

PROLASTIN-C - alpha-1-proteinase inhibitor (human)
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GRIFOLS USA, LLC

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 (Alpha₁-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 Alpha₁-Proteinase Inhibitor (Human) (Alpha₁-PI) indicated for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of Alpha₁-PI (alpha₁-antitrypsin deficiency). (1)

PROLASTIN-C increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid levels of Alpha₁-PI.

Limitations of Use:

- The effect of augmentation therapy with any Alpha₁-PI, including PROLASTIN-C, on pulmonary exacerbations and on the progression of emphysema in Alpha₁-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 Alpha₁-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 Alpha₁-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 Alpha₁-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 LLC at 1-800-520-2807 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PROLASTIN-C is an Alpha₁-Proteinase Inhibitor (Human) (Alpha₁-PI) indicated for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of Alpha₁-PI (alpha₁-antitrypsin deficiency).

PROLASTIN-C increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid levels of Alpha₁-PI.

Limitations of Use

- The effect of augmentation therapy with any Alpha₁-PI, including PROLASTIN-C, on pulmonary exacerbations and on the progression of emphysema in Alpha₁-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 Alpha₁-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 Alpha₁-PI product.
- The carton and the label on each vial of PROLASTIN-C show the actual amount of functionally active Alpha₁-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 Alpha₁-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 Alpha₁-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 LLC (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 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

	PROLASTIN®-C No. of subjects: 24	PROLASTIN® No. of subjects: 24
Adverse Reaction ^{*,†}	No. of Subjects with Adverse Reaction (percentage of all subjects)	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

	PROLASTIN®-C No. of infusions: 188	PROLASTIN® No. of infusions: 192
Adverse Reaction*	No. of Adverse Reactions (percentage of all infusions)	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

	PROLASTIN-C No. subjects: 38
Adverse Reaction*,†	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 Alpha₁-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 Alpha₁-PI in lyophilized powder form for reconstitution for intravenous infusion. Each vial contains approximately 1,000 mg of functionally active Alpha₁-PI as determined by capacity to neutralize porcine pancreatic elastase. The specific activity of PROLASTIN-C is ≥ 0.7 mg functional Alpha₁-PI per mg of total protein. PROLASTIN-C has a purity of $\geq 90\%$ Alpha₁-PI (Alpha₁-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 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 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 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 $\geq 5.4 \log_{10}$ 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

Alpha₁-PI deficiency is an autosomal, co-dominant, hereditary disorder characterized by low serum and lung levels of Alpha₁-PI. Smoking is an important risk factor for the development of emphysema in patients with Alpha₁-PI deficiency.(1,2) Because emphysema affects many, but not all individuals with the more severe genetic variants of Alpha₁-PI deficiency, augmentation therapy with Alpha₁-PI is indicated only in patients with severe Alpha₁-PI deficiency who have clinically evident emphysema.

Only some Alpha₁-PI alleles are associated with clinically apparent Alpha₁-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 Alpha₁-PI levels less than 35% of the average normal level. Individuals with the Pi(null)(null) variant have undetectable Alpha₁-PI protein in their serum. Individuals with these low serum Alpha₁-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 Alpha₁-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 Alpha₁-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 Alpha₁-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 Alpha₁-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 Alpha₁-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 Alpha₁-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 Alpha₁-PI above 11 μM have emphysema attributed to Alpha₁-PI deficiency. These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of Alpha₁-PI during augmentation therapy.

The pathogenesis of emphysema is understood as described in the “protease-antiprotease imbalance” model. Alpha₁-PI is understood to be the primary antiprotease in the lower respiratory tract, where it inhibits neutrophil elastase (NE). Normal healthy individuals produce sufficient Alpha₁-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 Alpha₁-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 Alpha₁-PI are subject to more rapid proteolysis of the alveolar walls leading to chronic lung disease. PROLASTIN[®]-C (Alpha₁-Proteinase Inhibitor [Human]) serves as Alpha₁-PI augmentation therapy in the patient population with severe Alpha₁-PI deficiency and emphysema, acting to increase and maintain serum and lung epithelial lining fluid levels of Alpha₁-PI.

12.2 Pharmacodynamics

Chronic augmentation therapy with the predecessor product, PROLASTIN[®] (Alpha₁-Proteinase Inhibitor [Human]), administered weekly at a dose of 60 mg/kg body weight, results in statistically significant increased levels of Alpha₁-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 Alpha₁-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 Alpha₁-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 Alpha₁-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.

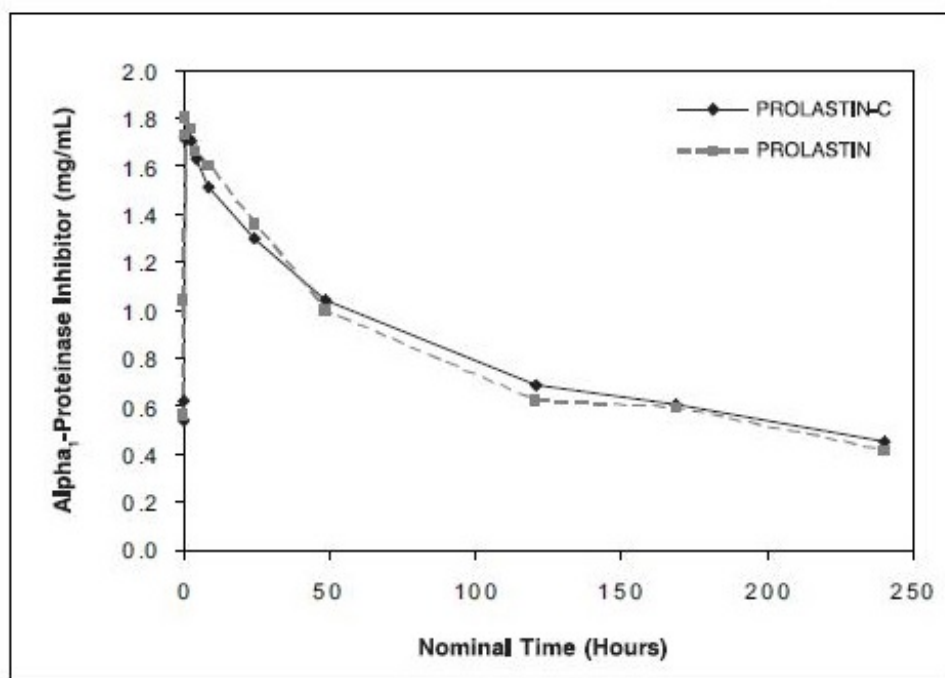
In the 8-week open-label treatment phase that followed the crossover period, all subjects received 60 mg/kg body weight of functional PROLASTIN-C.

The pharmacokinetic parameters of Alpha₁-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 Alpha₁-PI in Plasma

Treatment	AUC _{0-7 days} (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_{0-7days}) following 8 weeks of treatment with PROLASTIN-C or PROLASTIN. The 90% confidence interval (0.97-1.09) for the ratio of AUC_{0-7days} for PROLASTIN-C and PROLASTIN indicated that the 2 products are pharmacokinetically equivalent. Figure 1 shows the concentration (functional activity) vs. time curves of Alpha₁-PI after intravenous administration of PROLASTIN-C and PROLASTIN.

**Figure 1: Mean Plasma Alpha₁-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 μ M and PROLASTIN resulted in a mean trough of 16.7 ± 2.7 μ M. Using the functional activity assay, PROLASTIN-C resulted in a mean trough of 11.8 ± 2.2 μ M and PROLASTIN resulted in a mean trough of 11.0 ± 2.2 μ M.

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 Alpha₁-PI were maintained above 11 μM. Bronchoalveolar lavage studies demonstrated statistically significant increased levels of Alpha₁-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 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 Alpha₁-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 Alpha₁-PI deficiency. These groups were distributed evenly between the naïve and non-naïve cohorts.

15 REFERENCES

1. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med.* 2003;168:818-900.
2. Molloy K, Hersh CP, Morris VB, et al. Clarification of the risk of chronic obstructive pulmonary disease in α₁-antitrypsin deficiency PiMZ heterozygotes. *Am J Respir Crit Care Med.* 2014;7:419-27.
3. Crystal RG. α₁-Antitrypsin deficiency, emphysema, and liver disease; genetic basis and strategies for therapy. *J Clin Invest.* 1990;85:1343-52.
4. World Health Organization. Alpha-1-antitrypsin deficiency: Memorandum from a WHO meeting. *Bull World Health Organ.* 1997;75:397-415.
5. Turino GM, Barker AF, Brantly ML, Cohen AB, Connelly RP, Crystal RG, et al. Clinical features of individuals with Pi*SZ phenotype of α₁-antitrypsin deficiency. *Am J Respir Crit Care Med.* 1996;154:1718-25
6. American Thoracic Society. Guidelines for the approach to the patient with severe hereditary alpha-1-antitrypsin deficiency. *Am Rev Respir Dis.* 1989;140:1494-7.
7. Wewers MD, Casolaro MA, Sellers SE, Swayze SC, McPhaul KM, Wittes JT, et al. Replacement therapy for alpha₁-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 Alpha₁-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 Alpha₁-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 Alpha₁-PI product. *[see Clinical Studies (14)]*

Manufactured by:

GRIFOLS

Grifols Therapeutics LLC

Research Triangle Park, NC 27709 USA

U.S. License No. 1871

3052564

PACKAGE LABEL

NDC 13533-703-10

Alpha₁-Proteinase Inhibitor (Human)

PROLASTIN[®] C

Solvent detergent treated

Nanofiltered

GRIFOLS

Rx only

CONTENTS:

One vial of PROLASTIN[®]-C

20 mL diluent sterile water for injection, USP

One sterile double-ended transfer needle

One sterile filter needle

No preservative

For intravenous administration only

Sterile—nonpyrogenic

Store at temperatures not to exceed 25°C (77°F).
Do not freeze.

THIS PRODUCT IS PREPARED FROM LARGE POOLS OF HUMAN PLASMA WHICH MAY CONTAIN INFECTIOUS AGENTS. SEE PACKAGE INSERT WARNINGS.

The patient and physician should discuss the risks and benefits of this product.

The product when reconstituted with 20 mL diluent sterile water for injection, USP, has a sodium content of 100-210 mM, a chloride content of 60-180 mM, and a sodium phosphate content of 13-25 mM.

Administer within 3 hours after reconstitution.

Dosage and administration: Read enclosed package insert.

Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

GTIN XXXXXXXXXXXXXXXXXX
LOT XXXXXXXXXX
EXP DDMMMYYYY
mg α_1 -PI XXXX
SN XXXXXXXXXXXXXXXXXX

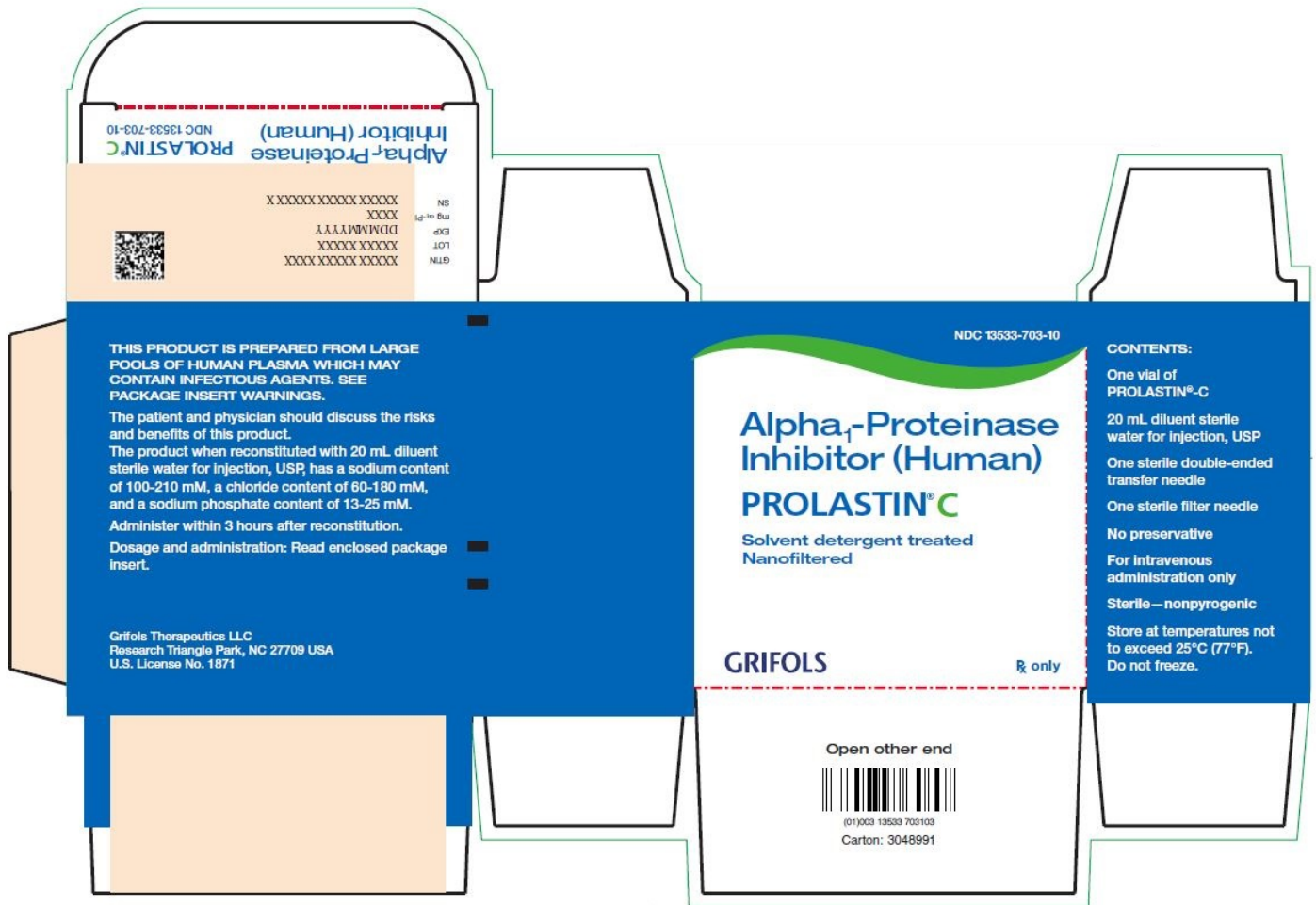
Alpha₁-Proteinase Inhibitor (Human)

PROLASTIN[®] C

NDC 13533-703-10

Open at other end

Carton: 3048991



NDC 13533-702-11

Alpha₁-Proteinase Inhibitor (Human)

PROLASTIN[®] C

**Solvent detergent treated
Nanofiltered**

GRIFOLS

Rx only

The patient and physician should discuss the risks and benefits of this product.

No preservative

For intravenous administration only

Sterile—nonpyrogenic

Reconstitute with 20 mL diluent sterile water for injection, USP.

Store at temperatures not to exceed 25°C (77°F). Do not freeze.

Dosage and administration: Read package insert.

Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

3048467

Lot

Exp.

mg α_1 -PI

3048467

Lot
Exp.
mg α_1 -PI

(01)003 13533 702113

NDC 13533-702-11

Alpha₁-Proteinase Inhibitor (Human)
PROLASTIN[®]C
Solvent detergent treated
Nanofiltered

GRIFOLS

Rx only

The patient and physician should discuss the risks and benefits of this product.

No preservative
For intravenous administration only
Sterile — nonpyrogenic

Reconstitute with 20 mL diluent sterile water for injection, USP.
Store at temperatures not to exceed 25°C (77°F). Do not freeze.

Dosage and administration:
Read package insert.

Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA
U.S. License No. 1871

NDC 13533-200-20

Sterile Water for Injection, USP

20 mL

Rx Only

For reconstitution of accompanying product

Single-Dose Container, Nonpyrogenic

Do not use unless clear. No antimicrobial agent or other substance has been added. Do not use for intravascular injection without making approximately isotonic by addition of suitable solute. Discard unused portion.

Mfd by: **Laboratorios Grifols, S. A.**, Parets del Vallès, Barcelona, 08150 Spain
Mfd for: **Grifols Therapeutics LLC**, Research Triangle Park, NC, 27709 USA

3048468

Lot / Exp.

3048468
Lot / Exp.



(01)003 13533 200206

NDC 13533-200-20

Sterile Water for Injection, USP

20 mL

Rx Only

For reconstitution of accompanying product

Single-Dose Container, Nonpyrogenic

Do not use unless clear. No antimicrobial agent or other substance has been added. Do not use for intravascular injection without making approximately isotonic by addition of suitable solute. Discard unused portion.

Mfd by: **Laboratorios Grifols, S. A.**, Parets del Vallès, Barcelona, 08150 Spain
Mfd for: **Grifols Therapeutics LLC**, Research Triangle Park, NC, 27709 USA

PROLASTIN-C

alpha-1-proteinase inhibitor (human) kit

Product Information

Product Type	PLASMA DERIVATIVE	Item Code (Source)	NDC:13533-700
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-700-02	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, SINGLE-DOSE	20 mL
Part 2	1 VIAL, SINGLE-DOSE	20 mL

Part 1 of 2

PROLASTIN-C

alpha-1-proteinase inhibitor (human) injection, powder, lyophilized, for solution

Product Information

Item Code (Source)	NDC:13533-702
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Route of Administration	INTRAVENOUS
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Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
.alpha.1-proteinase Inhibitor Human (UNII: F43I396OIS) (.alpha.1-proteinase Inhibitor Human - UNII:F43I396OIS)	.alpha.1-proteinase Inhibitor Human	1000 mg in 20 mL

Inactive Ingredients

Ingredient Name	Strength
Sodium Phosphate (UNII: SE337SVY37)	
Sodium Chloride (UNII: 451W47IQ8X)	

Product Characteristics

Color	WHITE (White to Beige)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-702-11	20 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103174	12/02/1987	

Part 2 of 2

STERILE WATER

water injection

Product Information

Item Code (Source)	NDC:13533-000
Route of Administration	INTRAVENOUS

Inactive Ingredients

Ingredient Name	Strength
Water (UNII: 059QF0KO0R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-000-06	20 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103174	12/02/1987	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103174	12/02/1987	

PROLASTIN-C

alpha-1-proteinase inhibitor (human) kit

Product Information

Product Type	PLASMA DERIVATIVE	Item Code (Source)	NDC:13533-701

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-701-01	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, SINGLE-DOSE	20 mL
Part 2	1 VIAL, SINGLE-DOSE	20 mL

Part 1 of 2

PROLASTIN-C

alpha-1-proteinase inhibitor (human) injection, powder, lyophilized, for solution

Product Information

Item Code (Source)	NDC:13533-702
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
.alpha.1-proteinase Inhibitor Human (UNII: F43I396OIS) (.alpha.1-proteinase Inhibitor Human - UNII:F43I396OIS)	.alpha.1-proteinase Inhibitor Human	1000 mg in 20 mL

Inactive Ingredients

Ingredient Name	Strength
Sodium Phosphate (UNII: SE337SVY37)	
Sodium Chloride (UNII: 451W47IQ8X)	

Product Characteristics

Color	WHITE (White to Beige)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-702-11	20 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103174	12/02/1987	

Part 2 of 2**STERILE WATER**

water injection

Product Information

Item Code (Source)	NDC:13533-100
Route of Administration	INTRAVENOUS

Inactive Ingredients

Ingredient Name	Strength
Water (UNII: 059QF0K00R)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-100-70	20 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103174	12/02/1987	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103174	12/02/1987	08/03/2018

PROLASTIN-C

alpha-1-proteinase inhibitor (human) kit

Product Information

Product Type	PLASMA DERIVATIVE	Item Code (Source)	NDC:13533-703
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-703-10	1 in 1 CARTON; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, SINGLE-DOSE	20 mL
Part 2	1 VIAL, SINGLE-DOSE	20 mL

Part 1 of 2**PROLASTIN-C**

alpha-1-proteinase inhibitor (human) injection, powder, lyophilized, for solution

Product Information

Item Code (Source)	NDC:13533-702
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Route of Administration INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
.alpha.1-proteinase Inhibitor Human (UNII: F43I396OIS) (.alpha.1-proteinase Inhibitor Human - UNII:F43I396OIS)	.alpha.1-proteinase Inhibitor Human	1000 mg in 20 mL

Inactive Ingredients

Ingredient Name	Strength
Sodium Phosphate (UNII: SE337SVY37)	
Sodium Chloride (UNII: 451W47IQ8X)	

Product Characteristics

Color	WHITE (White to Beige)	Score	
Shape		Size	
Flavor		Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-702-11	20 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103174	12/02/1987	

Part 2 of 2

STERILE WATER

water injection

Product Information

Item Code (Source)	NDC:13533-200
Route of Administration	INTRAVENOUS

Inactive Ingredients

Ingredient Name	Strength
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Water (UNII: 059QF0KO0R)

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13533-200-20	20 mL in 1 VIAL, SINGLE-DOSE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103174	12/02/1987	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA103174	12/02/1987	

Labeler - GRIFOLS USA, LLC (048987452)

Establishment

Name	Address	ID/FEI	Business Operations
GRIFOLS THERAPEUTICS LLC		611019113	manufacture(13533-700, 13533-701, 13533-703, 13533-702)

Revised: 1/2020

GRIFOLS USA, LLC