PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PRONEXTICA™ LIQUID

Alpha$_1$-Proteinase Inhibitor (Human) Injection

Solution - For Intravenous Use Only

1000 mg / 20 mL vial

Alpha$_1$-Antitrypsin Replenisher

Manufactured by:
Grifols Therapeutics LLC
8368 U.S. 70 Bus. Hwy West
Clayton, North Carolina 27520
U.S.A.

Imported and Distributed by:
Grifols Canada Ltd.
5060 Spectrum Way
Suite 405
Mississauga, Ontario
L4W 5N5

Prepared for:
Canadian Blood Services
and/or
Héma-Québec

Date of Initial Authorization:
November 10, 2023

Submission Control Number: 273683

**RECENT MAJOR LABEL CHANGES**

| | |
|---|---|
| Not Applicable | |

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**Sections or subsections that are not applicable at the time of authorization are not listed.**

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# PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

Indications have been granted on the basis of comparability between Pronextica™ Liquid and Prolastin®-C Liquid, a comparable product with an identical manufacturing process (i.e., except for the source of the plasma starting material).

PRONEXTICA LIQUID (alpha$_1$-proteinase inhibitor [human] injection) is indicated for:

- chronic replacement therapy of individuals having congenital deficiency of alpha$_1$-PI (alpha$_1$-antitrypsin deficiency), related to genotypes PiZZ, PiZ(null), Pi (null)(null), PiSZ or other deficiency causing alleles, and with clinically demonstrable emphysema.

Clinical and biochemical studies have demonstrated that with such therapy, it is possible to increase plasma levels of alpha$_1$-PI, and that levels of functionally active alpha$_1$-PI in the lung epithelial lining fluid are increased proportionately. As some individuals with alpha$_1$-antitrypsin deficiency will not go on to develop emphysema, only those with evidence of such disease should be considered for chronic replacement therapy with Alpha$_1$-Proteinase Inhibitor (Human). Subjects with the PiMZ or PiMS phenotypes of alpha$_1$-antitrypsin deficiency should not be considered for such treatment as they appear to be at small risk for emphysema. Clinical data are not available as to the long-term effects derived from chronic replacement therapy of individuals with alpha$_1$-antitrypsin deficiency with Alpha$_1$-Proteinase Inhibitor (Human). Only adult subjects have received Alpha$_1$-Proteinase Inhibitor (Human) to date.

### 1.1 Pediatrics

**Pediatrics (<18 years):** Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Pronextica Liquid in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

### 1.2 Geriatrics

**Geriatrics (≥65 years):** Of the 32 subjects randomized in the primary pharmacokinetic/safety study supporting Pronextica Liquid , 17 were ≥65 years of age. While the data was limited, no overall differences for Pronextica Liquid have been observed between patients 65 years of age and older and younger patients (See Section 7.1.4).

## 2 CONTRAINDICATIONS

Pronextica Liquid is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section
- individuals with selective immunoglobulin A (IgA) deficiencies, since these patients may experience severe reactions, including anaphylaxis, to IgA which may be present.
- individuals with a history of anaphylaxis or other severe systemic reaction to alpha$_1$-proteinase inhibitor (human) products.

# 4 DOSAGE AND ADMINISTRATION

## 4.1 Dosing Considerations

The "threshold" level of alpha$_1$-PI in the serum believed to provide adequate anti-elastase activity in the lung of individuals with alpha$_1$-antitrypsin deficiency is 80 mg/dL (based on commercial standards for alpha$_1$-PI immunologic assay). However, assays of alpha$_1$-PI based on commercial standards measure antigenic activity of alpha$_1$-PI, whereas the labeled potency value of alpha$_1$-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$_1$-PI determined using commercial immunologic assays may not accurately reflect actual functional alpha$_1$-PI levels.

Therefore, although it may be helpful to monitor serum levels of alpha$_1$-PI in individuals receiving Pronextica Liquid, using currently available commercial assays of antigenic activity, results of these assays should not be used to determine the required therapeutic dosage.

## 4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of Pronextica Liquid is 60 mg/kg body weight administered once weekly by intravenous infusion. This dose is intended to increase and maintain a level of functional alpha$_1$-PI in the epithelial lining of the lower respiratory tract, providing adequate anti-elastase activity in the lung of individuals with alpha$_1$-antitrypsin deficiency.

## 4.4 Administration

FOR INTRAVENOUS USE ONLY.

1) Allow unopened Pronextica Liquid to warm up to room temperature before administration.
2) Remove the plastic flip top from the vial.
3) Swab the exposed stopper surface with alcohol and allow to dry.
4) Parenteral drug products should be inspected visually for particulate matter and discoloration prior to pooling. Pronextica Liquid may contain a few protein particles. The solution is clear or slightly opalescent, and colorless or pale yellow or pale green or pale brown. Do not use if the product is discolored or cloudy.
5) Pronextica Liquid should be given alone, without mixing with other agents or diluting solutions.
6) Pool Pronextica Liquid from several vials to achieve the intended mg/kg body weight dose into an empty, sterile intravenous solution container using aseptic technique.
7) Keep pooled solution at room temperature and administer within three hours of entering the vials.
8) Pronextica Liquid may be given at a rate of 0.08 mL/kg/min or greater and must be administered intravenously. The recommended dosage of 60 mg/kg takes approximately 15 minutes to infuse.
9) Record brand name, Drug Identification Number (DIN) and the batch/lot number of the product for each patient (see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING).
10) Following administration, discard open vials, administration equipment and unused solution per local requirements

**Additional Instructions for Home-Treatment / Self-Administration by the Patient**

The first infusions of Pronextica Liquid should be administered under the supervision of a

healthcare professional experienced in the use of human alpha$_1$-proteinase inhibitor or in the treatment of alpha$_1$-antitrypsindeficiency.

Following proper training by a qualified healthcare professional, subsequent infusions may be administered by a caregiver or by the patient themselves. The decision of whether a patient is suitable for home-treatment/self-administration should be made by the physician, and the appropriateness of a patient continuing with home-treatment/self-infusion should be reviewed regularly. Potential risks associated with home-treatment/self-administration are related to the administration itself as well as to the handling of adverse drug reactions, particularly hypersensitivity.

## 5 OVERDOSAGE

To date, there have been no reported cases of overdose for Pronextica Liquid or other Alpha$_1$ Proteinase Inhibitor (Human) manufactured by Grifols. No data are available in regard to overdosage in humans.

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

**Table 1 – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Intravenous injection | Injectable Solution<br>1000 mg/20 mL vial<br>Human Alpha$_1$ proteinase inhibitor | Alanine, sodium phosphate |

Pronextica Liquid is supplied as a sterile, liquid in 20 mL single use vials with 1000 mg total alpha$_1$-PI functional activity. Primary packaging components are not made with natural rubber latex.

### Description

Pronextica Liquid (Alpha$_1$-Proteinase Inhibitor [Human]) is a sterile, stable preparation of highly purified human Alpha$_1$-Proteinase Inhibitor (alpha$_1$-PI), also known as alpha$_1$-antitrypsin. Alpha$_1$-Proteinase Inhibitor (Human) is intended for use in therapy of congenital alpha$_1$-antitrypsin deficiency.

Pronextica Liquid is prepared from pooled human plasma of normal donors by modification and refinements of the cold ethanol method of Cohn. See WARNINGS AND PRECAUTIONS.

Pronextica Liquid is produced through a modification of the earlier Alpha$_1$-proteinase inhibitor (Human) manufacturing process that results in improved product purity and a higher concentration of the same active substance, alpha$_1$-PI, in the reconstituted product.

# 7 WARNINGS AND PRECAUTIONS

## General

Pronextica Liquid is made from human plasma, and may carry a risk of transmitting infectious agents, e.g. such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob Disease (CJD) agent, despite steps designed to reduce this risk. Pronextica Liquid is purified from human plasma obtained from healthy donors. When medicinal biological products are administered, infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by: (1) epidemiological controls on the donor population and selection of individual donors by a medical interview; (2) screening of individual donations and plasma pools for viral infection markers; and (3) manufacturing procedures with demonstrated capacity to inactivate/remove pathogens.

ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Grifols Canada Ltd. [1-866-482-5226].

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

Administer only by the intravenous route.

As with any colloid solution, there will be an increase in plasma volume following intravenous administration of Alpha$_1$-Proteinase Inhibitor (Human). Caution should therefore be used in patients at risk for circulatory overload.

Product administration and handling of the needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious virus including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.

It is strongly recommended that every time Pronextica Liquid is administered, the name and batch number of the product are recorded in order to maintain a link between the patient and the specific batch used.

## Carcinogenesis and Mutagenesis

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

## 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 Pronextica Liquid infusion and begin appropriate therapy. Have epinephrine and other appropriate therapy available for the treatment of any acute anaphylactic or anaphylactoid reaction.

Pronextica Liquid 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.

**Sexual Health/Reproduction**

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

### 7.1 Special Populations

#### 7.1.1 Pregnant Women

Animal reproduction studies have not been conducted with Pronextica Liquid. It is also not known whether Pronextica Liquid can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Pronextica Liquid should be given to a pregnant woman only if clearly needed.

#### 7.1.2 Breast-feeding

It is not known whether $Alpha_1$-PI is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Pronextica Liquid is administered to a nursing woman.

#### 7.1.3 Pediatrics

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

#### 7.1.4 Geriatrics

The clinical pharmacokinetic/safety study supporting Pronextica Liquidrandomized 32 patients to a cross-over design for treatment with both the lyophilized and liquid formulations of human $alpha_1$-proteinase inhibitor (see Section 14.1). Among the 32 patients, 17 were aged 65 years or older (range: 65 to 71 years).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

Pronextica Liquid has been shown to be comparable to Prolastin®-C Liquid, a product with an identical manufacturing process (i.e., except for the source of the plasma starting material). Prolastin®-C Liquid was first authorized based bridging to its lyophilized powder predecessor, Prolastin®-C. The most common adverse reactions during Prolastin®-C Liquid clinical trials in > 5% of subjects, and expected to be similar for Pronextica Liquid, were diarrhea and fatigue, each of which occurred in 2 subjects (6%). There have been very rare cases of anaphylactic/anaphylactoid reactions reported in post-marketing use of $alpha_1$-proteinase inhibitor (Human) products.

### 8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

One clinical trial was conducted with Prolastin®-C Liquid: a 16 week, multicenter, randomized, double-blind crossover study to assess the safety, immunogenicity, and pharmacokinetic comparability of Prolastin®-C Liquid to Prolastin®-C (lyophilized formulation), in 32 subjects.

Adverse reactions (as defined in the footnote to Table 2) occurring in >5% of subjects during the 16 week double-blind crossover treatment period are shown in Table 2.

**Table 2: Adverse Reactions Occurring in >5% of Subjects during the Double-Blinded Crossover Treatment**

| | **Prolastin®-C Liquid** (N=32) | **Prolastin®-C (Lyophilized Formulation)** (N=31) |
|---|---|---|
| Adverse Reaction*,† | No. of Subjects with Adverse Reaction (percentage of all subjects) | No. of Subjects with Adverse Reaction (percentage of all subjects) |
| Diarrhea | 2 (6) | 0 |
| Fatigue | 2 (6) | 0 |

* An adverse reaction is defined as any adverse event that occurred where either a) the event was not considered “unrelated” to administration of the product, or b) the occurrence was during or within 72 hours of the end of the previous infusion of the product, or c) the investigator's causality assessment of the event was missing or indeterminate, or d) the incidence during treatment with 1 investigational product was 130% or more of the incidence during treatment with the other investigational product.

† Source: the randomized double-blinded comparator trial of Prolastin®-C Liquid vs Prolastin®-C.

Table 3 below displays the adverse reaction (defined as per Table 2) rate as a percentage of infusions received during the 16 week double-blinded treatment period.

**Table 3: Adverse Reaction Frequency as a Percent of All Infusions and Occurring More than Once in the Alpha$_1$-Proteinase Inhibitor (Human) Liquid Group during the 16 Week Double Blinded Treatment Period**

| Adverse Reaction* | **Prolastin®-C Liquid** No. of infusions: 252 | **Prolastin®-C (Lyophilized Formulation)** No. of infusions: 245 |
|---|---|---|
| | No. of Adverse Reactions (percentage of all infusions) | No. of Adverse Reactions (percentage of all infusions) |
| Diarrhea | 3 (1.2) | 0 |
| Fatigue | 2 (0.8) | 0 |

* Source: the randomized double-blinded comparator trial of Prolastin®-C Liquid vs Prolastin®-C.

A total of 23 COPD exacerbations were reported for a total of 18 subjects (3/18 subjects experienced a COPD exacerbation on both Prolastin®-C Liquid and Prolastin®-C (the Lyophilized Formulation). Twelve subjects (12/32, 38%) receiving Prolastin®-C Liquid had a total of 13 COPD exacerbations and 9 subjects (9/31, 29%) receiving Prolastin®-C had a total of 10 COPD exacerbations. All COPD exacerbations were of mild or moderate intensity. Of the subjects who experienced a COPD exacerbation, 2 subjects were naïve to Alpha$_1$-Proteinase Inhibitor (Human) augmentation therapy. Three COPD exacerbations occurred during the Follow-Up Period after Prolastin®-C Liquid treatment and 1 COPD exacerbation occurred after Prolastin®-C treatment. No COPD exacerbation was reported as a serious adverse event during Prolastin®-C Liquid treatment and all were reported as either mild or moderate in severity. No treatment-emergent COPD exacerbation resulted in early discontinuation from the study. None of the COPD exacerbations reported were considered to be related to the investigational product.

Immunogenicity testing was performed using a tiered approach which included screening, confirmatory and antibody titer enzyme-linked immunosorbent assay (ELISA) methods, and a neutralizing antibody method which utilized statistically derived cut points. All 32 enrolled subjects treated with Prolastin®-C Liquid and/or Prolastin®-C were tested for immunogenicity to detect alpha$_1$-PI antibodies. Blood samples for immunogenicity testing were drawn prior to investigational product administration at Week 1 (Baseline) and at Weeks 9, 17, and 20. Samples collected at Week 1 (Baseline) and at Weeks 9 and 20 were tested for immunogenicity while samples collected at Week 17 were to be tested for immunogenicity only if deemed appropriate (e.g. unexpected PK profile). Based on the PK profiles of the subjects, immunogenicity testing of the Week 17 samples was not needed. No immunogenicity response was observed in subjects dosed with Prolastin®-C Liquid or Prolastin®-C in the clinical study, demonstrating comparable safety profiles for the 2 treatments with respect to immunogenicity.

Two separate prior clinical studies were conducted with Prolastin®-C (the lyophilized formulation): Study 11815, a 20 week, open-label, safety study in 38 subjects, and Study 11816, a 16 week, randomized, double-blind, cross-over pharmacokinetic comparability study vs. Prolastin® (original product) in 24 subjects, followed by an 8 week open label treatment with Prolastin®-C.

**Table 4: Adverse Event Frequency as a % of all infusions (> 0.5%)**
***Irrespective of Causality***

| | **Prolastin®-C** No. of infusions: 1132 | **Prolastin®** No. of infusions: 192 |
|---|---|---|
| Adverse Event | No. of AE (percentage of all infusions) | No. of AE (percentage of all infusions) |
| Upper respiratory tract infection | 9 (0.8%) | 1 (0.5%) |
| Urinary tract infection | 8 (0.7%) | 0 |
| Nausea | 7 (0.6%) | 0 |
| Headache | 4 (0.4%) | 3 (1.6%) |
| Arthralgia | 2 (0.2%) | 2 (1.0%) |

Source: studies 11815 and 11816

**Table 5: Adverse Reactions Occurring during the First 8 Weeks of Each Double-Blinded Treatment**

| | **Prolastin®-C** (N=24) | **Prolastin®** (N=24) |
|---|---|---|
| Adverse Reaction*,† | No. of Subjects with Adverse Reaction (percentage of all subjects) | No. of Subjects with Adverse Reaction (percentage of all subjects) |
| Pruritus | 1 (4) | 0 |

* An adverse reaction is defined as any treatment-emergent adverse event that was considered drug "potentially related" to the investigational product.

† Source: 11816 study.

**Table 6: Adverse Reaction Frequency as a Percent of All Infusions during the First 8 Weeks of Each Double-Blinded Treatment**

| | **Prolastin®-C** No. of infusions: 188 | **Prolastin®** No. of infusions: 192 |
|---|---|---|
| Adverse Reaction*,† | No. of Adverse Reaction (percentage of all infusions) | No. of Adverse Reaction (percentage of all infusions) |
| Pruritus | 1 (0.5) | 0 |

* An adverse reaction is defined as any treatment-emergent adverse event that was considered drug "potentially related" to the investigational product.

† Source: 11816 study.

**Table 7: Adverse Reactions Occurring in Two or More Subjects (>5%) during the 20 Week Single-Arm Open-Label Trial**

| Adverse Reaction[*,†] | **Prolastin®-C** (N=38) |
|---|---|
| | No. of Subjects with Adverse Reaction (percentage of all subjects) |
| Chills | 2 (5) |

[*] An adverse reaction is defined as any treatment-emergent adverse event that was considered drug "potentially related" to the investigational product.

[†] Source: 11815 study.

The most common drug related adverse event was chills, which occurred in 3.2% of Prolastin®-C patients across both studies (n=2). The following drug related adverse events were reported in 1.6% of patients (one subject each) treated with Prolastin®-C: malaise, headache, rash (severe), hot flush, and pruritus.

In clinical studies with the original product, Prolastin®, six reactions were observed with 517 infusions, or 1.16%. None of the reactions was severe. The adverse reactions reported included delayed fever (maximum temperature rise was 38.9°C, resolving spontaneously over 24 hours) occurring up to 12 hours following treatment (0.77%), light-headedness (0.19%), and dizziness (0.19%). Mild transient leukocytosis and dilutional anemia several hours after infusion have also been noted.

### 8.5 Post-Market Adverse Reactions

Additionally, since market entry of $Alpha_1$-Proteinase Inhibitor (Human), occasional reports of the following events have been received: flu-like symptoms, allergic-like reactions, dyspnea, tachycardia, shortness of breath, bronchospasm, wheezing, urticaria, back pain, clamminess, sweating, diarrhea, and fatigue.

Less frequently, the following have also been reported: hypotension, anxiety, cyanosis, swelling of hands and feet, angio-, facial and lip edema, nasal congestion, sinusitis, abdominal pains or cramps, pallor, and weakness.

Rare cases of hypersensitivity reactions, transient increase in blood pressure or hypertension and chest pain have also been reported.

Very rare cases of anaphylactic/anaphylactoid reactions have also been reported.

## 9 DRUG INTERACTIONS

### 9.1 Drug-Drug Interactions

Interactions with other drugs have not been established.

### 9.2 Drug-Food Interactions

Interactions with food have not been established.

### 9.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.4 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Alpha$_1$-antitrypsin deficiency is a chronic, hereditary, usually fatal, autosomal co-dominant disorder in which a low concentration of alpha$_1$-PI (alpha$_1$-antitrypsin)[1] is associated with slowly progressive severe emphysema that most often manifests itself in the third to fourth decades of life. The emphysema is typically worse in the lower lung zones. The pathogenesis of development of emphysema in alpha$_1$-antitrypsin deficiency is not well understood at this time. It is believed, however, to be due to a chronic biochemical imbalance between elastase (an enzyme capable of degrading elastin tissues, released by inflammatory cells, primarily neutrophils, in the lower respiratory tract) and alpha$_1$-PI (the principal inhibitor of neutrophil elastase), which is deficient in alpha$_1$-antitrypsin disease. As a result, it is believed that alveolar structures are unprotected from chronic exposure to elastase released from a chronic, low-level burden of neutrophils in the lower respiratory tract, resulting in progressive degradation of elastin tissues. The eventual outcome is the development of emphysema. Neonatal hepatitis with cholestatic jaundice appears in approximately 10% of newborns with alpha$_1$-antitrypsin deficiency. In some adults, alpha$_1$-antitrypsin deficiency is complicated by cirrhosis. Since severe alpha$_1$-antitrypsin deficiency is one of the most common serious genetic conditions, it is recommended that families of index cases also be screened for deficiency of the alpha$_1$-PI protein.

A large number of phenotypic variants of alpha$_1$-antitrypsin deficiency exists. The most severely affected individuals are those with the PiZZ variant, typically characterized by alpha$_1$-PI serum levels <35% normal. Epidemiologic studies of individuals with various phenotypes of alpha$_1$-antitrypsin deficiency have demonstrated that individuals with endogenous serum levels of alpha$_1$-PI $\leq$ 50 mg/dL (based on commercial standards) have a risk of >80% of developing emphysema over a lifetime. However, individuals with endogenous alpha$_1$-PI levels >80 mg/dL, in general, do not manifest an increased risk for development of emphysema above the general population background risk. From these observations, it is believed that the “threshold” level of alpha$_1$-PI in the serum required to provide adequate anti-elastase activity in the lung of individuals with alpha$_1$-antitrypsin deficiency is about 80 mg/dL (11 µM), based on commercial standards for immunologic assay of alpha$_1$-PI. The maintenance of blood serum levels of alpha$_1$-PI above 80 mg/dL (11 µM) is historically thought to provide therapeutically relevant anti-neutrophil elastase protection.

### 10.2 Pharmacodynamics

In clinical studies, patients received Alpha$_1$-Proteinase Inhibitor (Human) replacement therapy,

[1] Although the terms "Alpha$_1$-Proteinase Inhibitor" and "alpha$_1$-antitrypsin" are used interchangeably in the scientific literature, the hereditary disorder associated with a reduction in the serum level of alpha$_1$-PI is conventionally referred to as "alpha$_1$-antitrypsin deficiency" while the deficient protein is referred to as “Alpha$_1$-Proteinase Inhibitor”

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).

No drug attributable pharmacodynamic changes were observed in any of the clinical studies to date. Increased anti-neutrophil elastase activity is achieved in both serum and ELF following intravenous administration. Development of antibodies directed against alpha$_1$-PI has not been reported in any of the studies. Similarly, transmission of viral disease has not been seen.

### 10.3 Pharmacokinetics

In clinical studies, the mean *in vivo* recovery of alpha$_1$-PI was 4.2 mg (immunologic)/dL per mg (functional)/kg body weight administered. The half-life of alpha$_1$-PI *in vivo* was approximately 6 days.

In another study, several individuals with the PiZ phenotype of alpha$_1$-antitrypsin deficiency were treated with a partially purified preparation of alpha$_1$-PI. Using this material, five adults with severe serum alpha$_1$-antitrypsin deficiency (PiZ phenotype) and advanced emphysema received 4 grams of Alpha$_1$-Proteinase Inhibitor (Human), intravenously, at weekly intervals for four doses. During this period of weekly replacement therapy alpha$_1$-PI serum levels were maintained at ≥70 mg/dL, the level likely required for effective anti-elastase protection of the lung.

In a subsequent study, nineteen subjects with alpha$_1$-antitrypsin deficiency received Prolastin® (the original lyophilized formulation), intravenously 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 (see CLINICAL TRIALS).

A further study evaluated an intravenous dosage of 250 mg/kg of human alpha$_1$-Proteinase Inhibitor (Prolastin®) administered every 28 days in an attempt to assess whether the intervals between dosing could be increased beyond one week, while still retaining protective anti-neutrophil elastase alpha$_1$-PI levels in the serum and the epithelial lining fluid (ELF). Nine subjects were included. Analysis of the repeated dosage data indicated that overall, the serum alpha$_1$-PI levels fell to below 80 mg/dL at about 18-21 days after the administration of the 250 mg/kg dosage, reaching a nadir of about 50 mg/dL at 28 days. A serum level of 70 to 80 mg alpha$_1$-PI/dL equates to a pulmonary alveolar ELF level of 1.2 µmol. This is the ELF level which is considered protective against elastase activity in the normal subject.

## 11 STORAGE, STABILITY AND DISPOSAL

Pronextica Liquid should be stored refrigerated at 2-8°C. Do not freeze. Product may be stored at room temperatures not exceeding 25ºC for up to one month, after which the product must be used or immediately discarded. Administer within 3 hours after entering the vial.

## 12 SPECIAL HANDLING INSTRUCTIONS

None.

# PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

### Drug Substance

Proper name: Alpha$_1$-Proteinase Inhibitor (Human)

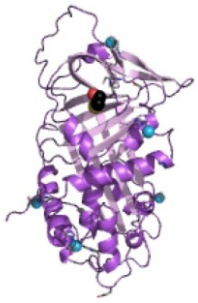
Chemical name: $\alpha_1$-antitrypsin [CAS 9041-92-3]

Molecular formula: 394 amino acid sequence (see below)

```
1    EDPQGDAAQKTDTSHHDQDHPTFNKITPNLAEFAFSLYRQLAHQSNSTNI
51   FFSPVSIATAFAMLSLGTKADTHDEILEGLNFNLTEIPEAQIHEGFQELL
101  RTLNQPDSQLQLTTGNGLFLSEGLKLVDKFLEDVKKLYHSEAFTVNFGDT
151  EEAKKQINDYVEKGTQGKIVDLVKELDRDTVFALVNYIFFKGKWERPFEV
201  KDTEEEDFHVDQVTTVKVPMMKRLGMFNIQHCKKLSSWVLLMKYLGNATA
251  IFFLPDEGKLQHLENELTHDIITKFLENEDRRSASLHLPKLSITGTYDLK
301  SVLGQLGITKVFSNGADLSGVTEEAPLKLSKAVHKAVLTIDEKGTEAAGA
351  MFLEAIPMSIPPEVKFNKPFVFLMIEQNTKSPLFMG KVVNPTQK
```

Molecular mass: 51 000 Daltons

Structural formula: 3D Structure of uncleaved Alpha$_1$ Protease Inhibitor (Alpha$_1$-PI)



Physicochemical properties: isoelectric point of 4.4 to 4.8; functions by forming a tight complex with target proteases; glycoprotein (12% carbohydrate) with 3 N-asparagine linked chains which are externally exposed and cover the surface of the protein

### Product Characteristics:

Pronextica Liquid is prepared from pooled human plasma of normal donors by modification and refinements of the cold ethanol plasma fractionation method first described by Cohn. Alpha$_1$-proteinase inhibitor (Human) is obtained from Fraction IV-1 paste, which undergoes several purification steps, including the viral inactivation steps discussed below. The specific activity of Pronextica Liquid is $\geq$ 0.7 mg functional alpha$_1$-PI per mg total protein, and the concentration of alpha$_1$-PI is $\geq$ 40 mg/mL. Pronextica Liquid has a pH of 6.6-7.4, a total sodium concentration of $\leq$ 100 mEq/L, a sodium phosphate content of 13-25 mM, and is stabilized with 200-300 mM alanine.

Each vial of Pronextica Liquid contains 1000 mg functionally active alpha$_1$-PI, as determined by capacity to neutralize porcine pancreatic elastase. Alpha$_1$-Proteinase Inhibitor (Human) contains no preservative and must be administered by the intravenous route.

**Viral Inactivation**

When medicinal biological products are administered, infectious diseases due to transmission of pathogens cannot be totally excluded. However, in the case of products prepared from human plasma, the risk of transmission of pathogens is reduced by epidemiological surveillance of the donor population and selection of individual donors by medical interview; testing of individual donations and plasma pools; and the presence in the manufacturing processes of steps with demonstrated capacity to inactivate/remove pathogens.

In the manufacturing process of Pronextica Liquid, there are several steps with the capacity for virus inactivation or removal. The main steps of the manufacturing process that contribute to the virus clearance capacity are as follows:

- Cold ethanol fractionation
- PEG precipitation
- Depth filtration
- Solvent Detergent treatment
- 15 nm Nanofiltration

Cold Ethanol Fractionation, PEG Precipitation, and Depth Filtration are important steps for purifying $alpha_1$-PI and they have a very high pathogen removal capacity. Two additional steps, Solvent/Detergent Treatment and 15 nm Nanofiltration, are included in the process as dedicated steps with pathogen clearance capacity. The Solvent/Detergent Treatment step can effectively inactivates enveloped viruses. The 15 nm Nanofiltration step has been implemented because of its high capacity to remove enveloped and non-enveloped viruses as small as 18 nm.

To provide additional assurance of the pathogen safety of the final product, the capacity of the Pronextica Liquid manufacturing process to remove and/or inactivate viruses has been demonstrated by laboratory spiking studies on a scaled down process model using a wide range of viruses with diverse physicochemical properties.

The combination of all of the above mentioned measures provides the final product with a high margin of safety from the potential risk of transmission of infectious 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. These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed by the manufacturing process.

## 14 CLINICAL TRIALS

Studies described in this section have been conducted with either Prolastin®-C Liquid (a product comparable to Pronextica Liquid except for source of the plasma starting material), or one of two lyophilized products (Prolastin®-C or it's predecessor Prolastin®). The original

lyophilized Alpha$_1$-Proteinase Inhibitor (Human), approved and marketed in Canada was Prolastin®. This was replaced with Prolastin®-C, which is produced through a modification of the Prolastin® manufacturing process that results in improved product purity, a higher concentration of the same active substance, and a greater demonstrated margin of safety from the risk of transmission of infectious pathogens. Pronextica Liquid and Prolastin®-C Liquid are manufactured using the same process as Prolastin®-C, except that they are not lyophilized, and sodium chloride content is replaced with a stabilizer (alanine).

### 14.1 Trial Design and Study Demographics

Prolastin®-C Liquid

The pharmacokinetic (PK) study was a randomized, double-blind, crossover trial comparing Prolastin®-C Liquid to Prolastin®-C conducted in 32 adult subjects age 44 to 71 years with severe Alpha$_1$-antitrypsin deficiency. Eighteen subjects were male and 14 subjects were female. Sixteen subjects were randomized to each treatment sequence. All but one subject had the PiZZ genotype and the remaining subject was PiSZ. Twenty-eight subjects had received prior Alpha$_1$-PI augmentation therapy and 4 subjects were naïve to Alpha$_1$-PI augmentation therapy. Study subjects were randomly assigned to receive either 60 mg/kg body weight of functional Prolastin®-C Liquid or Prolastin®-C 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, 8, and 9, as well as before infusion at Weeks 14, 15, 16, and 17. A final PK sample was drawn at Week 20 (4 weeks after the last dose) to correct for endogenous Alpha$_1$-PI levels.

Prolastin®-C (lyophilized product) Studies

Prolastin®-C has been studied in 62 individual subjects in 2 separate clinical trials. The first study was a crossover pharmacokinetic study (Study 11816) involving 24 adult subjects with severe Alpha$_1$-antitrypsin deficiency. The primary pharmacokinetic endpoint was the $AUC_{0\text{-}7days}$ following 8 weeks of treatment with Prolastin®-C or Prolastin®.

The second clinical trial was a multi-center, open-label safety study conducted to evaluate the safety and tolerability of Prolastin®-C (Study 11815). In this study, 38 subjects were treated with weekly IV infusions of 60 mg/kg body weight of Prolastin®-C for 20 weeks. Half the subjects were naïve to previous 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$_1$-antitrypsin 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$_1$-antitrypsin deficiency. These groups were distributed evenly between the naïve and non-naïve cohorts.

Prolastin® Studies

In earlier clinical studies conducted with Prolastin® (Alpha$_1$-Proteinase Inhibitor (Human)), 23 subjects with the PiZZ variant of congenital alpha$_1$-antitrypsin deficiency and documented destructive lung disease participated in a study of acute and/or chronic replacement therapy with Alpha$_1$-Proteinase Inhibitor (Human).

## 14.2 Study Results

Prolastin®-C (lyophilized product) Studies

Results from the multi-center, open-label safety study conducted to evaluate the safety and tolerability of Prolastin®-C (Study 11815) indicate that Prolastin®-C is safe and well-tolerated.

Prolastin® Studies

In 23 subjects with the PiZZ variant of congenital alpha1-antitrypsin deficiency and documented destructive lung disease, the mean *in vivo* recovery of $alpha_1$-PI was 4.2 mg (immunologic)/dL per mg (functional)/kg body weight administered. The half-life of $alpha_1$-PI *in vivo* was approximately 4.5 days. Based on these observations, a program of chronic replacement therapy was developed. Nineteen of the subjects in these studies received Prolastin® replacement therapy, 60 mg/kg body weight, once weekly for up to 26 weeks (average 24 weeks of therapy). With this schedule of replacement therapy, blood levels of $alpha_1$-PI were maintained above 80 mg/dL (based on the commercial standards for $alpha_1$-PI immunologic assay). Within a few weeks of commencing this program, bronchoalveolar lavage studies demonstrated significantly increased levels of $alpha_1$-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 $Alpha_1$-Proteinase Inhibitor (Human).

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. All subjects remained seronegative for HIV antibody. None of the subjects developed any detectable antibody to $alpha_1$-PI or other serum protein.

Long-term controlled clinical trials to evaluate the effect of chronic replacement therapy with $Alpha_1$-Proteinase Inhibitor (Human) on the development of or progression of emphysema in patients with congenital $alpha_1$-antitrypsin deficiency have not been performed. Estimates of the sample size required of this rare disorder and the slow, progressive nature of the clinical course have been considered impediments in the ability to conduct such a trial. Studies to monitor the long-term effects have continued since the approval of Prolastin®. Open-label assessments of patient registries, using untreated patients as controls, have evaluated the effects of long-term (up to 7 years) treatment with $Alpha_1$-Proteinase Inhibitor (Human) on patients with $alpha_1$ antitrypsin deficiency. The results of these assessments, while not as definitive as randomized, controlled trials, indicate that patients treated with $Alpha_1$-Proteinase Inhibitor (Human) have significantly reduced mortality and significantly slowed decline in $FEV_1$ compared to untreated patients with $alpha_1$-antitrypsin deficiency.

## 14.3 Comparative Bioavailability Studies

Prolastin®-C Liquid

The key pharmacokinetic parameter was the area under the serum $Alpha_1$-PI concentration-by-antigenic-assay-time curve ($AUC_{0\text{-}7\ days}$) following 8 weeks of treatment with Prolastin®-C Liquid or Prolastin-C. The 90% confidence interval (1.03-1.08) for the ratio of $AUC_{0\text{-}7days}$ for Prolastin®-C Liquid and Prolastin®-C indicated that the 2 products are bioequivalent, i.e. the entire range falls within the 0.80–1.25 interval. $AUC_{0\text{-}7days}$ of the serum-equivalent $Alpha_1$-PI concentration

by functional assay and $C_{max}$ by antigenic and functional assays gave comparable results for Prolastin®-C Liquid and Prolastin®-C, as shown in Table 8.

**Table 8: Results of Statistical Analysis of Pharmacokinetic Parameters at Steady-State (PK Population)**

| | $AUC_{0\text{-}7days}$ (mg*h/mL) | | | | | |
|---|---|---|---|---|---|---|
| | Antigenic Content | | | Functional Activity | | |
| Treatment | Geometric LSM | Geometric LSM Ratio | 90% CI of Geometric LSM Ratio | Geometric LSM | Geometric LSM Ratio | 90% CI of Geometric LSM Ratio |
| Prolastin®-C Liquid n=30 | 203.57 | 1.05 | 1.03, 1.08 | 169.86 | 1.04 | 1.01, 1.07 |
| Prolastin®-C n=28 | 193.71 | | | 163.52 | | |
| Treatment | $C_{max}$ (mg/mL) | | | | | |
| Prolastin®-C Liquid n=30 | 2.517 | 1.04 | 1.00, 1.09 | 2.062 | 1.04 | 1.00, 1.07 |
| Prolastin®-C n=28 | 2.415 | | | 1.992 | | |

The half-life ($t_{1/2}$) for antigenic content was comparable, specifically 156.39 hours versus 164.10 hours for Prolastin®-C Liquid versus Prolastin®-C, respectively. Similar half-life was also observed when assessed by functional activity between Prolastin®-C Liquid versus Prolastin®-C (126.57 hours versus 126.82 hours respectively).

Figure 1 shows the serum-equivalent concentration (functional activity) vs. time curves of Alpha$_1$-PI after intravenous administration of Prolastin®-C Liquid and Prolastin®-C.

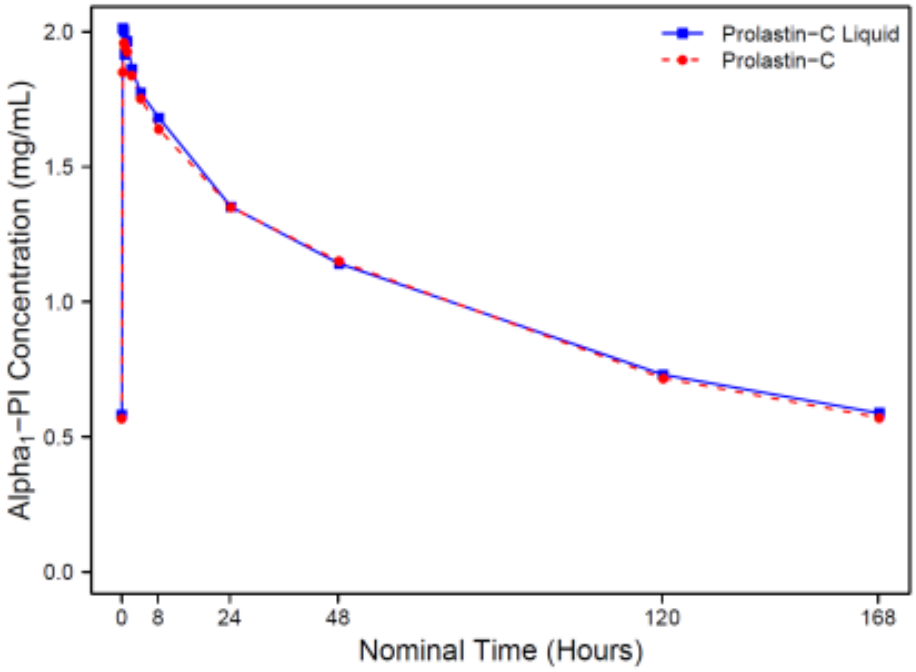



**Figure 1: Mean Serum-equivalent Alpha$_1$-PI Concentration (functional activity) vs. Time Curves Following Treatment with Prolastin®-C Liquid or Prolastin®-C**

Serum trough levels measured at steady state during the PK study using an antigenic content assay showed Prolastin®-C Liquid resulted in a mean trough of 17.7 µM and Prolastin®-C resulted in a mean trough of 16.9 µM.

Prolastin®-C (lyophilized product) Studies

The geometric least-squares mean ratio for Prolastin®-C vs. Prolastin® was 1.03, with a 90% confidence interval of 0.97-1.09. A ratio so close to 1.0 indicates a high degree of concordance between treatments.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

### General Toxicology:

Single-dose Toxicity

The acute toxicity of alpha$_1$-PI administered intravenously, was determined in mice, rats, and rabbits and compared to the acute toxicity of the excipient control substance. At an infusion rate of 3 mL/min, the $LD_{50}$ of alpha$_1$-PI in mice was 3750 mg/kg bw (150±6 mL/kg) and that of the control was >156 mL/kg. In rabbits, there was no indication of any toxicity at the highest dose of alpha$_1$-PI tested, 517 mg/kg bw (20.7 mL/kg), which was infused at a rate of 6 mL/min although one of three rabbits each in the groups receiving 172 mg/kg bw and 517 mg/kg bw, respectively, of alpha$_1$-PI died during the observation period. These two deaths were not related to administration of alpha$_1$-PI. An additional three rabbits were administered alpha$_1$-PI at a dose of 517 mg/kg bw without any sign of adverse effect throughout the 14-day observation period.

Repeat-dose Toxicity

A series of rabbits also received alpha$_1$-PI or excipient control substance, 227 mg/kg bw (9.1 mL/kg), administered intravenously at a rate of 6 mL/min, daily on five successive days. All rabbits in the study gained weight and there were no significant differences in weight gain on the 6th day or 33rd day of the study between animals receiving alpha$_1$-PI compared to those receiving control substance. No significant hematologic abnormalities were noted on the 6th or 33rd days of the study following five consecutive days of administration of alpha$_1$-PI. An unexplained decrease in the cholesterol level of animals receiving alpha$_1$-PI was seen on day six in one series of animals but was not seen when repeated in another group. Two rabbits died during the course of the study, both of which were receiving alpha$_1$-PI. One rabbit died on day 4, with diarrhea present, and its death was felt to be related to infection. The other rabbit died on day 27 (three weeks after the infusion period) and histopathology revealed no probable cause of death. Overall, no effects directly ascribable to administration of alpha$_1$-PI were detected in animals undergoing necropsy and histopathologic analysis on days 6 or 33 of the study.

No studies were performed regarding subchronic or chronic toxicity.

### Genotoxicity:

No studies were performed regarding genotoxicity.

### Reproductive and Developmental Toxicology:

No studies were performed regarding reproductive toxicity.

## PATIENT MEDICATION INFORMATION

### READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

### PRONEXTICA™ LIQUID

### (Alpha$_1$-Proteinase Inhibitor (Human))

Read this carefully before you start taking Pronextica Liquid and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about Pronextica Liquid.

### What is Pronextica Liquid used for?

Alpha$_1$ Antitrypsin Deficiency, also known as Alpha$_1$, is an inherited disorder that causes significant reduction in the naturally occurring protein alpha$_1$ antitrypsin (AAT).

Scientists also call this protein Alpha$_1$-Proteinase Inhibitor (alpha$_1$-PI) because it inhibits not only trypsin but also other enzymes called proteinases.

It is believed that Alpha$_1$ affects as many as 100,000 people in the United States and similar numbers in Europe. Alpha$_1$ is most common among Caucasians of Northern European and Iberian descent. It is the most common cause of genetic liver disease in children and genetic emphysema in adults.

Lung disease (emphysema) is the most common problem associated with a deficiency of AAT. AAT is produced by the liver and shields the body from damage caused by neutrophil elastase. Neutrophil elastase is an enzyme produced by white blood cells.

Under normal conditions, neutrophil elastase helps fight bacteria that cause infection. However, if not neutralized by AAT, neutrophil elastase can destroy healthy lung tissue.

Alveoli are tiny air sacs in the lungs, which are responsible for taking in oxygen and releasing carbon dioxide. When adequate levels of AAT are not present, the enzymatic activity of neutrophil elastase is not blocked and the fine elastic tissue supporting the alveoli is destroyed. Over time, enough alveoli are destroyed to cause the lungs to lose much of their elasticity, resulting in emphysema. Therefore, people with a deficiency of AAT are at high risk for developing emphysema.

There are many components to treating AAT. The goal is to maintain better lung function. This can be done through smoking cessation, asthma medications (if necessary), infection control, good nutrition, environment modifications, exercise, and stress management.

Pronextica Liquid is a treatment that helps restore the natural balance of enzymes in the lungs and protects them from the damage caused by neutrophil elastase.

### How does Pronextica Liquid work?

Pronextica Liquid , made from human plasma, is a concentrated form of AAT. Given as prescribed, Pronextica Liquid raises the blood and lung levels of AAT. This may help lessen damage to the lungs caused by the enzymatic activity of neutrophil elastase. Because Pronextica Liquid therapy augments or replaces AAT, it is known as "augmentation" or "replacement" therapy.

**What are the ingredients in Pronextica Liquid?**

Medicinal ingredients: Human alpha$_1$-proteinase inhibitor

Non-medicinal ingredients: alanine and sodium phosphate

**Pronextica Liquid comes in the following dosage forms:**

single use vials with a functional activity of 1000 mg (in 20 mL)

**Do not use Pronextica Liquid if:**

- you are allergic to alpha$_1$-proteinase inhibitor or to any ingredient in the formulation or component of the container
- your body does not make enough immunoglobulin A (IgA), which could cause you to have an allergic reaction to blood products that contain IgA
- you have previously had an allergic reaction to any alpha$_1$-proteinase inhibitor product

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Pronextica Liquid. Talk about any health conditions or problems you may have, including if you:**

- are pregnant or breastfeeding
- have had an allergic reaction to alpha$_1$-proteinase inhibitor or any of the other ingredients in the medicine

**Other warnings you should know about:**

Pronextica Liquid like other products made from human plasma, part of our blood, may contain viruses or other agents that can cause infection and illness. However, the processes used to make Pronextica liquid are specifically designed with the ability to destroy or remove these agents if they are present. You should discuss the risks and benefits of this product with your healthcare professional.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**How to take Pronextica Liquid:**

A doctor, nurse or other caregiver trained to give injections will give you your first treatments. In many cases, a healthcare professional will continue to give all treatments. However, in some cases you or a caregiver may also be trained to administer Pronextica Liquidyourself at home. A doctor must first determine whether this kind of home infusion by a caregiver or yourself is appropriate in your situation.

Before you or a caregiver administers Pronextica Liquid at home, you will be trained by a healthcare professional (nurse or doctor) on how to prepare the medication, how to safely infuse the medication, how to identify potential side-effects, and what to do if you experience such side-effects. Be sure to closely follow all instructions from your doctor and/or nurse. The

instructions below are provided as an example – any instructions from your doctor and/or nurse should be followed, even if they differ slightly from this information.

1) *Before using the Pronextica Liquid vials, it is important to check:*

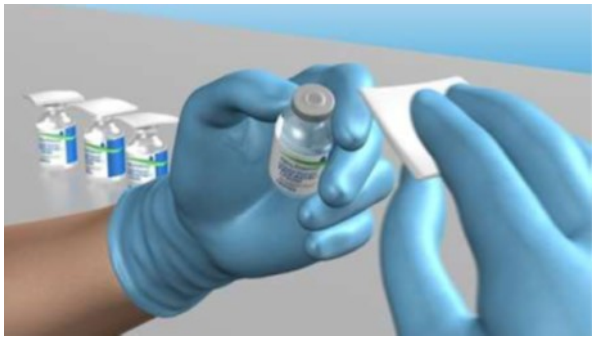
- The name of the drug on the carton and vial. Ensure it is Pronextica Liquid
- The expiry date on the carton and vial label. Do not use Pronextica Liquid after the expiry date. If the product was stored at room temperature, verify that no more than 30 days has gone by since the Pronextica Liquid was removed from the refrigerator.
- The protective cap(s). Do not use the product if the cap is not present or if it is broken or damaged.
- The product appearance. The product should be clear and colourless or pale yellow or pale green or pale brown and may contain a small number of protein particles. Do not use if the solution is discoloured or cloudy.

2) *Prepare a clean, flat surface for organizing your supplies, by wiping down with alcohol and using sterile technique at all times:*

- Remove the Pronextica Liquid vial(s) from the refrigerator and allow the vial(s) to warm to room temperature before proceeding. Do not apply heat to the vial(s). Do not place vial(s) in hot water or microwave.
- Collect all supplies:
    - Vial(s) of Pronextica Liquid as prescribed.
    - Alcohol wipes and sterile disposable gloves (not provided with product)
    - Intravenous (IV) Infusion Kit (not provided with product)
    - Normal saline solution to flush IV set (not provided with product)
    - Sharps container and infusion logbook (not provided with product)
    - If prescribed by your healthcare professional due to possible severe allergic symptoms: epinephrine injector. Keep near and easily accessible for every infusion, and carefully follow your healthcare professional's instructions if the need to use arises.

3) *Prepare the infusion dose using sterile technique at all times:*

- Wash and dry your hands thoroughly before preparing and administering Pronextica Liquid. Your healthcare professional may recommend that you use antibacterial soap or that you wear sterile, disposable gloves.
- Remove the protective cap and disinfect the stopper:
    - Remove the protective cap from the vial to expose the middle portion of the stopper.
    - Wipe the stopper with an alcohol swab and allow to air-dry.

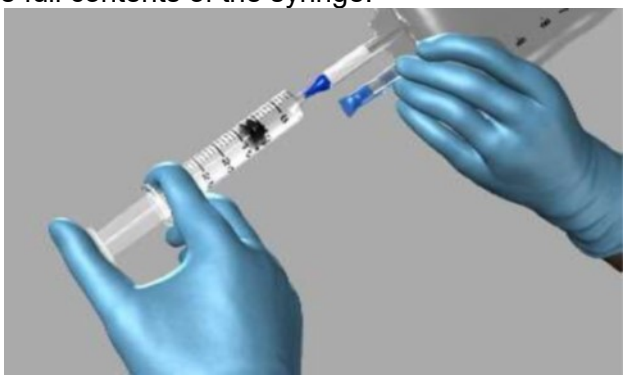


- Following your healthcare professional's directions, you may infuse directly from the vial, or pool (combine) the contents of the recommended number of Pronextica Liquid vials into an empty, sterile container (bag) for IV infusion, as described in the next step.
- If you have been instructed to pool the recommended number of Pronextica Liquid vials:
    - Attach the vented transfer spike securely to a sterile syringe by twisting it into place.
    - Next, insert the spike into the center of the stopper of the Pronextica Liquid vial.

    - Turn the vial upside down with the syringe attached. Pull back on the end of the plunger to draw the Pronextica Liquid solution from the vial into the syringe. Only touch the end of the plunger, do not touch the plunger shaft.

    - Remove (untwist) the syringe from the vented transfer spike.

- With the syringe tip pointing up, gently push the end of plunger up towards the body of the syringe to remove any air.
- Then attach the supplied needle to the syringe.
- Using an alcohol swab, wipe the injection port of the empty sterile container (bag) and allow to air-dry.
- Carefully remove the needle's protective cover.
- Insert the needle into the injection port of the empty sterile container (bag).
- Push the end of plunger up towards the body of the syringe, filling the bag with the full contents of the syringe.



- Repeat these steps with the number of Pronextica Liquid vials recommended to obtain the prescribed dose.
- The prepared product must be used within 3 hours of entering the first vial.

4) *Instructions for preparing the infusion set:*

- On the IV infusion set, close the roller clamp.
- An extension set can be attached if necessary.
- After removing the cap from the spike at the end of the IV infusion set, insert the spike into the infusion port on the IV bag containing Pronextica Liquid. The bag can then be hung on the IV pole or hook.
- The drip chamber located at the top of the IV infusion set should be squeezed until the drip chamber is half-full.
- Slowly open the roller clamp on the IV set and allow the tube to be filled with Pronextica Liquid to remove air bubbles.

5) *Instructions for preparing the infusion site(s):*

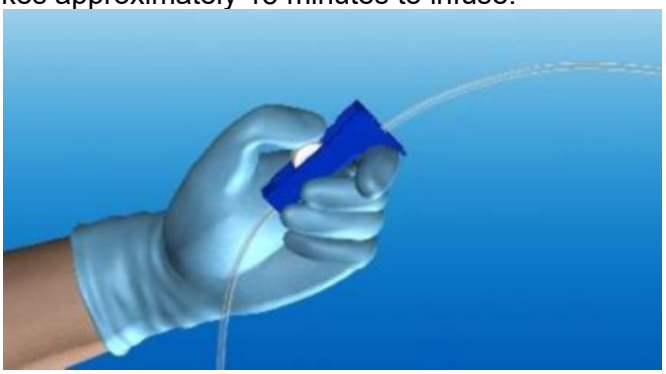
- Follow your healthcare professional's recommendations on selecting, preparing and rotating the infusion site.

6) *Instructions on inserting and securing the intravenous needle set:*

- Apply a tourniquet to your upper arm.
- Using an alcohol swab, wipe the skin well at the injection site. Wait for the skin to air-dry before proceeding.
- Carefully remove the needle cover and insert the butterfly needle into the vein.
- Release the tourniquet.
- Attach a syringe containing normal saline to the butterfly infusion set.
- To check for proper placement of the needle, flush the butterfly IV needle set with the normal saline. If proper placement was not successful, repeat steps.
- Once proper placement is achieved, remove the saline syringe. Attach the filled IV infusion set that is connected to the IV bag containing Pronextica Liquid solution.

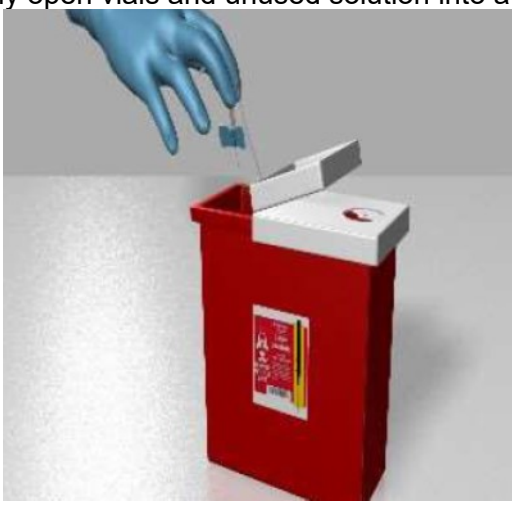
7) *Instructions for infusing Pronextica Liquid:*

- Open the roller clamp and administer the room temperature Pronextica Liquid solution at the recommended rate. This rate will be determined by your healthcare professional. The maximum recommended infusion rate for Pronextica Liquid is 0.08 milliliter per kilogram body weight per minute; the recommended dose of 60 mg/kg takes approximately 15 minutes to infuse.



- Check the site of infusion occasionally throughout the infusion, monitoring for signs of infusion related side effects, such as redness, swelling, or product leaking out at the infusion site.
- Follow your healthcare professional's instructions if infusion related adverse reactions occur.
- After completion of the infusion, remove the needle from the vein.
- Using sterile gauze, apply pressure to the infusion site for several minutes. The site can then be covered with a sterile bandage.

- **Important:** Do not recap the IV needle set. This needle set must be placed into a hard-walled sharps container. Do not dispose of the infusion supplies in regular household trash.
- Discard any open vials and unused solution into a sharps container.



*8) Instructions for documenting the infusion:*

- In your infusion log:
  - Record the lot number and the expiry date of the vial(s).
  - Record the date, the time the infusion started and stopped, the dose, the site of infusion, and any reactions.

Report all side effects to your healthcare professional

**Usual dose:**

Your doctor will determine the amount of Pronextica Liquid that is right for you, and when your treatments should be given.

**Overdose:**

There have been no reported cases of overdose for Pronextica Liquid or other Alpha$_1$ Proteinase Inhibitor (Human) products manufactured by Grifols. The effects of an overdose are not known.

If you think you, or a person you are caring for, have taken too much Pronextica Liquid, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**Missed Dose:**

It is important that you receive Pronextica Liquid as instructed by your healthcare professional. You should consult him/her if a treatment is missed.

**What are possible side effects from using Pronextica Liquid?**

These are not all the possible side effects you may have when taking Pronextica Liquid. If you experience any side effects not listed here, tell your healthcare professional.

Pronextica Liquid is well tolerated, but side effects are occasionally reported. The most common side effects were diarrhea and fatigue, each of which occurred in 6% of subjects enrolled in clinical studies. Talk with your healthcare provider if you have the following side effects following treatment: fever, light-headedness, dizziness, flu-like symptoms, allergic-like reactions, chills, trouble breathing, rash, abnormal heartbeat, changes in blood pressure, or chest pain.

| **Serious side effects and what to do about them** | | | |
|---|---|---|---|
| Symptom / effect | Talk to your healthcare professional | | Stop taking drug and get immediate medical help |
| | Only if severe | In all cases | |
| **Severe allergic reaction** (e.g. rash, hives, itching, difficulty breathing or swallowing, swelling of hands, face or mouth) | | √ | √ |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Pronextica Liquid should be stored refrigerated (2-8ºC). It may also be stored for up to one month at room temperature (not to exceed 25°C) after which the product must be used or discarded. It should not be frozen. Administer within 3 hours after first entering the vial.

Keep out of reach and sight of children.

**If you want more information about Pronextica Liquid:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes

this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; or by calling 1-866-482-5226.

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