FULL PRESCRIBING INFORMATION

INSTRUCTIONS AND USAGE

PROLASTIN-C (Alpha, Prohibitive Inhibitor) (Human) (Alfa) (PI) indicated for chronic augmentation and maintenance therapy to stabilize with clinical evidence of emphysema due to severe lability by the manufacturer or downstream products, the total amount of functionally active Alpha 1-PI in milligrams is printed on the vial label and carton. In the single-arm, open-label safety trial, chronic treatment failure rate of 30% subjects who were normo-vascular reaction (defined as a bone-marrow derived cell count < 5,000 x 10^6/L), in the absence of bone-marrow derived cell count ≥ 5,000 x 10^6/L and should be treated with other vasoactive agents such as vasopressin or ephedrine. Patient Registry (TARR) to report all infections thought by a physician possibly to have been transmitted by this product to Grifols Therapeutics Inc. at 1-800-238-0397 or FDA at 1-888-358-4285 or at www.grifols.com/registry.

ADVERSE REACTIONS

The most serious adverse event observed during clinical trials with PROLASTIN-C was death observed within 60 days of starting treatment with PROLASTIN-C, which led to withdrawal of the subject from the trial. One subject was reported in clinical studies. PROLASTIN-C caused 3 cardiovascular deaths, 2 pneumonia, 1 gastrointestinal hemorrhage, 1 hypotension, 1 meningitis, 1 myocardial infarction, 1 renal failure, and 1 thrombosis.

1. Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, may occur. Monitor vital signs and observe the patient carefully throughout the infusion. Should hypersensitivity symptoms be observed, promptly discontinue the infusion and treat the patient appropriately. The treatment is characterized by a systemic reaction to PROLASTIN-C or another Alpha 1-PI product.

2. Pain

Pain may occur during or after infusion, especially around the intravenous site. Treatment is not required unless the pain is severe. Pain may be reduced by use of acetaminophen or aspirin.

3. Hematologic

In the U.S. general population, the estimated background risk of major birth defect and miscarriage in infants born to women exposed to PROLASTIN-C is approximately 10% (0.01-0.1). The risk of major birth defects is 10% (0.01-0.1) in the absence of any vasoactive agents such as vasopressin or ephedrine. It is unknown whether PROLASTIN-C causes death. The overall rate of pulmonary exacerbations during treatment with either product was 0.03 exacerbations per subject-year.

Table 4: Five-Year Radon Data for the PROLASTIN-C Manufacturing Process

<table>
<thead>
<tr>
<th>Year</th>
<th>Radon Concentration (pCi/L)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>124</td>
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5.4 log 10 of West Nile virus, a clinically relevant enveloped virus.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of virus (HAV), as well as the following model viruses: bovine viral diarrhea virus (BVDV), a surrogate for hepatitis C virus; pseudorabies virus (PRV), a surrogate for large enveloped DNA viruses (e.g., herpes viruses); vesicular stomatitis virus (VSV), a model for enveloped viruses; reovirus type 3 (R3), a model for double-stranded RNA viruses.

The goal of the investigational HBV NAT test is to detect low levels of viral nucleic acid; however, the significance of a negative result for the investigational HBV NAT test has not been established. By in-process testing, all Sigma Francis' ACA was 6739, and the final Sigma Francis' ACA was 1219.

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

6.4 Pregnancy

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Job No.: 238703 / 238692 / 239051

Date: 3/30/2016, 4/8, 4/11, 4/14, 5/31, 6/15

Client: Grifols Therapeutics Inc.

Cat. No.: 38041626

ID: 1.43

Size: 15x11

Spec. #: 026427 / 088773

Proof: 6

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6.2 Pregnancy

There are no data with PROLASTIN-C use in pregnant women to inform a drug-associated risk. Because PROLASTIN-C can cause fetal harm when administered to a pregnant woman, and can result in neonatal death, PROLASTIN-C should be given to pregnant women only if clearly needed.

6.1 Clinical Trial Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice, and the significance of any differences cannot be assumed. The incidence of serious adverse reactions was not increased compared with placebo. However, the incidence of serious adverse reactions was not increased compared with placebo. However, the incidence of serious adverse reactions was not increased compared with placebo. However, the incidence of serious adverse reactions was not increased compared with placebo.
The pharmacokinetic parameters of Alpha 1-PI in plasma, based on functional activity assays, showed comparability between PROLASTIN-C treatment and PROLASTIN treatment, as shown in Table 5.

Table 5: Pharmacokinetic Parameters of Alpha 1-PI in Plasma

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PROLASTIN-C</th>
<th>PROLASTIN</th>
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<tbody>
<tr>
<td>Tmax (h)</td>
<td>1.2 (1.1)</td>
<td>1.2 (1.1)</td>
</tr>
<tr>
<td>Cmax (µM)</td>
<td>0.2 (0.1)</td>
<td>0.2 (0.1)</td>
</tr>
<tr>
<td>AUC (h*µM)</td>
<td>0.4 (0.3)</td>
<td>0.4 (0.3)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.6 (1.5)</td>
<td>1.6 (1.5)</td>
</tr>
</tbody>
</table>

Alpha 1-PI functional activity, in milligram, is stated on the label of the PROLASTIN-C vial.

A total of 25 subjects with the FZZ genotype and documented emphysema were enrolled in a single-blind, randomized, crossover clinical trial with PROLASTIN. None of the subjects received PROLASTIN, 60 mg, once weekly for up to 24 weeks (average 20 weeks). Blood levels of Alpha 1-PI were maintained above 11 µM. Bronchial lavage studies demonstrated statistically significant increased levels of Alpha 1-PI and functional AN1 in the epithelial lining fluid of the lower respiratory tract of the lung, as compared to levels prior to dosing. A total of 25 individual subjects were enrolled in clinical trials. In addition to the crossover pharmacokinetic study, 16 subjects were randomized and received PROLASTIN prior to entering the study. A degree of severe Alpha 1-PI deficiency was confirmed by the demonstration of the FZZ genotype in 24 of 38 (63.2%) subjects, and 6 of 38 (15.8%) subjects presented with other Alpha 1-PI deficiency. These groups were distributed equally between the male and non-male cohorts.


14. HOW SUPPLIED/STORAGE AND HANDLING

PROLASTIN-C is supplied in a kit comprising a single vial of PROLASTIN-C lyophilized powder one 28 mL of sterile Water for Injection, USP, a transfer needle, and a filter needle. The total dose of PROLASTIN-C activity, in milligram, is stated on the label of the PROLASTIN-C kit. PROLASTIN-C is supplied in the following two presentations. The two kits are equivalent, differing only in the manufacturer of the sterile Water for Injection.

- **Aggregatobe Alpha-1-PI (PROLASTIN-C)**
  - NDC Number: 0002-580-12 or 0003-30-16
  - 1.90 mg
  - 20 mL

- **PROLASTIN-C** does not exceed 22°C (72°F) for the period indicated by the expiry date label on its container.

15. PATIENT CONSULTATION INSTRUCTIONS

- Inform patients of the signs of hypersensitivity reactions including fever, generalized edema, rashes, urticaria, immediate or delayed. In the event of anaphylaxis, patients must be instructed to immediately stop infusion, seek emergency medical assistance, and report the reaction to the manufacturer. Patients must be informed that immediate emergency care, including epinephrine, is required. In the event of severe reactions, intravenous epinephrine should be administered in addition to supportive care, including oxygen, IV fluids, airway support, and appropriate inotropic support.

- Inform patients that PROLASTIN-C is made from human plasma and may carry a risk of transmitting infectious agents that can cause disease (e.g., viruses, the V-CJD agent and, theoretically, the CJD agent). Explain that the risk of PROLASTIN-C transmitting an infectious agent has been reduced by pooling plasma donors for this product to select certain infective agents. By pooling plasma from multiple donors, dilution reduces the risk. There have been no reports of infectious agents during manufacturing. The risk of transmission is extremely low. This product is not made from human plasma and contains no human protein.