 alpha₁-PI levels in the serum and the epithelial lining fluid (ELF) (24). Nine subjects were included. Analysis of the repeated dosage data indicated that overall, the serum alpha₁-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 alpha₁-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.

Pharmacodynamics

No drug attributable pharmacodynamic changes were observed in any of the clinical studies to date (4,24). As mentioned in the section on Pharmacokinetics, increased anti-neutrophil elastase activity is achieved in both serum and ELF following intravenous administration. Development of antibodies directed against alpha₁-PI has not been reported in any of the studies. Similarly transmission of viral disease has not been seen.

TOXICOLOGY

Animal Studies

Acute Toxicity

The acute toxicity of alpha₁-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 LD₅₀ of alpha₁-PI in mice was 150±6 mL/kg (3,750 mg/kg) and that of the control was >156 mL/kg. In rabbits, there was no indication of any toxicity at the highest dose of alpha₁-PI tested, 20.7 mL/kg, which was infused at a rate of 6 mL/kg (517 mg/kg) although one of three rabbits each in the groups receiving 6.9 mL and 20.7 mL/kg, respectively, of alpha₁-PI died during the observation period. These two deaths were not related to administration of alpha₁-PI. An additional three rabbits were administered alpha₁-PI at a dose of 20.7 mL/kg without any sign of adverse effect throughout the 14-day observation period.

Subacute Toxicity

A series of rabbits also received alpha₁-PI or excipient control substance, 9.1 mL/kg (227 mg/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 alpha₁-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 alpha₁-PI. An unexplained decrease in the cholesterol level of animals receiving alpha₁-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 alpha₁-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 alpha₁-PI were detected in animals undergoing necropsy and histopathologic analysis on days 6 or 33 of the study.

Repeated Dose Toxicity

No studies were performed regarding subchronic or chronic toxicity.

Reproductive Toxicology

No studies were performed regarding reproductive toxicity.

Mutagenesis

No studies were performed regarding genotoxicity.

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PART III: CONSUMER INFORMATION

PROLASTIN[®]-C

Alpha₁-Proteinase Inhibitor (Human), Highly Purified

This leaflet is Part 3 of a three-part "Product Monograph" published when PROLASTIN[®]-C was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PROLASTIN[®]-C. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

Alpha₁ Antitrypsin Deficiency, also known as Alpha₁, is an inherited disorder that causes significant reduction in the naturally occurring protein alpha₁ antitrypsin (AAT).

Scientists also call this protein Alpha₁-Proteinase Inhibitor (alpha₁-PI) because it inhibits not only trypsin but also other enzymes called proteinases.

It is believed that Alpha₁ affects as many as 100,000 people in the United States and similar numbers in Europe. Alpha₁ 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.

What it does:

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.

When it should not be used:

You should not use PROLASTIN[®]-C if you are allergic to albumin or to any ingredient in the formulation or component of the container.

You should not use this medicine if your body does not make enough immunoglobulin A (IgA), which could cause you to have an allergic reaction to blood products that contain IgA.

See also SIDE EFFECTS AND WHAT TO DO ABOUT THEM.

What the medicinal ingredient is:

PROLASTIN[®]-C contains human alpha₁-proteinase inhibitor (at a concentration of ≥ 40 mg/mL when diluted as directed).

What the nonmedicinal ingredients are:

PROLASTIN[®]-C also contains sodium (at a concentration of 100-210 mM), chloride (at a concentration of 60-180 mM), and sodium phosphate (at a concentration of 15-25 mM).

What dosage forms it comes in:

PROLASTIN[®]-C comes in 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.

WARNINGS AND PRECAUTIONS

PROLASTIN[®]-C like other products made from human plasma, part of our blood, may contain viruses or other agents

HOW TO STORE IT

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 provider.

BEFORE you use PROLASTIN[®]-C talk to your doctor or pharmacist if:

you are pregnant or breastfeeding

you have had an allergic reaction to alpha₁-proteinase inhibitor or any of the other ingredients in the medicine

INTERACTIONS WITH THIS MEDICATION

No interactions are known.

See also ABOUT THIS MEDICATION: When it should not be used, and SIDE EFFECTS AND WHAT TO DO ABOUT THEM.

PROPER USE OF THIS MEDICATION

Usual dose

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

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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

PROLASTIN[®]-C is well tolerated, but side effects are occasionally reported. 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.

This is not a complete list of side effects. For any unexpected effects while taking PROLASTIN[®]-C, contact your doctor or pharmacist.

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

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected side effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance :

| | |
|-------------------------|--|
| By toll-free telephone: | 866-234-2345 |
| By toll-free fax: | 866-678-6789 |
| Online | www.healthcanada.gc.ca/medeffect |
| By email: | CanadaVigilance@hc-sc.gc.ca |
| By regular mail: | Canada Vigilance National Office Marketed Health Products Safety and Effectiveness Information Bureau Marketed Health Products Directorate Health Products and Food Branch Health Canada Tunney's Pasture, AL 0701C Ottawa ON K1A 0K9 |

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document, plus the full product monograph prepared for health professionals, can be obtained by contacting Grifols Canada Ltd., at 1-866-482-5226.

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