

# Alpha<sub>1</sub>-Proteinase Inhibitor (Human)

## Prolastin®

FOR INTRAVENOUS USE ONLY

### DESCRIPTION

Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin® is a sterile, stable, lyophilized preparation of purified human Alpha<sub>1</sub>-Proteinase Inhibitor (alpha<sub>1</sub>-PI), also known as alpha<sub>1</sub>-antitrypsin. Prolastin is intended for use in therapy of congenital alpha<sub>1</sub>-antitrypsin deficiency.

Prolastin is prepared from pooled human plasma of normal donors by modification and refinements of the cold ethanol method of Cohn.<sup>1</sup> Part of the fractionation may be performed by another licensed manufacturer. In order to reduce the potential risk of transmission of infectious agents, Prolastin has been heat-treated in solution at 60±0.5°C for not less than 10 hours. However, no procedure has been found to be totally effective in removing viral infectivity from plasma fractionation products. *In vitro* studies designed to evaluate the capacity of the Prolastin manufacturing process to remove/inactivate viruses have been conducted to provide additional assurance of the viral safety profile as shown in the table below.

Process Step	Log <sub>10</sub> Virus Reduction					
	HIV-1*	BVDV**	PRV***	Reo†	HAV††	PPV‡
Fractionation of Effluent I to II + III	3.4	3.5	3.9	2.1	1.4	1.0
PEG Precipitation	4.4	3.2	3.4	3.4	3.1	3.3
Depth Filtration	≥4.7	4.1	≥4.7	≥4.0	≥2.8	≥4.3
Pasteurization	≥6.3	4.8	≥4.8	N/A	N/A	N/A
Accumulated Log <sub>10</sub> Reduction	≥18.8	15.6	≥16.8	≥9.5	≥7.3	≥8.6

\* Human immunodeficiency virus, type 1

\*\* Bovine viral diarrhea virus (BVDV) was chosen to model hepatitis C virus

\*\*\* Pseudorabies virus (PRV) was used as a surrogate for the human herpes viruses and other large enveloped DNA viruses

† Reovirus type 3 (Reo) was chosen to model non-enveloped viruses

†† Human hepatitis A virus (HAV)

‡ Porcine parvovirus (PPV) was selected as a surrogate for human parvovirus B19

The specific activity of Prolastin is ≥0.35 mg functional alpha<sub>1</sub>-PI/mg protein and when reconstituted as directed, the concentration of alpha<sub>1</sub>-PI is ≥20 mg/mL. When reconstituted, Prolastin has a pH of 6.6–7.4, a sodium content of 100–210 mEq/L, a chloride content of 60–180 mEq/L, a sodium phosphate content of 0.015–0.025 M, a polyethylene glycol content of not more than (NMT) 5 ppm, and NMT 0.1% sucrose. Prolastin contains small amounts of other plasma proteins including alpha<sub>2</sub>-plasmin inhibitor, alpha<sub>1</sub>-antichymotrypsin, C<sub>1</sub>-esterase inhibitor, haptoglobin, antithrombin III, alpha<sub>1</sub>-lipoprotein, albumin, and IgA.<sup>1</sup>

Each vial of Prolastin contains the labeled amount of functionally active alpha<sub>1</sub>-PI in milligrams per vial (mg/vial), as determined by capacity to neutralize porcine pancreatic elastase.<sup>1</sup> Prolastin contains no preservative and must be administered by the intravenous route.

### CLINICAL PHARMACOLOGY

Alpha<sub>1</sub>-proteinase inhibitor deficiency is a chronic, hereditary, autosomal, co-dominant disorder that is usually fatal in its severe form. Low blood levels of alpha<sub>1</sub>-PI are most commonly associated with progressive, severe emphysema that becomes clinically apparent by the third to fourth decade of life. However, an unknown percentage of individuals with severe alpha<sub>1</sub>-PI deficiency apparently never develop clinically evident emphysema during their lifetimes. A recent registry study showed 54% of

alpha<sub>1</sub>-PI deficient subjects had emphysema.<sup>2</sup> Another registry study showed 72% of alpha<sub>1</sub>-PI deficient subjects had pulmonary symptoms.<sup>3</sup> Smoking is an important risk factor for the development of emphysema in patients with alpha<sub>1</sub>-PI deficiency. Less commonly, low blood levels of alpha<sub>1</sub>-PI are associated with liver disease and liver cirrhosis.<sup>4-6</sup> Approximately 100 genetic variants of alpha<sub>1</sub>-PI deficiency can be identified electrophoretically, only some of which are associated with the clinical disease.<sup>7,8</sup> Ninety-five percent of alpha<sub>1</sub>-PI deficient individuals are of the severe PiZZ phenotype. Up to 39% of alpha<sub>1</sub>-PI deficient patients may have an asthmatic component to their lung disease, as evidenced by symptoms and/or bronchial hyperreactivity.<sup>2</sup> Pulmonary infections, including pneumonia and acute bronchitis, are common in alpha<sub>1</sub>-PI deficient patients and contribute significantly to the morbidity of the disease. The most direct approach to therapy for alpha<sub>1</sub>-PI deficiency in patients with emphysema has been to partially replace the missing protease inhibitor by intravenous infusion and, thus, attempt to ameliorate the imbalance in the anti-neutrophil elastase protection of the lower respiratory tract. Individuals with endogenous levels of alpha<sub>1</sub>-PI below 11 μM, in general, manifest a significantly increased risk for development of emphysema above the general population background risk.<sup>4,5,8,9</sup> Therefore, the maintenance of blood serum levels of alpha<sub>1</sub>-PI (antigenically measured) above 11 μM is historically thought to provide therapeutically relevant antineutrophil elastase protection.<sup>10</sup> However, the hypothesis that maintaining a serum level of antigenic alpha<sub>1</sub>-PI will restore protease-antiprotease balance and prevent further lung damage has never been tested in an adequately-powered controlled clinical trial.

### **Clinical Studies**

In clinical studies of Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin, 23 subjects with the PiZZ variant of congenital deficiency of alpha<sub>1</sub>-antitrypsin deficiency and documented destructive lung disease participated in a study of acute and/or chronic replacement therapy with Prolastin.<sup>11</sup> The mean in vivo recovery of alpha<sub>1</sub>-PI was 4.2 mg (immunologic)/dL per mg (functional)/kg body weight administered.<sup>11,12</sup> The half-life of alpha<sub>1</sub>-PI in vivo was approximately 4.5 days.<sup>11,12</sup> Based on these observations, a program of chronic augmentation therapy was developed. Nineteen of the subjects in these studies received Prolastin augmentation therapy, 60 mg/kg body weight, once weekly for up to 26 weeks (average 24 weeks of therapy). With this schedule of augmentation therapy, blood levels of alpha<sub>1</sub>-PI were maintained above 80 mg/dL (based on the commercial standards for alpha<sub>1</sub>-PI immunologic assay).<sup>11-13</sup> Within a few weeks of commencing this program, bronchoalveolar lavage studies demonstrated significantly increased levels of alpha<sub>1</sub>-PI and functional antineutrophil elastase capacity in the epithelial lining fluid of the lower respiratory tract of the lung, as compared to levels prior to commencing the program of chronic replacement therapy with Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin.<sup>11-13</sup>

All 23 individuals who participated in the investigations were immunized with Hepatitis B Vaccine and received a single dose of Hepatitis B Immune Globulin (Human) on entry into the investigation. Although no other steps were taken to prevent hepatitis, neither hepatitis B nor non-A, non-B hepatitis occurred in any of the subjects.<sup>11,12</sup> All subjects remained seronegative for HIV antibody. None of the subjects developed any detectable antibody to alpha<sub>1</sub>-PI or other serum protein.

Long-term controlled clinical trials to evaluate the effect of chronic replacement therapy with Prolastin on the development of or progression of emphysema in patients with congenital alpha<sub>1</sub>-antitrypsin deficiency have not been performed.

## **INDICATIONS AND USAGE**

### **Congenital Alpha<sub>1</sub>-Antitrypsin Deficiency**

Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin is indicated for chronic augmentation and maintenance therapy of individuals having congenital deficiency of alpha<sub>1</sub>-PI (alpha<sub>1</sub>-antitrypsin deficiency) with clinically demonstrable panacinar emphysema. Clinical and biochemical studies have demonstrated that with such therapy, it is possible to increase plasma levels of alpha<sub>1</sub>-PI, and that levels of functionally active alpha<sub>1</sub>-PI in the lung epithelial lining fluid are increased proportionately.<sup>11-13</sup> As some individuals with alpha<sub>1</sub>-antitrypsin deficiency will not go on to develop panacinar emphysema, only those with

evidence of such disease should be considered for chronic replacement therapy with Prolastin.<sup>14</sup> Clinical data are not available as to the long-term effects derived from chronic replacement therapy of individuals with alpha<sub>1</sub>-antitrypsin deficiency with Prolastin. Only adult subjects have received Prolastin to date.

### **CONTRAINDICATIONS**

Individuals with selective IgA deficiencies who have known antibody against IgA (anti-IgA antibody) should not receive Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin, since these patients may experience severe reactions, including anaphylaxis, to IgA which may be present.

### **WARNINGS**

**Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g. viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Talecris Biotherapeutics, Inc. [1-800-520-2807].**

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

Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin has been heat-treated in solution at 60°C for 10 hours in order to reduce the potential for transmission of infectious agents.<sup>1</sup> However, as all individuals received prophylaxis against hepatitis B, no conclusion can be drawn at this time regarding potential transmission of hepatitis B virus. There was a single seroconversion for Parvovirus B19 in the Prolastin arms in each of 2 separate randomized controlled trials that each included a study arm comprised of approximately 14 subjects who were administered weekly infusions of Prolastin for a period of 10 weeks. Community-acquired parvovirus infection could not be ruled out.

### **PRECAUTIONS**

#### **General**

1. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.
2. Administer only by the intravenous route.
3. As with any colloid solution, there will be an increase in plasma volume following intravenous administration of Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin.<sup>15</sup> Caution should therefore be used in patients at risk for circulatory overload.
4. Prolastin should be given alone, without mixing with other agents or diluting solutions.
5. Product administration and handling of the needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious virus including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

Place needles in sharps container after single use. Discard all equipment including any reconstituted Prolastin product in accordance with biohazard procedures.

#### **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

**Pregnancy Category C**

Animal reproduction studies have not been conducted with Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin®. It is also not known whether Prolastin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Prolastin should be given to a pregnant woman only if clearly needed.

**Nursing Mothers**

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

**Pediatric Use**

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

**ADVERSE REACTIONS**

Therapeutic administration of Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin, 60 mg/kg weekly, has been demonstrated to be well tolerated. In clinical studies, six reactions were observed with 517 infusions of Prolastin, or 1.16%. None of the reactions was severe.<sup>11</sup> The adverse reactions reported included delayed fever (maximum temperature rise was 38.9°C, resolving spontaneously over 24 hours) occurring up to 12 hours following treatment (0.77%), light-headedness (0.19%), and dizziness (0.19%).<sup>11</sup> Mild transient leukocytosis and dilutional anemia several hours after infusion have also been noted.<sup>11</sup> Since market entry, occasional reports of other flu-like symptoms, allergic-like reactions, chills, dyspnea, rash, tachycardia, and, rarely, hypotension have also been received. Rare cases of transient increase in blood pressure or hypertension and chest pain have also been reported.

**DOSAGE AND ADMINISTRATION****FOR INTRAVENOUS USE ONLY**

Each bottle of Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin has the functional activity, as determined by inhibition of porcine pancreatic elastase,<sup>1</sup> stated on the label of the bottle.

The maintenance of blood serum levels of alpha<sub>1</sub>-PI (antigenically measured) above 11 μM is historically thought to provide therapeutically relevant antineutrophil elastase protection.<sup>10</sup> However, the hypothesis that maintaining a serum level of antigenic alpha<sub>1</sub>-PI will restore protease-antiprotease balance and prevent further lung damage has never been tested in an adequately-powered clinical trial. However, assays of alpha<sub>1</sub>-PI based on commercial standards measure antigenic activity of alpha<sub>1</sub>-PI, whereas the labeled potency value of alpha<sub>1</sub>-PI is expressed as actual functional activity, i.e., actual capacity to neutralize porcine pancreatic elastase. As functional activity may be less than antigenic activity, serum levels of alpha<sub>1</sub>-PI determined using commercial immunologic assays may not accurately reflect actual functional alpha<sub>1</sub>-PI levels. Therefore, although it may be helpful to monitor serum levels of alpha<sub>1</sub>-PI in individuals receiving Prolastin, using currently available commercial assays of antigenic activity, results of these assays should not be used to determine the required therapeutic dosage.

The recommended dosage of Prolastin is 60 mg/kg body weight administered once weekly. This dose is intended to increase and maintain a level of functional alpha<sub>1</sub>-PI in the epithelial lining of the lower respiratory tract, providing augmented anti-elastase activity in the lung of individuals with alpha<sub>1</sub>-antitrypsin deficiency.

Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin may be given at a rate of 0.08 mL/kg/min or greater and must be administered intravenously. The recommended dosage of 60 mg/kg takes approximately 30 minutes to infuse.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Safety and effectiveness in pediatric patients have not been established.

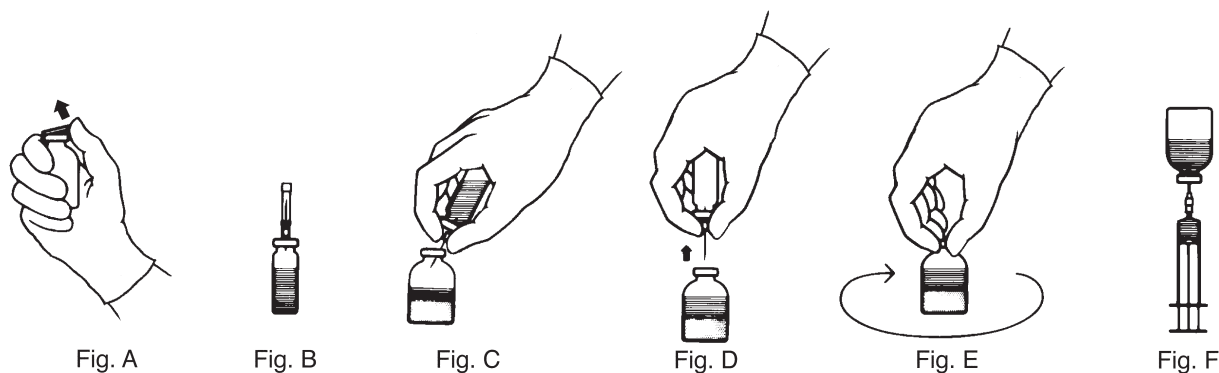
## Reconstitution

### Vacuum Transfer

Note: Aseptic technique should be carefully followed. All needles and vial tops that will come into contact with the product to be administered via the intravenous route should not come in contact with any nonsterile surface. Any contaminated needles should be discarded by placing in a puncture-proof container and new equipment should be used.

1. After removing all items from the box, warm the sterile water (diluent) to room temperature (25°C, 77°F).
2. Remove the plastic flip tops from each vial (Fig. A). Cleanse vial tops (grey stoppers) with alcohol swab and allow surface to dry. After cleaning, do not allow anything to touch the latex (rubber) stopper.
3. Carefully remove the plastic sheath from the short end of the transfer needle. Insert the exposed needle into the diluent vial to the hub (Fig. B).
4. Carefully grip the sheath of the other end of the transfer needle and twist to remove it.
5. Invert the diluent vial and insert the attached needle into the vial of concentrate at a 45° angle (Fig. C). This will direct the stream of diluent against the wall of the concentrate vial and minimize foaming. The vacuum will draw the diluent into the concentrate vial.
6. Remove the diluent bottle and transfer needle (Fig. D).
7. Gently swirl the concentrate bottle until the powder is completely dissolved (Fig. E). The vial should then be visually inspected for particulate matter and discoloration prior to administration.
8. Clean the top of the vial of reconstituted Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin again with alcohol swab and let surface dry.
9. Attach the filter needle (from the package) to sterile syringe. Withdraw the Prolastin solution into the syringe through the filter needle (Fig. F).
10. Remove the filter needle from the syringe and replace with an appropriate injection needle for administration. Discard filter needle into a puncture-proof container.
11. The contents of more than one bottle of Prolastin may be drawn into the same syringe before administration. If more than one bottle of Prolastin is used, withdraw contents from bottles using aseptic technique. Place contents into an administration container (plastic minibag or glass bottle) using a syringe. \* Avoid pushing an I.V. administration set spike into the product container stopper as this has been known to force the stopper into the vial, with a resulting loss of sterility.

\*For a patient of average weight (about 70 kg) the volume needed will exceed the limit of one syringe.



A number of factors could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly, that the directions be followed carefully during use, and that the risk of transmitting viruses be carefully weighed before the product is prescribed.

**HOW SUPPLIED**

Alpha<sub>1</sub>-Proteinase Inhibitor (Human), Prolastin is supplied in the following single use vials with the total alpha<sub>1</sub>-PI functional activity, in milligrams, stated on the label of each vial. A suitable volume of Sterile Water for Injection, USP, is provided.

<b>NDC Number</b>	<b>Approximate Alpha<sub>1</sub>-PI Functional Activity</b>	<b>Diluent</b>
13533-601-30	500 mg	20 mL
13533-601-35	1000 mg	40 mL

**STORAGE**

Prolastin should be stored at temperatures not to exceed 25°C (77°F). Freezing should be avoided as breakage of the diluent bottle might occur.

R<sub>x</sub> only

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