12.2 Pharmacodynamics

Chronic augmentation therapy with the predecessor product, PROLASTIN, administered weekly at a dose of 60 mg/kg body weight, results in statistically significant increased levels of $Alpha_1$-PI and functional anti-neutrophil elastase capacity in the epithelial lining fluid of the lower respiratory tract of the lung, as compared to levels prior to commencing therapy with PROLASTIN.[7] However, the clinical benefit of the increased levels at the recommended dose has not been demonstrated in adequately powered, randomized, controlled clinical trials for any $Alpha_1$-PI product.

12.3 Pharmacokinetics

The crossover pharmacokinetic (PK) study was a randomized, double-blind trial comparing PROLASTIN-C to PROLASTIN conducted in 24 adult subjects age 40 to 72 with severe $Alpha_1$-PI deficiency. Ten subjects were male and 14 subjects were female. Twelve subjects were 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 with 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 intravenous infusion during the first 8-week treatment period. Following the last dose in the first 8-week treatment period, subjects underwent serial blood sampling for PK analysis 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 blood sampling for PK analysis. 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 pharmacokinetic parameters of $Alpha_1$-PI in plasma, based on functional activity assays, showed comparability between PROLASTIN-C treatment and PROLASTIN treatment, as shown in Table 5.

Table 5: Pharmacokinetic Parameters of $Alpha_1$-PI in Plasma

Treatment	$AUC_{0\text{-}7days}$ (hr*mg/mL) Mean (%CV)	C_{max} (mg/mL) Mean (%CV)	$t_{1/2}$ (hr) Mean (%CV)
PROLASTIN®-C (n=22 or 23)	155.9 (17%)	1.797 (10%)	146.3 (16%)
PROLASTIN® (n=22 or 23)	152.4 (16%)	1.848 (15%)	139.3 (18%)

The key pharmacokinetic parameter was the area under the plasma concentration-time curve ($AUC_{0\text{-}7days}$) following 8 weeks of treatment with PROLASTIN-C or PROLASTIN. The 90% confidence interval (0.97-1.09) for the ratio of $AUC_{0\text{-}7days}$ for PROLASTIN-C and PROLASTIN indicated that the 2 products are pharmacokinetically equivalent. Figure 1 shows the concentration (functional activity) vs. time curves of $Alpha_1$-PI after intravenous administration of PROLASTIN-C and PROLASTIN.

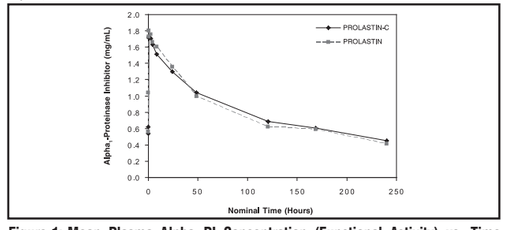

Figure 1: Mean Plasma $Alpha_1$-PI Concentration (Functional Activity) vs. Time Curves Following Treatment with PROLASTIN-C or PROLASTIN

Trough levels measured during the crossover PK study via an antigenic content assay showed PROLASTIN-C treatment resulted in a mean trough of 16.9 ± 2.3 µM and PROLASTIN resulted in a mean trough of 16.7 ± 2.7 µM. Using the functional activity assay, PROLASTIN-C resulted in a mean trough of 11.8 ± 2.2 µM and PROLASTIN resulted in a mean trough of 11.0 ± 2.2 µM.

14 CLINICAL STUDIES

The clinical efficacy of PROLASTIN-C in influencing the course of pulmonary emphysema or pulmonary exacerbations has not been demonstrated in adequately powered, randomized, controlled clinical trials.

A total of 23 subjects with the PiZZ variant and documented emphysema were studied in a single-arm, open-label clinical trial with PROLASTIN, the predecessor product. Nineteen of the subjects received PROLASTIN, 60 mg/kg, once weekly for up to 26 weeks (average 24 weeks). Blood levels of $Alpha_1$-PI were maintained above 11 µM. Bronchoalveolar lavage studies demonstrated statistically significant increased levels of $Alpha_1$-PI and functional ANEC in the epithelial lining fluid of the lower respiratory tract of the lung, as compared to levels prior to dosing.

A total of 62 individual subjects were studied in 2 clinical trials. In addition to the crossover pharmacokinetic study *[see Clinical Pharmacology (12.3)]*, a multi-center, open-label single arm safety study was conducted to evaluate the safety and tolerability of PROLASTIN-C. In this study, 38 subjects were treated with weekly intravenous 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 $Alpha_1$-PI 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 $Alpha_1$-PI deficiency. These groups were distributed evenly between the naïve and non-naïve cohorts.

15 REFERENCES

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2. Molloy K, Hersh CP, Morris VB, et al. Clarification of the risk of chronic obstructive pulmonary disease in α_1-antitrypsin deficiency PiMZ heterozygotes. Am J Respir Crit Care Med. 2014;7:419-27.
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7. Wewers MD, Casolaro MA, Sellers SE, Swayze SC, McPhaul KM, Wittes JT, et al. Replacement therapy for $alpha_1$-antitrypsin deficiency associated with emphysema. N Eng J Med. 1987;316:1055-62.

16 HOW SUPPLIED/STORAGE AND HANDLING

- PROLASTIN-C is supplied in a kit containing a single-use vial of PROLASTIN-C lyophilized powder, one 20 mL vial of Sterile Water for Injection, USP, a transfer needle, and a filter needle. The total $Alpha_1$-PI functional activity, in milligrams, is stated on the label of the PROLASTIN-C vial.
- Components of the packaging do not contain natural rubber latex.
- PROLASTIN-C is supplied in the following two presentations. The two kits are equivalent, differing only in the manufacturer of the Sterile Water for Injection:

NDC Number Carton (kit)	Approximate $Alpha_1$–PI Functional Activity	Diluent
13533-700-02 or 13533-703-10	1,000 mg	20 mL

- Store PROLASTIN-C at temperatures not to exceed 25°C (77°F) for the period indicated by the expiration date on its label.
- Avoid freezing as breakage of the diluent bottle might occur.

17 PATIENT COUNSELING INFORMATION

- Inform patients of the signs of hypersensitivity reactions including pruritus; generalized urticaria; flushing; swollen lips, tongue, or uvula; wheezing; tightness of the chest; dyspnea; hypotension; and syncope. Advise patients to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur. *[see Warnings and Precautions (5.1)]*
- Inform patients that PROLASTIN-C is made from human plasma and may carry a risk of transmitting infectious agents that can cause disease (e.g., viruses, the vCJD agent and, theoretically, the CJD agent). Explain that the risk of PROLASTIN-C transmitting an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents, by testing the donated plasma for certain current virus infections, and by inactivating and/or removing infectious agents during manufacturing. *[see Warnings and Precautions (5.2)]*
- Inform patients that administration of PROLASTIN-C has been demonstrated to raise the plasma level of $Alpha_1$-PI, but that the effect of this augmentation on pulmonary exacerbations and on the rate of progression of emphysema has not been demonstrated in adequately powered, randomized, controlled clinical trials for any $Alpha_1$-PI product. *[see Clinical Studies (14)]*

Manufactured by:

GRIFOLS

Grifols Therapeutics Inc.
Research Triangle Park, NC 27709 USA
U.S. License No. 1871
3045807
Revised: 02/2017

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROLASTIN®-C safely and effectively. See full prescribing information for PROLASTIN-C.

PROLASTIN®-C ($Alpha_1$-Proteinase Inhibitor [Human])
Lyophilized Powder for Solution for Intravenous Injection
Initial U.S. Approval: 1987

----------RECENT MAJOR CHANGES----------

Warnings and Precautions, Hypersensitivity Reactions (5.1) 2/2017

----------INDICATIONS AND USAGE----------

PROLASTIN-C is an $Alpha_1$-Proteinase Inhibitor (Human) ($Alpha_1$-PI) indicated for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of $Alpha_1$-PI ($alpha_1$-antitrypsin deficiency). (1)
PROLASTIN-C increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid levels of $Alpha_1$-PI.
Limitations of Use:

- The effect of augmentation therapy with any $Alpha_1$-PI, including PROLASTIN-C, on pulmonary exacerbations and on the progression of emphysema in $Alpha_1$-PI deficiency has not been conclusively demonstrated in randomized, controlled clinical trials.
- Clinical data demonstrating the long-term effects of chronic augmentation or maintenance therapy with PROLASTIN-C are not available.
- PROLASTIN-C is not indicated as therapy for lung disease in patients in whom severe $Alpha_1$-PI deficiency has not been established.

----------DOSAGE AND ADMINISTRATION----------

For intravenous use after reconstitution only.
Dose: 60 mg/kg body weight intravenously once per week.
Administration: 0.08 mL/kg/min as determined by patient response and comfort.
If small particles are visible after reconstitution, remove them by passage through a sterile filter, such as a 15 micron filter used for administering blood products (not supplied).
Dose ranging studies using efficacy endpoints have not been performed with any $Alpha_1$-PI product, including PROLASTIN-C. (2)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: approximately 1,000 mg as lyophilized powder in a single-use vial. Reconstitute with Sterile Water for Injection, USP, provided in a separate 20 mL vial. (3)

----------CONTRAINDICATIONS----------

- Immunoglobulin A (IgA) deficient patients with antibodies against IgA. (4)
- History of anaphylaxis or other severe systemic reaction to $Alpha_1$-PI.

----------WARNINGS AND PRECAUTIONS----------

- Severe hypersensitivity and anaphylactic reactions may occur in IgA deficient patients with antibodies against IgA. Discontinue administration of the product and initiate appropriate emergency treatment if hypersensitivity reactions occur. (5.1)
- Because PROLASTIN-C is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. (5.2)

----------ADVERSE REACTIONS----------

The most common adverse reaction during clinical trials in > 5% of subjects was upper respiratory tract infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Grifols Therapeutics Inc. at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION. **Revised: 2/2017**

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

Grifols Therapeutics Inc.
FULL PRESCRIBING INFORMATION

$Alpha_1$-Proteinase Inhibitor (Human)

PROLASTIN®-C

Lyophilized Preparation

1 INDICATIONS AND USAGE

PROLASTIN-C is an $Alpha_1$-Proteinase Inhibitor (Human) ($Alpha_1$-PI) indicated for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of $Alpha_1$-PI ($alpha_1$-antitrypsin deficiency).

PROLASTIN-C increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid levels of $Alpha_1$-PI.

Limitations of Use

- The effect of augmentation therapy with any $Alpha_1$-PI, including PROLASTIN-C, on pulmonary exacerbations and on the progression of emphysema in $Alpha_1$-PI deficiency has not been conclusively demonstrated in randomized, controlled clinical trials.
- Clinical data demonstrating the long-term effects of chronic augmentation or maintenance therapy with PROLASTIN-C are not available.
- PROLASTIN-C is not indicated as therapy for lung disease in patients in whom severe $Alpha_1$-PI deficiency has not been established.

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dose

- The recommended dose of PROLASTIN-C is 60 mg/kg body weight administered intravenously once weekly.
- Dose ranging studies using efficacy endpoints have not been performed with any $Alpha_1$-PI product.
- The carton and the label on each vial of PROLASTIN-C show the actual amount of functionally active $Alpha_1$-PI in milligrams (as determined by the capacity to neutralize porcine pancreatic elastase).

2.2 Preparation and Reconstitution

1. Allow unopened PROLASTIN-C and diluent vials to warm up to room temperature before reconstitution.
2. Remove the plastic flip tops from each vial.
3. Swab the exposed stopper surfaces with alcohol and allow to dry.
4. Remove the plastic cover from the short end of the transfer needle. Insert the exposed end of the needle through the center of the stopper in the diluent vial.
5. Remove the cover at the other end of the transfer needle by twisting it carefully.
6. Invert the diluent vial and insert the attached needle into the PROLASTIN-C vial at a 45° angle (Figure A below). 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 PROLASTIN-C vial.
7. Remove the diluent vial and transfer needle.
8. 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 B below). Some foaming will occur, but does not affect the quality of the product.
9. Inspect the reconstituted PROLASTIN-C visually for particulate matter and discoloration prior to pooling. A few small particles may remain after reconstitution. If particles are visible, remove by passage through a sterile filter, such as a 15 micron filter used for administering blood products (not supplied).
10. Pool reconstituted PROLASTIN-C from several vials into an empty, sterile intravenous solution container using aseptic technique. Use the sterile filter needle provided for this purpose.
11. Keep reconstituted solution at room temperature for administration within three hours.

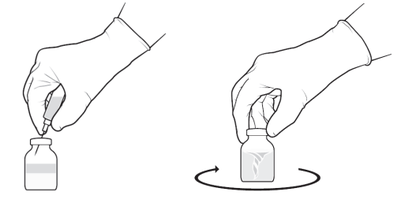

FIGURE A **FIGURE B**

2.3 Administration

- Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Infuse PROLASTIN-C separately, without mixing with other agents or diluting solutions.
- Infuse PROLASTIN-C intravenously at 0.08 mL/kg/min as determined by patient response and comfort. The recommended dosage of 60 mg/kg takes approximately 15 minutes to infuse.

3 DOSAGE FORMS AND STRENGTHS

PROLASTIN-C is available as a lyophilized powder in a single-use vial of approximately 1,000 mg. Reconstitute with Sterile Water for Injection, USP, provided in a separate 20 mL vial. The actual amount of functionally active $Alpha_1$-PI in milligrams is printed on the vial label and carton.

4 CONTRAINDICATIONS

PROLASTIN-C is contraindicated in:

- IgA deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity.
- Patients with a history of anaphylaxis or other severe systemic reaction to $Alpha_1$-PI.

5 WARNINGS AND PRECAUTIONS

5.1 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. *[see Patient Counseling Information (17)]*

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.

5.2 Transmissible Infectious Agents

Because PROLASTIN-C is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. The risk of transmission of infectious agents has been reduced by screening plasma donors for prior exposure to certain infectious agents, by testing for the presence of certain virus infections, and by including steps in the manufacturing process with the demonstrated capacity to inactivate and/or remove certain infectious agents. Despite these measures, this product may still potentially transmit disease.

Report all infections thought by a physician possibly to have been transmitted by this product to Grifols Therapeutics Inc. (1-800-520-2807)

6 ADVERSE REACTIONS

The most serious adverse reaction observed during clinical trials with PROLASTIN-C was an abdominal and extremity rash in one subject. *[see Warnings and Precautions (5.1)]*

The most common adverse reaction observed at a rate of > 5% in subjects receiving PROLASTIN-C was upper respiratory tract infection.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other clinical trials and may not reflect the rates observed in practice.

Two separate clinical trials were conducted with PROLASTIN-C: 1.) a 20 week, open-label, single arm safety study in 38 subjects (single-arm open-label trial), and 2.) a 16 week, randomized, double-blind, crossover pharmacokinetic comparability study vs. PROLASTIN® ($Alpha_1$-Proteinase Inhibitor [Human]) in 24 subjects, followed by an 8 week open-label treatment with PROLASTIN-C (randomized double-blinded comparator trial). Thus, 62 subjects were exposed to PROLASTIN-C in clinical trials.

The most serious adverse reaction observed during clinical trials with PROLASTIN-C was an abdominal and extremity rash in one subject. The rash resolved subsequent to outpatient treatment with antihistamines and steroids. Two instances of a less severe, pruritic abdominal rash were observed upon rechallenge despite continued antihistamine and steroid treatment, which led to withdrawal of the subject from the trial.

Grifols assessed the randomized double-blinded comparator trial for adverse reactions (as defined in the footnote to Table 1) occurring during each 8 week double-blind crossover treatment period, as shown in Table 1.

Table 1: Adverse Reactions Occurring during the First 8 Weeks of Each Double-Blinded Treatment

Adverse Reaction*,†	PROLASTIN®-C No. of subjects: 24 No. of Subjects with Adverse Reaction (percentage of all subjects)	PROLASTIN® No. of subjects: 24 No. of Subjects with Adverse Reaction (percentage of all subjects)
Upper respiratory tract infection	3 (12.5%)	1 (4.2%)
Headache	1 (4.2%)	2 (8.3%)
Pruritus	1 (4.2%)	0
Urticaria	1 (4.2%)	0
Nausea	1 (4.2%)	0
Peripheral edema	1 (4.2%)	0
Pyrexia	1 (4.2%)	0

* An adverse reaction is defined as any adverse event where either a) the incidence with Prolastin-C was greater than with Prolastin, or b) the occurrence was within 72 hours of treatment, or c) the event was otherwise considered related or possibly related to the drug.

† Source: the randomized double-blinded comparator trial

Table 2 below displays the adverse reaction (defined as per Table 1) rate as a percentage of infusions received during the 8 weeks of each double-blinded treatment.

Table 2: Adverse Reaction Frequency as a Percent of All Infusions during the First 8 Weeks of Each Double-Blinded Infusion Treatment

Adverse Reaction*	PROLASTIN®-C No. of infusions: 188 No. of Adverse Reactions (percentage of all infusions)	PROLASTIN® No. of infusions: 192 No. of Adverse Reactions (percentage of all infusions)
Upper respiratory tract infection	3 (1.6%)	1 (0.5%)
Headache	1 (0.5%)	3 (1.6%)
Pruritus	1 (0.5%)	0
Urticaria	1 (0.5%)	0
Nausea	1 (0.5%)	0
Peripheral edema	1 (0.5%)	0
Pyrexia	1 (0.5%)	0

* Source: the randomized double-blinded comparator trial.

Table 3 below displays the adverse reactions occurring in two or more subjects during the single-arm open-label trial.

Table 3: Adverse Reactions Occurring in Two or More Subjects (> 5%) during the 20 Week Single-Arm Open-Label Trial

Adverse Reaction*,†	PROLASTIN®-C No. of subjects: 38 No. of Subjects with Adverse Reaction (percentage of all subjects)
Upper respiratory tract infection	6 (15.8%)
Urinary tract infection	5 (13.2%)
Nausea	4 (10.5%)
Chest pain	3 (7.9%)
Back pain	2 (5.3%)
Chills	2 (5.3%)
Cough	2 (5.3%)
Dizziness	2 (5.3%)
Dyspnea	2 (5.3%)
Headache	2 (5.3%)
Hot flush	2 (5.3%)
Oral candidiasis	2 (5.3%)

* An adverse reaction is defined as any adverse event that occurred where either a) the occurrence was within 72 hours of treatment, or b) the event was otherwise considered related or possibly related to the drug.

† Source: the single-arm, open-label trial.

Ten exacerbations of chronic obstructive pulmonary disease were reported by 8 subjects in the 24 week crossover pharmacokinetic study. During the 16 week double-blind crossover phase, 4 subjects (17%) had a total of 4 exacerbations during PROLASTIN-C treatment and 4 subjects (17%) had a total of 4 exacerbations during PROLASTIN treatment. Two additional exacerbations in 2 subjects (8%) occurred during the 8 week open-label treatment period with PROLASTIN-C. The overall rate of pulmonary exacerbations during treatment with either product was 0.9 exacerbations per subject-year.

Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to PROLASTIN-C with the incidence of antibodies to other products may be misleading.

In the single-arm, open-label safety clinical trial, three treatment naïve subjects out of 36 subjects evaluated developed antibody to $Alpha_1$-PI at week 24 after receiving PROLASTIN-C. A fourth subject (non-naïve) was positive prior to and after receiving PROLASTIN-C, but levels were unchanged during the study. None of the four antibody specimens was able to neutralize the protease inhibitor capacity of PROLASTIN-C. In the randomized, crossover pharmacokinetic clinical trial, none of 24 subjects developed antibodies to PROLASTIN-C.

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

The reactions which have been chosen for inclusion due to their seriousness, frequency of reporting, possible causal connection to PROLASTIN–C, or a combination of these factors, are:

- **General/Body as a Whole:** Fatigue, malaise, influenza-like illness, pain, asthenia
- **Immune system:** Hypersensitivity including anaphylactoid/anaphylactic reactions
- **Cardiovascular:** Tachycardia
- **Musculoskeletal:** Arthralgia, myalgia
- **Gastrointestinal:** Vomiting, diarrhea
- **Investigation:** Blood pressure increased

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with PROLASTIN-C use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with PROLASTIN-C. It is 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. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of PROLASTIN-C in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PROLASTIN-C and any potential adverse effects on the breastfed infant from PROLASTIN-C.

8.4 Pediatric Use

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

8.5 Geriatric Use

Clinical studies of PROLASTIN-C did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

11 DESCRIPTION

PROLASTIN-C is a sterile, white to beige-colored concentrate of $Alpha_1$-PI in lyophilized powder form for reconstitution for intravenous infusion. Each vial contains approximately 1,000 mg of functionally active $Alpha_1$-PI as determined by capacity to neutralize porcine pancreatic elastase. The specific activity of PROLASTIN-C is ≥ 0.7 mg functional $Alpha_1$-PI per mg of total protein. PROLASTIN-C has a purity of ≥ 90% $Alpha_1$-PI ($Alpha_1$-PI protein/total protein). When reconstituted with 20 mL of Sterile Water for Injection, USP, 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 13–25 mM. PROLASTIN-C contains no preservative.

PROLASTIN-C is produced from pooled human plasma through modifications of the PROLASTIN® ($Alpha_1$-Proteinase Inhibitor [Human]) process using purification by polyethylene glycol (PEG) precipitation, anion exchange chromatography, and cation exchange chromatography. All Source Plasma used in the manufacture of PROLASTIN-C is non-reactive (negative) by FDA-licensed serological test methods for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis C virus (HCV) and human immunodeficiency virus types 1 and 2 and negative by FDA-licensed Nucleic Acid Technologies (NAT) for HCV and human immunodeficiency virus type 1 (HIV-1). In addition, all Source Plasma is negative for hepatitis B virus (HBV) by either an FDA-licensed or investigational NAT assay. The goal of the investigational HBV NAT test is to detect low levels of viral nucleic acid; however, the significance of a negative result for the investigational HBV NAT test has not been established. By in-process NAT, all Source Plasma is negative for hepatitis A virus (HAV). As a final plasma safety step, all plasma manufacturing pools are tested by serological test methods and NAT.

To evaluate further the virus safety profile of PROLASTIN-C, *in vitro* studies have been conducted to validate the capacity of the manufacturing process to reduce the infectious titer of a wide range of viruses with diverse physicochemical properties. These studies evaluated the inactivation/removal of clinically relevant viruses, including human immunodeficiency virus type 1 (HIV-1) and hepatitis A virus (HAV), as well as the following model viruses: bovine viral diarrhea virus (BVDV), a surrogate for hepatitis C virus; pseudorabies virus (PRV), a surrogate for large enveloped DNA viruses (e.g., herpes viruses); vesicular stomatitis virus (VSV), a model for enveloped viruses; reovirus type 3 (Reo3), a non-specific model for non-enveloped viruses; and porcine parvovirus (PPV), a model for human parvovirus B19.

The PROLASTIN-C manufacturing process has several steps (Cold Ethanol Fractionation, PEG Precipitation, and Depth Filtration) that are important for purifying $Alpha_1$-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 in 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 ≥ 5.4 log_{10} of West Nile virus, a clinically relevant enveloped virus.

Table 4: Virus Reduction (Log_{10}) for the PROLASTIN®-C Manufacturing Process

Process Step	Enveloped Viruses				Non-enveloped Viruses		
	HIV-1	BVDV	PRV	VSV	Reo3	HAV	PPV
Cold Ethanol Fractionation	1.5	1.7	2.5	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	≥ 23.6	≥ 17.8	≥ 20.1	≥ 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.

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 log_{10} 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

$Alpha_1$-PI deficiency is an autosomal, co-dominant, hereditary disorder characterized by low serum and lung levels of $Alpha_1$-PI. Smoking is an important risk factor for the development of emphysema in patients with $Alpha_1$-PI deficiency.[1,2] Because emphysema affects many, but not all individuals with the more severe genetic variants of $Alpha_1$-PI deficiency, augmentation therapy with $Alpha_1$-PI is indicated only in patients with severe $Alpha_1$-PI deficiency who have clinically evident emphysema.

Only some $Alpha_1$-PI alleles are associated with clinically apparent $Alpha_1$-PI deficiency.[3,4] Approximately 95% of all severely deficient patients are homozygous for the PiZ allele.[4] Individuals with the PiZZ variant typically have serum $Alpha_1$-PI levels less than 35% of the average normal level. Individuals with the Pi(null)(null) variant have undetectable $Alpha_1$-PI protein in their serum. Individuals with these low serum $Alpha_1$-PI levels, i.e., less than 11 µM, have a markedly increased risk for developing emphysema over their lifetimes. In addition, PiSZ individuals, whose serum $Alpha_1$-PI levels range from approximately 9 to 23 µM[5], are considered to have moderately increased risk for developing emphysema, regardless of whether their serum $Alpha_1$-PI levels are above or below 11 µM.

Augmenting the levels of functional protease inhibitor by intravenous infusion is an approach to therapy for patients with $Alpha_1$-PI deficiency. The intended theoretical goal is to provide protection to the lower respiratory tract by correcting the imbalance between neutrophil elastase and protease inhibitors. Whether augmentation therapy with any $Alpha_1$-PI product actually protects the lower respiratory tract from progressive emphysematous changes has not been demonstrated in adequately powered, randomized controlled, clinical trials. Although the maintenance of blood serum levels of $Alpha_1$-PI (antigenically measured) above 11 µM has been historically postulated to provide therapeutically relevant anti-neutrophil elastase protection[6], this has not been proven. Individuals with severe $Alpha_1$-PI deficiency have been shown to have increased neutrophil and neutrophil elastase concentrations in lung epithelial lining fluid compared to normal PiMM individuals, and some PiSZ individuals with $Alpha_1$-PI above 11 µM have emphysema attributed to $Alpha_1$-PI deficiency. These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of $Alpha_1$-PI during augmentation therapy.

The pathogenesis of emphysema is understood as described in the "protease-antiprotease imbalance" model. $Alpha_1$-PI is understood to be the primary antiprotease in the lower respiratory tract, where it inhibits neutrophil elastase (NE). Normal healthy individuals produce sufficient $Alpha_1$-PI to control the NE produced by activated neutrophils and are thus able to prevent inappropriate proteolysis of the lung tissue by NE. Conditions that increase neutrophil accumulation and activation in the lung, such as respiratory infection and smoking, will in turn increase levels of NE. However, individuals who are severely deficient in endogenous $Alpha_1$-PI are unable to maintain an appropriate antiprotease defense, and, in addition, they have been shown to have increased lung epithelial lining fluid neutrophil and NE concentrations. Because of these factors, many (but not all) individuals who are severely deficient in endogenous $Alpha_1$-PI are subject to more rapid proteolysis of the alveolar walls leading to chronic lung disease. PROLASTIN-C serves as $Alpha_1$-PI augmentation therapy in the patient population with severe $Alpha_1$-PI deficiency and emphysema, acting to increase and maintain serum and lung epithelial lining fluid levels of $Alpha_1$-PI.