DESCRIPTION

Alpha1-Proteinase Inhibitor (Human), Prolastin® is a sterile, lyophilized preparation of purified human Alpha1-Proteinase Inhibitor (alpha1-PI), also known as alpha1-antitrypsin. Prolastin is intended for use in therapy of congenital alpha1-antitrypsin deficiency.

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

<table>
<thead>
<tr>
<th>Process Step</th>
<th>Log10 Virus Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td>≥4.4</td>
</tr>
<tr>
<td>BVDV</td>
<td>≥3.2</td>
</tr>
<tr>
<td>PRV</td>
<td>≥3.4</td>
</tr>
<tr>
<td>EV71</td>
<td>≥3.3</td>
</tr>
<tr>
<td>PEG Precipitation</td>
<td>≥3.3</td>
</tr>
<tr>
<td>Depth Filtration</td>
<td>≥2.4</td>
</tr>
<tr>
<td>Pasteurization</td>
<td>≥2.3</td>
</tr>
<tr>
<td>Accumulated Log10 Reduction ≥2.8</td>
<td></td>
</tr>
</tbody>
</table>

The specific activity of Prolastin is ≥0.35 mg functional alpha1-PI/mg protein and when reconstituted as directed, the concentration of alpha1-PI is ≤20 mg/mL. When reconstituted, Prolastin has a pH of 6.6–7.4, a sodium content of 100–210 mEq/L, a chloride content of 60–180 mEq/L, a sodium phosphate content of 0.015–0.025 M, a polyethylene glycol content of not more than (NMT) 5 ppm, and NMT 0.1% sucrose. Prolastin contains small amounts of other plasma proteins including alpha1-plasmin inhibitor, alpha1-antichymotrypsin, C1-esterase inhibitor, haptoglobin, antithrombin III, alpha1-lipoprotein, albumin, and IgA.

Each vial of Prolastin contains the labeled amount of functionally active alpha1-PI in milligrams per vial (mg/vial), as determined by capacity to neutralize porcine pancreatic elastase. Prolastin contains no preservative and must be administered by the intravenous route.

CLINICAL PHARMACOLOGY

Alpha1-antitrypsin deficiency is a chronic, hereditary, usually fatal, autosomal recessive disorder in which the low concentration of alpha1-PI (alpha1-antitrypsin) is associated with slowly progressive, severe panacinar emphysema that most often manifests itself in the third to fourth decades of life.2-9 Although the terms "Alpha1-Proteinase Inhibitor" and "alpha1-antitrypsin" are used interchangeably in the scientific literature, the hereditary disorder associated with a reduction in the serum level of alpha1-PI is conventionally referred to as "alpha1-antitrypsin deficiency" while the deficient protein is referred to as "Alpha1-Proteinase Inhibitor".16 The emphysema is typically worse in the lower lung zones.4,8,9 The pathogenesis of development of emphysema in alpha1-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 elastic fibers) released from chronic exposure to elastase released from a chronic, low-level burden of elastase in the lower respiratory tract, resulting in progressive degradation of elastic tissues.6,7 The eventual outcome is the development of emphysema. Neontal hepatitis with cholestatic jaundice appears in approximately 10% of newborns with alpha1-antitrypsin deficiency.11 The spectrum of disease in some adults with alpha1-antitrypsin deficiency is complicated by cirrhosis.15

A large number of phenotypic variants of alpha1-antitrypsin deficiency exists.11 The most severely affected individuals are those with the PIZZ variant, typically characterized by alpha1-PI serum levels ≤20 mg/mL.11,12,18 Epidemiologic studies of individuals with various phenotypes of alpha1-antitrypsin deficiency have demonstrated that individuals with endogenous serum levels of alpha1-PI ≤50 mg/dL (based on commercial standards) have a risk of >80% of developing emphysema over a lifetime.2,3,6,11 However, individuals with endogenous alpha1-PI levels >80 mg/dL, in general, do not manifest an increased risk for development of emphysema.11 Complete blood counts, liver chemistries, and serum protein electrophoresis were performed in all patients. There were no clinical or laboratory indications that patients were jaundiced.

Long-term controlled clinical trials to evaluate the effect of chronic replacement therapy with Prolastin on the development of or progression of emphysema in patients with congenital alpha1-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 study such a trial.17 Studies to monitor the long-term effects will continue as part of the postapproval process.

INDICATIONS AND USAGE

Congenital Alpha1-Antitrypsin Deficiency

Alpha1-Proteinase Inhibitor (Human), Prolastin is indicated for chronic replacement therapy of individuals having congenital deficiency of alpha1-PI (alpha1-antitrypsin deficiency) with clinically demonstrable panacinar emphysema. Clinical and biochemical studies have demonstrated that with such therapy, it is possible to increase plasma levels of alpha1-PI, and that levels of functionally active alpha1-PI in the lung epithelial lining fluid are increased proportionately.10-20 As some individuals with alpha1-antitrypsin deficiency will not go on to develop panacinar emphysema, only those with evidence of such disease should be considered for chronic replacement therapy with Prolastin.21,22 Subjects with the PMZ or PIMS phenotypes of alpha1-antitrypsin deficiency should not be considered for such treatment as they appear to be at small risk for panacinar emphysema.23 Clinical data are not available on the long-term effects derived from chronic replacement therapy of individuals with alpha1-antitrypsin deficiency with Prolastin. Only adult subjects have received Prolastin to date. Prolastin is not indicated for use in patients other than those with PIZZ, PIZ(null) or PIZ(null)(null) phenotypes.

CONTRAINdications

Individuals with selective IgA deficiencies who have known antibody against IgA (anti-IgA antibody) should not receive Alpha1-Proteinase Inhibitor (Human). Prolastin, since these patients may experience severe reactions, including anaphylaxis, to IgA which may be present.

WARNINGS

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

The physician should discuss the risks and benefits of this product with the patient, before prescribing it to a patient. Prolastin therapy may be continued for as long as the patient and the physician believe it to be appropriate.

Alpha1-Proteinase Inhibitor (Human), Prolastin has been heat-treated in solution at 60°C for 10 hours in order to reduce the potential for transmission of infectious agents.21 No cases of hepatitis B or hepatitis C have been recorded to date in individuals receiving Prolastin. However, as with all products which are heat treated, the possibility of transmission of unknown agents to recipients cannot be excluded.

PRECAUTIONS

General

1. Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.

2. Administer only by the intravenous route.

3. As with any colloid solution, there will be an increase in plasma volume following intravenous administration of Alpha1-Proteinase Inhibitor (Human). Prolastin.25 Caution should therefore be used in patients at risk for circulatory overload.

4. Prolastin should be given alone, without mixing with other agents or diluting solutions.

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Animal reproduction studies have not been conducted with Alpha1-Proteinase Inhibitor (Human), Prolastin®. It is also not known whether Prolastin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Prolastin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

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

Pediatric Use

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

ADVERSE REACTIONS

Therapeutic administration of Alpha1-Proteinase Inhibitor (Human), Prolastin, 60 mg/kg weekly, has been demonstrated to be well tolerated. In clinical studies, six reactions were observed with 517 infusions of Prolastin, or 1.16%. None of the reactions was severe.18 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%).18 Mild transient leukocytosis and dilutional anemia several hours after infusion have also been noted.18 Since market entry, occasional reports of other flu-like symptoms, allergic-like reactions, chills, dyspnea, rash, tachycardia, and, rarely, hypotension have also been received. Rare cases of transient increase in blood pressure or hypertension and chest pain have also been reported.

DOSAGE AND ADMINISTRATION

FOR INTRAVENOUS USE ONLY

Each bottle of Alpha1-Proteinase Inhibitor (Human), Prolastin has the functional activity, as determined by inhibition of porcine pancreatic elastase,1 stated on the label of the bottle.

The “threshold” level of alpha1-PI in the serum believed to provide adequate anti-elastase activity in the lung of individuals with alpha1-antitrypsin deficiency is 80 mg/dL (based on commercial standards for alpha1-PI immunologic assay).12,14,15 However, assays of alpha1-PI based on commercial standards measure antigenic activity of alpha1-PI, whereas the labeled potency value of alpha1-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 alpha1-PI determined using commercial immunologic assays may not accurately reflect actual functional alpha1-PI levels. Therefore, although it may be helpful to monitor serum levels of alpha1-PI in individuals receiving Prolastin, using currently available commercial assays of antigenic activity, results of these assays should not be used to determine the required therapeutic dosage.

The recommended dosage of Prolastin is 60 mg/kg body weight administered once weekly. This dose is intended to increase and maintain a level of functional alpha1-PI in the epithelial lining of the lower respiratory tract, providing adequate anti-elastase activity in the lung of individuals with alpha1-antitrypsin deficiency.

Alpha1-Proteinase Inhibitor (Human), Prolastin may be given at a rate of 0.08 mL/kg/min or greater and must be administered intravenously. The recommended dosage of 60 mg/kg takes approximately 30 minutes to infuse.

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

STORAGE

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

REFERENCES


Talecris Biotherapeutics, Inc.
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U.S. License No. 1716

Talecris Biotherapeutics, Inc.

Cat. No. 08937789 Fonts: Attriumvirate Color: BLACK ID: 1.58
Size: 10.25 x 11.25 Date(s): 11/21, 11/28, 11/30, 12/19/06, 2/1, 1/10, 2/5, 2/6/07 Proof 16