Attachment 1: Product information for PROLASTIN®-C Alpha -Proteinase Inhibitor (Human) Registered Product Information - Grifols Australia Pty Ltd - PM-2014-04721-1-5 - Final 11 October 2017. This Product Information was approved at the time this AusPAR was published.

NAME OF THE MEDICINE

Prolastin®-C [Alpha$_1$-Proteinase Inhibitor (Human)], 1000 milligrams, powder for injection, vial with diluent vial

CAS: 9041-92-3

DESCRIPTION

PROLASTIN-C, is a sterile, white to beige-colored, lyophilised powder of Alpha-1-proteinase inhibitor (Alpha$_1$-PI). PROLASTIN-C is produced from pooled human plasma using purification by polyethylene glycol (PEG) precipitation, anion exchange chromatography, and cation exchange chromatography.

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). Each vial contains approximately 1,000 mg of functionally active Alpha$_1$-PI as determined by capacity to neutralize porcine pancreatic elastase. When reconstituted with 20 mL of Sterile Water for Injection, 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 and must be administered by the intravenous route.

PROLASTIN-C is prepared from pooled human plasma collected from donors in the USA.

The PROLASTIN-C manufacturing process includes 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 human immunodeficiency virus type 1

[HIV-1], vesicular stomatitis virus [VSV], hepatitis B virus [HBV], hepatitis C virus [HCV], and West Nile virus [WNV]). 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.

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.

Excipients:

- sodium chloride, USP
- sodium phosphate – monobasic, USP
- sterile water for injection

PHARMACOLOGY

Congenital Alpha-1-Proteinase Inhibitor Deficiency

$Alpha_1$-PI deficiency (alpha-1-antitrypsin deficiency, AAT 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. Because emphysema affects many, but not all individuals with the more severe genetic variants of $Alpha_1$-PI deficiency, augmentation therapy with $Alpha_1$-Proteinase Inhibitor (Human) 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. Approximately 95% of all severely $Alpha_1$-PI deficient patients are homozygous for the PiZ allele. 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, 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. 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. 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.

Mechanism of Action

The pathogenesis of emphysema is understood to evolve 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. Normal healthy individuals produce sufficient $Alpha_1$-PI to control the neutrophil elastase produced by activated neutrophils and are thus able to prevent inappropriate proteolysis of the lung tissue by neutrophil elastase. Conditions that increase neutrophil accumulation and activation in the lung, such as respiratory infection and smoking, will in turn increase levels of neutrophil elastase. However, individuals who are severely deficient in endogenous $Alpha_1$-PI are unable to maintain an appropriate antiprotease defence, and, in addition, they have been shown to have increased lung epithelial lining fluid neutrophil and neutrophil elastase 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.

Pharmacodynamics

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

Pharmacokinetics

The pharmacokinetic (PK) profile of PROLASTIN-C was evaluated in a randomised, double-blind, crossover clinical 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 randomised 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.

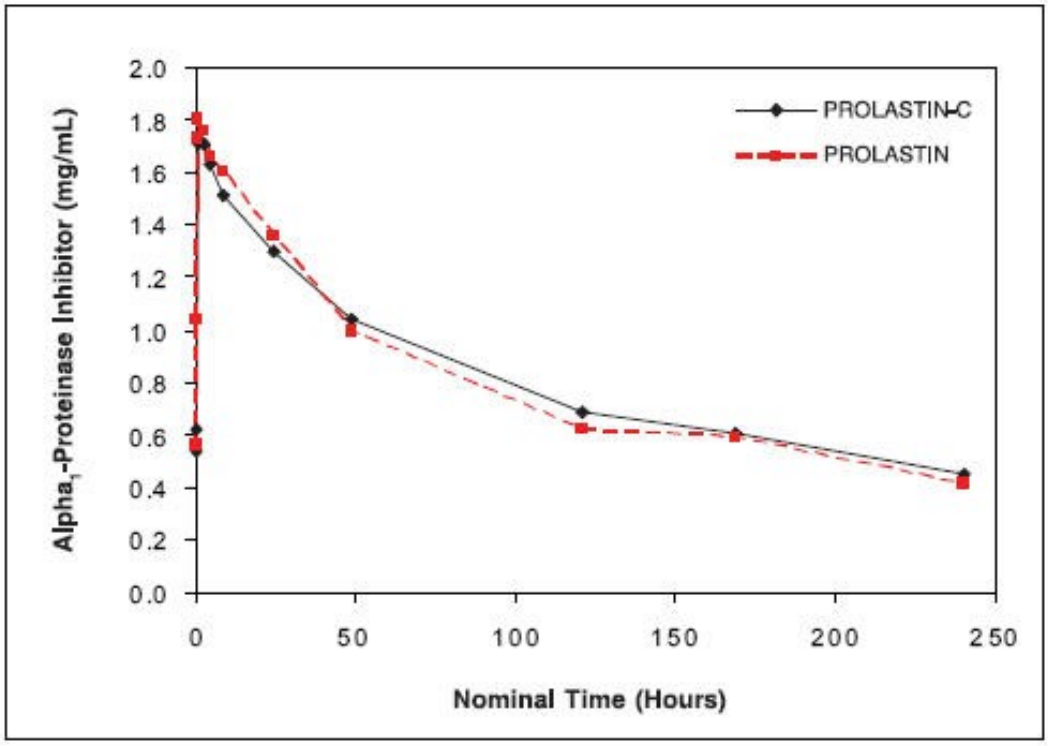
The pharmacokinetic parameters of Alpha$_1$-PI in plasma, based on functional activity assays, showed comparability between PROLASTIN-C treatment and PROLASTIN treatment, as shown in Table 1.

Table 1 Pharmacokinetic Parameters of Alpha$_1$-PI in Plasma

Treatment	$AUC_{0\text{-}7\ days}$ (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 ($AUC_{0\text{-}7days}$) 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.

CLINICAL TRIALS

Efficacy

A randomised, placebo-controlled study, EXAcerbations and CT scan as Lung Endpoints (EXACTLE), was conducted with the precursor product, Prolastin to assess the loss of lung tissue and effect of augmentation therapy in AAT deficiency using computed tomography (CT) densitometry. In total, 77 patients with AAT deficiency (three centers) were randomised to receive weekly infusions of either 60 mg/kg human AAT (Prolastin) or placebo (2% albumin) over 2 to 2.5 years. CT was performed at baseline, 12, 24, and 30 months. The primary endpoint was the 15^{th} percentile of whole lung density assessed by CT scan. Four prospectively defined methods were used for statistical analyses. A trend of reduced loss of

lung tissue in patients with AAT deficiency receiving augmentation therapy versus those on placebo was demonstrated when data were analyzed via any of the four methods. While this trial was not powered to achieve statistical significance, the four analyses resulted in p-values between 0.049 and 0.084. Prolastin was also found to modify exacerbations. The duration of the exacerbation in the Prolastin group was about 10% shorter than the placebo group and there were significantly fewer severe exacerbations in the Prolastin group. Other lung function parameters (FEV1, KCO, DLCO SVC, TLC, IVC, ERV, FRC and ERV/FRC) consistently reflected a similar deterioration of lung function in both treatment groups. The quality of life as determined with the percentage score of the SGRQ remained on average unchanged.

The clinical efficacy of PROLASTIN-C or any $Alpha_1$-PI product in influencing the course of pulmonary emphysema or pulmonary exacerbations has not been demonstrated in adequately powered, randomised, controlled clinical trials.

INDICATIONS

PROLASTIN-C is an alpha-1-proteinase inhibitor (human, $Alpha_1$-PI) indicated to increase serum $Alpha_1$-PI levels in adults with congenital deficiency of alpha-1 antitrypsin and with clinically significant emphysema (FEV_1 <80%).

The data for clinical efficacy of PROLASTIN-C is derived from changes in the biomarkers alpha-1 anti-protease level and CT lung density. Efficacy on FEV_1 or patient relevant endpoints such as quality of life or pulmonary exacerbations has not been established in randomised clinical trials.

Clinical trials have only included patients who were not smoking.

CONTRAINDICATIONS

PROLASTIN-C is contraindicated in IgA deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity.

PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity reactions may occur. Should evidence of an acute hypersensitivity reaction be observed, promptly stop the infusion and begin appropriate therapy.

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. PROLASTIN-C is contraindicated in patients with antibodies against IgA.

Transmissible Infectious Agents

Because PROLASTIN-C is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

Discuss the risks and benefits of this product with the patient, before prescribing or administering it to a patient. Report all infections thought by a physician possibly to have been transmitted by this product to Grifols Australia Pty Ltd 1800 339 479.

Effects on Fertility

No studies have been conducted on the effect of PROLASTIN-C on fertility.

Use in Pregnancy

Category B2. 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.

Use in Lactation

It is not known whether PROLASTIN-C 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.

Paediatric Use

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

Use in the Elderly

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

Genotoxicity

Genotoxicity studies have not been conducted with PROLASTIN-C.

Carcinogenicity

Carcinogenicity studies have not been conducted with PROLASTIN-C.

Effects on Laboratory Tests

Alpha-1-proteinase inhibitor is a normal constituent of human blood plasma so no specific effects on laboratory testing should be anticipated.

INTERACTIONS WITH OTHER MEDICINES

None known.

ADVERSE EFFECTS

Clinical Studies

The most serious adverse reaction observed during clinical studies 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.

The most common drug-related adverse reactions observed at a rate of ≥ 1% in subjects receiving PROLASTIN-C were chills, malaise, headache, rash, hot flush and pruritus.

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

Two separate clinical studies were conducted with PROLASTIN-C: (1) A 20 week, open-label, single arm safety study in 38 subjects, and (2) A 16 week, randomised, double-blind, crossover pharmacokinetic comparability study vs. PROLASTIN 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.

Adverse reactions considered drug related by the investigators occurring in 1.6% of subjects (one subject each) treated with PROLASTIN-C were malaise, headache, rash, hot flush, and pruritus. Drug related chills occurred in 3.2% (2 subjects) of PROLASTIN-C subjects.

Adverse events occurring irrespective of causality in ≥ 5% of subjects in the first 8 weeks of treatment are shown in Table 2. Adverse events which occurred in the first 8 weeks of treatment are shown in the table in order to control for the differing treatment durations of the safety and PK studies (20 weeks vs. two 8 week periods).

Table 2: Adverse Events Occurring in ≥ 5% of Subjects in the First 8 Weeks of Treatment Irrespective of Causality

Adverse Event	PROLASTIN®-C No. of subjects: 62	PROLASTIN® No. of subjects: 24
	No. of subjects with AE (% of all subjects)	No. of subjects with AE (% of all subjects)
Nausea	4 (6.5%)	0
Urinary Tract Infection	4 (6.5%)	0
Headache	3 (4.8%)	2 (8.3%)
Arthralgia	2 (3.2%)	2 (8.3%)

Table 3 below displays the overall adverse event rate (> 0.5%), irrespective of causality, as a percentage of infusions received.

Table 3: Adverse Event Frequency as a Percentage of All Infusions (> 0.5%) Irrespective of Causality

Adverse Event	PROLASTIN®-C No. of infusions: 1132	PROLASTIN® No. of infusions: 192
	No. of AE (% of all infusions)	No. of AE (% 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%)

Table 4 below displays the overall rates of adverse events (≥ 5%), in the first eight weeks of treatment, that began during or within 72 hours of the end of an infusion of PROLASTIN-C or PROLASTIN.

Table 4: Adverse Events Occurring in ≥ 5% of Subjects during or within 72 hours of the End of an Infusion, in the First 8 Weeks of Treatment Irrespective of Causality

Adverse Event	PROLASTIN® -C No. of subjects: 62	PROLASTIN® No. of subjects: 24
	No. of subjects with AE (% of all subjects)	No. of subjects with AE (% of all subjects)
Urinary Tract Infection	4 (6.5%)	0
Headache	3 (4.8%)	2 (8.3%)

Ten exacerbations of chronic obstructive pulmonary disease were reported by 8 subjects in the 24 week pharmacokinetic crossover 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.

Post-marketing Surveillance

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**: Chest discomfort/chest pain, chills, malaise, influenza-like illness, fatigue
- **Nervous system**: Dizziness, headache
- **Skin and subcutaneous system**: Pruritus and rash including urticaria
- **Respiratory system**: Dyspnea
- **Immune system**: Hypersensitivity including anaphylactoid/anaphylactic reactions
- **Cardiac**: Tachycardia

DOSAGE AND ADMINISTRATION

For intravenous use only.

Treatment must be initiated and monitored by a respiratory physician, and should be in conjunction with other pharmacological and non-pharmacological therapies.

To be eligible for treatment, patients must be diagnosed with alpha-1 antitrypsin deficiency on the basis of genotype, as well as have levels of alpha-1 antitrypsin < 11 µM/L, and clinical symptoms of emphysema.

Dosage

- 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 $alpha_1$-proteinase inhibitor product.
- The label on each vial of PROLASTIN-C shows the amount of functionally active $Alpha_1$-PI in milligrams (as determined by the capacity to neutralize porcine pancreatic elastase).

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 to15 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

Administration

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit.

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.

Infuse PROLASTIN-C separately, without mixing with other agents or diluting solutions.

Administer within 3 hours of reconstitution.

OVERDOSAGE

To date, there have been no reported cases of overdose for alpha-1-proteinase inhibitor (human). No data are available concerning overdose in humans.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

PROLASTIN-C is supplied as a composite pack in one single-use carton containing

- one glass vial of approximately 1,000 mg alpha-1-proteinase inhibitor (human) powder for reconstitution for injection
- one glass vial of diluent, 20 mL Sterile Water for Injection
- one sterile filter needle
- one color-coded transfer needle.

PROLASTIN-C is supplied as a sterile, preservative-free, non-pyrogenic, white to beige powder. The total $Alpha_1$-PI functional activity, in milligrams, is stated on the label of the PROLASTIN-C vial.

Storage Conditions

Store at or below 25°C.

Do not use after the expiration date on its label.

Special Precautions for Storage

Do not freeze as breakage of the diluent vial might occur.

NAME AND ADDRESS OF THE SPONSOR

Grifols Australia Pty Ltd

Unit 5/80 Fairbank Road,

Clayton South, VIC 3169

Australia

Medical Information: 1800 339 479

POISON SCHEDULE OF THE MEDICINE

Schedule 4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

10 November 2016