Answers to

Frequently Asked Questions

for Patients Transitioning From Lyophilized (Powder) PROLASTIN®-C to PROLASTIN®-C LIQUID

The same therapy trusted by patients with alpha-1 and their doctors for more than 25 years in a convenient, ready-to-use liquid formulation

Now that PROLASTIN-C LIQUID is available, you may have some questions. The following includes answers to some common questions you may have right now. Take comfort in knowing that the PROLASTIN DIRECT® program will be there for you every step of the way as you transition from PROLASTIN-C powder to PROLASTIN-C LIQUID.

After reading this information, if you have additional questions, contact the PROLASTIN DIRECT program toll free at 1-800-305-7881.

Please see Important Safety Information on the back cover, and see enclosed full Prescribing Information for PROLASTIN-C LIQUID.
**Will my PROLASTIN DIRECT® program benefits, services, or support change?**

No, with PROLASTIN®-C LIQUID, you will still receive the same ongoing, personalized support you have always received from the PROLASTIN DIRECT program. You will continue to work with your PROLASTIN DIRECT program Patient Service Coordinator, infusion nurse, and AlphaNet Coordinator.

**Does PROLASTIN-C LIQUID work the same as PROLASTIN-C powder?**

Yes, PROLASTIN-C LIQUID is the same medicine you have been receiving in a powder formulation. PROLASTIN-C LIQUID has been proven to effectively raise alpha1-antitrypsin protein levels in patients with alpha-1.

**What are the side effects of PROLASTIN-C LIQUID?**

The overall frequency of adverse events was similar between PROLASTIN-C LIQUID and PROLASTIN-C powder formulation, and no adverse events led to treatment withdrawal. The most common adverse reactions during clinical trials in >5% of subjects were diarrhea and fatigue, each of which occurred in 2 subjects (6%).

**How do I obtain PROLASTIN-C LIQUID?**

To transition to PROLASTIN-C LIQUID, you will need a new prescription. Contact EVERSANA, the only specialty pharmacy that fills PROLASTIN-C LIQUID prescriptions, and they will happily handle the process for you.

**Is PROLASTIN-C LIQUID still shipped and stored the same way?**

PROLASTIN-C LIQUID continues to be shipped directly from EVERSANA to the same address on file. It will continue to ship in the same packaging currently used to deliver your PROLASTIN-C. Store in your refrigerator at 36-46°F (2-8°C) for the period indicated by the expiration date on its label. Product may be stored at room temperatures not exceeding 77°F (25°C) for up to one month, after which the product must be used or immediately discarded. Do not freeze.

Please see Important Safety Information on the back cover, and see enclosed full Prescribing Information for PROLASTIN-C LIQUID.
**Frequently Asked Questions (cont'd)**

**Does PROLASTIN-C LIQUID need to be mixed?**

No, PROLASTIN-C LIQUID is ready to infuse. That means it no longer needs to be mixed by you or your infusion nurse before your infusion, which will shorten your preparation time.

**Does the liquid mean more volume for my infusions?**

No, your infusion volume will be the same as your current PROLASTIN-C.

**Does the product include latex?**

No, the PROLASTIN-C LIQUID vial stopper is latex free.

**Does the liquid take longer to infuse?**

No, the average PROLASTIN-C LIQUID infusion takes about 15 minutes when given at the recommended rate of 0.08 mL/kg/min—the same as PROLASTIN-C powder, but without the added mixing time.

**Is PROLASTIN-C LIQUID covered by my insurance?**

Insurance coverage of PROLASTIN-C LIQUID is typically the same as PROLASTIN-C, but every insurance plan is different. Once your prescription has been updated, the PROLASTIN DIRECT program insurance specialists will automatically verify your specific coverage for PROLASTIN-C LIQUID.

If your health insurance plan doesn’t cover PROLASTIN-C LIQUID today, the insurance specialists at PROLASTIN DIRECT will continue to monitor your health insurance plan and keep you informed as they coordinate the monthly delivery of your PROLASTIN-C powder formulation.

After reading this information, if you have additional questions, contact the PROLASTIN DIRECT program toll free at 1-800-305-7881.
Important Safety Information

PROLASTIN®-C LIQUID is an alpha,1-proteinase inhibitor (human) (alpha,1-PI) indicated for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of alpha,1-PI (alpha,1-antitrypsin deficiency).

Limitations of Use

- The effect of augmentation therapy with any alpha,1-PI, including PROLASTIN-C LIQUID, on pulmonary exacerbations and on the progression of emphysema in alpha,1-PI deficiency has not been conclusively demonstrated in randomized, controlled clinical trials.

- Clinical data demonstrating the long-term effects of chronic augmentation or maintenance therapy with PROLASTIN-C LIQUID are not available.

- PROLASTIN-C LIQUID is not indicated as therapy for lung disease in patients in whom severe alpha,1-PI deficiency has not been established.

PROLASTIN-C LIQUID is contraindicated in immunoglobulin A (IgA)-deficient patients with antibodies against IgA or patients with a history of anaphylaxis or other severe systemic reaction to alpha,1-PI products.

Hypersensitivity reactions, including anaphylaxis, may occur. Monitor vital signs and observe the patient carefully throughout the infusion. If hypersensitivity symptoms occur, promptly stop PROLASTIN-C LIQUID infusion and begin appropriate therapy.

Because PROLASTIN-C LIQUID is made from human plasma, it may carry a risk of transmitting infectious agents, eg, viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens.

The most common adverse reactions during PROLASTIN-C LIQUID clinical trials in >5% of subjects were diarrhea and fatigue, each of which occurred in 2 subjects (6%).

Please see enclosed full Prescribing Information for PROLASTIN-C LIQUID.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.
FULL PRESCRIBING INFORMATION
USING IN SPECIFIC POPULATIONS
HIGHLIGHTS OF PRESCRIBING INFORMATION
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2 DOSAGE AND ADMINISTRATION
3 CONTRAINDICATIONS
4 WARNINGS AND PRECAUTIONS
5 HYPERSENSITIVITY REACTIONS
6 ADVERSE REACTIONS
7 USE IN SPECIFIC POPULATIONS
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The most common adverse reactions observed at a rate of >5% in subjects receiving PROLASTIN® C LIQUID were diarrhea and fatigue, each of which occurred at an incidence of 5% to 10%.

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reactions observed in the clinical trials may not reflect the rates observed in practice, and may not reflect the rates observed during longer term or widespread community use, or may not reflect dosages and monitoring conditions prevailing in clinical practice.

One clinical trial was conducted with PROLASTIN® C LIQUID: a 16-week, multicenter, randomized, double-blind, crossover clinical trial to assess the pharmacokinetic comparability of PROLASTIN® C LIQUID vs PROLASTIN® C (Alpha 1-PI) in healthy subjects. Adverse reactions (as defined in the footnote to Table 1) occurring in >5% of subjects during the 16-week double-blind crossover treatment period are shown in Table 1.

Table 1: Adverse Reactions Occurring in >5% of Subjects During the 16-Week Double-Blinded Crossover Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>No. of Subjects with Adverse Reaction (percentage of all subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>2 (5.3%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (5.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (10.5%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (7.9%)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (5.3%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (5.3%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2 (5.3%)</td>
</tr>
</tbody>
</table>

6.4.2 Postmarketing Experience
Ten exacerbations of chronic obstructive pulmonary disease were reported by 6 subjects in the 20-week single-arm open-label clinical trial comparing PROLASTIN® C to PROLASTIN® C LIQUID. In 4 subjects (5%) during the 8-week single-arm open-label treatment period, and in 6 subjects (7%) during the 16-week double-blind crossover trial, 4 subjects (7%) had a total of 4 exacerbations during the double-blind crossover phase, 4 subjects (17%) had a total of 4 exacerbations during PROLASTIN® C treatment, and 2 subjects (9%) had a total of 2 exacerbations during PROLASTIN® C LIQUID treatment. Two additional exacerbations in 2 subjects (8%) occurred during the 8-week open-label treatment period with PROLASTIN® C LIQUID. The overall rate of pulmonary exacerbations during treatment with either product was 6.9 exacerbations per subject-year.

6.5 Other Tumor Types
As an adverse event-allergic reactions occurred in any event that occurred at the event rather than at a rate of >5%, with an incidence of >1% in subjects receiving PROLASTIN® C LIQUID whose treatment was 130% or more of the incidence during treatment with 1 investigational product was 130% or more of the incidence during the treatment with PROLASTIN® C LIQUID. The overall rate of pulmonary exacerbations during treatment with either product was 6.9 exacerbations per subject-year.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the incidence of antibodies to PROLASTIN® C LIQUID is based on the expected postmarketing experience for PROLASTIN® C LIQUID clinical trials in >5% of subjects in >2 clinical trials (28 subjects in 2 subjects [6%]).

Table 3: Adverse Reactions Occurring During the First 8 Weeks of Each Double-Blinded Treatment

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PROLASTIN® C LIQUID (N=32)</th>
<th>PROLASTIN® C (N=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>3 (9.4%)</td>
<td>2 (6.5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (3.1%)</td>
<td>2 (6.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (15.6%)</td>
<td>5 (16.1%)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (3.1%)</td>
<td>2 (6.5%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (3.1%)</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1 (3.1%)</td>
<td>1 (3.2%)</td>
</tr>
</tbody>
</table>

6.2 Postmarketing Experience
Because postmarketing reporting of adverse reactions is voluntary and from a variety of sources, the incidence of adverse reactions reported here may not reflect the rates observed in practice, and may not reflect the rates observed during longer term or widespread community use, or may not reflect dosages and monitoring conditions prevailing in clinical practice.

Adverse Reactions occurring in ≥5% of subjects treated with PROLASTIN® C LIQUID are listed in Table 2 below. Adverse reactions occurring in ≥5% of subjects treated with PROLASTIN® C are listed in Table 3 below. Adverse reactions occurring in ≥5% of subjects treated with PROLASTIN® C LIQUID during the 8-week single-arm open-label treatment period are listed in Table 4 below.
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 prion disease. No evidence of TSE infectivity was detected. These studies provide reasonable assurance that low levels of vCJD infectivity, if present in the starting material, would be removed.

12. PHARMACOKINETICS

12.1 Mechanism of Action

Alpha-PI deficiency is an autosomal, co-dominant, hereditary disorder characterized by low levels of Alpha-PI in plasma. Smoking is an important risk factor for the development of emphysema in patients with Alpha-PI deficiency.1,2 Because emphysema is more prevalent only in patients with severe deficiency of Alpha-PI, deficiency, augmentation therapy with Alpha-PI is indicated only in patients with Alpha-PI deficiency who have additional risk factors.

Some Alpha-PI alleles are associated with clinically apparent Alpha-PI deficiency.4 Approximately 66% of all deficiency patients are homozygous for the PiZZ genotype, 28% of deficiency patients have a PiSZ genotype, and 6% of deficiency patients have a PiMZ genotype. It is important to note that the PiMZ genotype does not necessarily result in decreased levels of functional Alpha-PI.

Augmenting the levels of functional pro tease inhibitor by intravenous infusion is an appropriate therapeutic intervention to mitigate the increased risk associated with severe deficiency. The primary goal is to provide protection to the lower respiratory tract by correcting the imbalance between neutrophil elastase and protease inhibitors. With Alpha-PI infusion, the protease activity of any Alpha-PI product actually protects the lower respiratory tract from progressive emphysema changes that have not been demonstrated in adequately powered clinical trials. Although the maintenance of blood levels of Alpha-PI (antigenically measured) above 11 μg/mL has been historically postulated to provide therapeutic benefit, it is important to note that this has not been proven. Individuals with severe Alpha-PI deficiency have been shown to have increased neutrophil and elastase elevations in tracheal aspirates. However, several studies have demonstrated that treatment with normal levels of Alpha-PI can reduce lung epithelial lining fluid normal from normal individuals, and some PiMZ individuals, with Alpha-PI levels above 1 mg/mL have emphysema attributed to Alpha-PI deficiency.

The pharmacokinetics of Alpha-PI in patients with Alpha-PI deficiency and normal controls are well described. Approximately 90% of the administered dose remains in the circulation, and the remaining 10% is cleared by the liver. The plasma half-life is proportional to the administration dose, with increases in the PiZ allele.4 Individuals with the PiZZ variant typically have serum Alpha-PI levels 10 to 15 times lower than normal controls and an increased risk for developing emphysema over their lifetimes. In addition, PiSZ individuals, whose serum Alpha-PI levels are intermediate to PiZZ and normal controls, will inherit both the PiZ and PiM alleles.

In a controlled clinical trial, the PiZZ allele was demonstrated to be associated with an increased risk for developing emphysema, regardless of whether their serum Alpha-PI levels were lower or higher than normal controls.

12.2 Pharmacokinetic Parameters

Serum Alpha-PI concentrations 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 μg/mL and a mean AUC 0-7 days of 55.3 mg·h/mL. 

A randomized, double-blind, crossover pharmacokinetic (PK) study comparing PROLASTIN-C LIQUID to PROLASTIN was conducted in 24 adult subjects aged 40 to 72 with severe Alpha-1-PI deficiency. All subjects were receiving chronic augmentation therapy with Alpha-PI at the time of the study. Sixteen subjects were naïve to previous Alpha-1-PI augmentation therapy; the remaining eight subjects had received prior augmentation therapy with PROLASTIN or PROLASTIN-C. The double-blind portion of the study was designed the same as the randomized, double-blind, crossover PK study comparing PROLASTIN-C LIQUID to PROLASTIN described above.

The pharmacokinetic parameters of Alpha-PI in plasma, based on serum-equivalent functional activity assays, showed comparability between PROLASTIN-C treatment and PROLASTIN treatment, as shown in Table 8.

Table 8: Pharmacokinetic Parameters of Alpha-PI in Plasma

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean (CV%)</th>
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</tr>
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<tbody>
<tr>
<td>PROLASTIN-C LIQUID</td>
<td>155.9 (32%)</td>
<td>157.8 (31%)</td>
</tr>
<tr>
<td>PROLASTIN-C</td>
<td>154.7 (32%)</td>
<td>154.6 (32%)</td>
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</table>

13. NONCLINICAL

13.1 Toxicology

Intravenous administration of five daily doses of PROLASTIN-C LIQUID to rabbits at doses of 60 mg/kg per day (10-fold higher dose than the recommended human dose of 6 mg/kg administered weekly) did not result in any toxicity. However, there were no differences in safety and tolerability of PROLASTIN-C LIQUID and PROLASTIN.

14. CLINICAL STUDIES

The clinical efficacy of PROLASTIN-C LIQUID in influencing the course of pulmonary emphysema in adult patients with severe Alpha-1-PI deficiency is based on a limited number of adequately powered, randomized, controlled clinical trials.

A randomized, double-blind, crossover trial of Alpha-PI documented emphysema were performed in a single-arm, open-label clinical trial with PROLASTIN, the predecessor product. Fourteen subjects, 12 adult patients with severe Alpha-1-PI deficiency (median age 56 years, range 28-67), received PROLASTIN-C LIQUID for 20 weeks. Half the subjects were naïve to previous Alpha-1-PI augmentation prior to entering the study. A diagnosis of severe Alpha-1-PI deficiency was confirmed by the demonstration of the PiZZ genotype in 32 of 38 (84.2%) subjects, and 6 of 38 (15.8%) had the PiSZ genotype. Nineteen of the subjects received PROLASTIN, 60 mg/kg, once weekly for up to 20 weeks. The clinical efficacy of PROLASTIN-C LIQUID and PROLASTIN-C treatment in influencing the course of pulmonary emphysema in patients with severe Alpha-1-PI deficiency was studied in an open-label, randomized, crossover trial described above, in which 31 subjects received PROLASTIN-C LIQUID, PROLASTIN-C, and PROLASTIN in a crossover design. The first treatment was PROLASTIN-C LIQUID for 20 weeks, followed by PROLASTIN-C or PROLASTIN. The second treatment was PROLASTIN-C or PROLASTIN, followed by PROLASTIN-C LIQUID for 20 weeks. The clinical efficacy of PROLASTIN-C LIQUID treatment was assessed using a variety of clinical efficacy endpoints.

15. HOW SUPPLIED/STORAGE AND HANDLING

PROLASTIN-C LIQUID is supplied in a single-use vial with the total Alpha-PI functional activity in milligrams, labeled on the vial and label. Components of the packaging do not contain natural rubber latex .

Table 6: Pharmacokinetic Parameters of Alpha-PI in Plasma

<table>
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<tr>
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<td>PROLASTIN-C LIQUID</td>
<td>154.7 (32%)</td>
<td>154.6 (32%)</td>
</tr>
</tbody>
</table>

16. PATIENT COUNSELING INSTRUCTIONS

Inform patients of the signs of hypersensitivity reactions including urticaria, asthma, bronchospasm, angioedema, or anaphylaxis; chest; headache; hypotension; and syncope. Advise patients to discontinue use of the product if these symptoms occur. Advise patients to seek medical attention if the symptoms occur. Inform patients of the signs of thromboembolism including chest pain, shortness of breath, and dyspnea; headache; chills; fever; and syncope. Advise patients to seek medical attention if these symptoms occur. Inform patients of the signs of neurologic disorders including headache; emotional lability; memory loss; confusion; delirium; and seizures. Advise patients to seek medical attention if these symptoms occur.

17. PATIENT INFORMATION

Inform patients that PROLASTIN-C LIQUID is made from human plasma and may carry a risk of transmitting infectious agents that can cause disease (e.g., viruses, the human immunodeficiency virus). In addition, some viral infections may still be found in the donated plasma for certain current virus infections, and by inactivating any remaining infectious agents during manufacturing. (see Warnings and Precautions (5.7)).

Inform patients that administration of PROLASTIN-C LIQUID has been demonstrated to cause anaphylactic reactions, anaphylaxis, urticaria, and angioedema. Advise patients to discontinue use of the product if any of these symptoms occur. Advise patients that the use of PROLASTIN-C LIQUID for prophylaxis of pulmonary exacerbations and on the rate of progression of emphysema has not been demonstrated in adequately powered, randomized, controlled clinical trials for any Alpha-1-PI product. (see Clinical Studies (14))