



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Alpha₁-Proteinase Inhibitor (Human) (Aralast NP™, Aralast™, Glassia®, Prolastin®, Zemaira®)

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Hyperlink to Related Coverage Policies

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers intravenous alpha₁-proteinase inhibitor (human) (Aralast™, Glassia®, Prolastin®, Zemaira®) as medically necessary for the treatment of congenital alpha₁-proteinase inhibitor deficiency-associated lung disease when all of the following criteria are met:

- alpha₁-antitrypsin (AAT) concentration < 80 milligrams per deciliter (mg/dl) [or <11 micromolar (µM)]
- obstructive lung disease as defined by a forced expiratory volume in one second (FEV₁) of 30–65% of predicted or a rapid decline in lung function defined as a change in FEV₁ of > 120 mL/year
- non-smoker

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to Alpha₁-Proteinase Inhibitor (Human) (Aralast NP™, Aralast™, Glassia®, Prolastin®, Zemaira®) therapy.

CIGNA does not cover alpha₁-proteinase inhibitor (human) as a treatment for ANY of the following since each is considered experimental, investigational, or unproven (this list may not be all inclusive):

- isolated alpha₁-proteinase inhibitor deficiency-associated liver disease in the absence of obstructive lung disease
- cystic fibrosis

- diabetes mellitus

CIGNA does not cover the inhalation form of alpha1-proteinase inhibitor (human) since it is considered experimental, investigational, or unproven.

FDA Approved Indications

Aralast and Aralast NP

Aralast and Aralast NP are indicated for chronic augmentation therapy in patients having congenital deficiency of alpha₁-proteinase inhibitor (alpha₁-PI) with clinically evident emphysema. Clinical and biochemical studies have demonstrated that with such therapy, Aralast and Aralast NP is effective in maintaining target serum alpha₁-PI trough levels and increasing alpha₁-PI levels in epithelial lining fluid (ELF). Clinical data demonstrating the long-term effects of chronic augmentation or replacement therapy of individuals with Aralast and Aralast NP are not available. Safety and effectiveness in pediatric patients have not been established. Aralast and Aralast NP are not indicated as therapy for lung disease patients in whom congenital alpha₁-PI deficiency has not been established.

Glassia

Glassia is an alpha1-proteinase inhibitor that is indicated for chronic augmentation and maintenance therapy in adults with emphysema due to congenital deficiency of alpha1-proteinase inhibitor (Alpha1-PI), also known as alpha1antitrypsin deficiency. Glassia is not indicated as therapy for lung disease in patients in whom severe Alpha1-PI deficiency has not been established.

Prolastin

Prolastin is indicated for chronic replacement therapy of individuals having congenital deficiency of alpha₁-PI (alpha₁-antitrypsin deficiency) with clinically demonstrable panacinar emphysema.

Zemaira

Zemaira is indicated for chronic augmentation and maintenance therapy in individuals with alpha₁-PI deficiency and clinical evidence of emphysema. Zemaira increases antigenic and functional (ANEC) serum levels and lung epithelial lining fluid levels of alpha₁-PI. Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with Zemaira are not available. Safety and effectiveness in pediatric patients have not been established. Zemaira is not indicated as therapy for lung disease patients in whom severe congenital alpha₁-PI deficiency has not been established.

FDA Recommended Dosing

Aralast and Aralast NP

The recommended dosage of Aralast and Aralast NP is 60 mg/kg body weight administered once weekly by intravenous infusion. Aralast should be administered at a rate not exceeding 0.08 mL/kg body weight/minute. If adverse events occur, the rate should be reduced or the infusion interrupted until the symptoms subside. The infusion may then be resumed at a rate tolerated by the subject.

Glassia

For intravenous use only, dose = 60 mg/kg body weight once weekly. The infusion rate should not exceed 0.04 mL/kg body weight per minute (2.3).

Prolastin

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.

Zemaira

The recommended dose of Zemaira is 60 mg/kg body weight administered once weekly. When reconstituted as directed, Zemaira may be administered intravenously at a rate of approximately 0.08 mL/kg/min as determined

by the response and comfort of the patient. The recommended dosage of 60 mg/kg body weight will take approximately 15 minutes to infuse.

Drug Availability

Aralast and Aralast NP

Aralast and Aralast NP are supplied as a sterile, nonpyrogenic, lyophilized powder in single-dose vials. The following product packages are available: 0.5 g and 1.0 g. A suitable volume of sterile water for injection, USP diluent is provided (25 mL/0.5 g vial; 50 mL/1.0 g vial). Each vial is labeled with the total α_1 -PI functional activity in mg.

Glassia

Each carton of Glassia contains a single use vial containing 1 gram of functional Alpha1-PI in 50 mL of solution and a sterile filter needle.

Prolastin

Prolastin is supplied in 500mg/20ml and 1000mg/40 ml single use vials with the total of alpha1-PI functional activity stated on the label of each vial in milligrams. A suitable amount of sterile water for injection, USP is provided.

Zemaira

Zemaira is supplied in a single use vial containing the labeled amount of functionally active A1-PI, as stated on the label. Each product package contains one single use vial of Zemaira, one 20 mL vial of sterile water for injection, USP (diluent), and one vented transfer device.

General Background

Pharmacology/Disease Overview

Alpha₁-PI is a naturally occurring inhibitor of serine proteases, enzymes that aid in proteolytic destruction of the alveolar walls and connective tissue framework of the lung parenchyma. Exogenous administration of alpha₁-PI (human) in patients with congenital alpha₁-PI deficiency provides another source of enzyme inhibitor that protects lung tissues from proteolytic destruction.

Severe forms of alpha₁-PI deficiency (also called alpha₁-antitrypsin deficiency [AATD]) are associated with the development of slowly progressive, moderate to severe panacinar emphysema. However, because some individuals with alpha₁-PI deficiency will not develop panacinar emphysema, only those with evidence of such disease (i.e., clinically evident emphysema) should be considered for long-term replacement therapy with alpha₁-PI (human).

Guidelines

The American Thoracic Society and the European Respiratory Society (ATS/ERS) issued standards for the diagnosis and management of individuals with AATD in 2003. These standards recommend augmentation therapy with alpha₁-PI (human) for patients who are deficient in alpha₁-antitrypsin (AAT) (i.e., defined as serum concentration < 11 micromoles) with obstructive lung disease defined by a forced expiratory volume in one second (FEV₁) of 30–65% of predicted or a rapid decline in lung function defined as a change in FEV₁ of > 120 mL/year.

The ATS/ERS state that alpha₁-PI (human) does not confer benefit in, and is not recommended for, patients who have alpha₁-proteinase inhibitor deficiency-associated liver disease. Likewise, alpha₁-PI (human) is not indicated as treatment for patients with lung disease in whom congenital alpha₁-PI deficiency has not been established. The three available alpha₁-PI products are derived from pooled human plasma and are administered intravenously. The half-life of alpha₁-PI (human) is approximately 4.5 days.

Clinical Efficacy

Clinical and biochemical studies have demonstrated that the administration of alpha₁-PI (human) increases plasma levels of alpha₁-PI, and that levels of functionally active alpha₁-PI in the lung epithelial lining fluid are increased proportionately. However, long-term controlled clinical trials to evaluate the effect of chronic replacement therapy with alpha₁-PI (human) on the development or progression of emphysema in patients with

congenital AATD have not yet 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 trials. However, studies to monitor the long-term effects are continuing as part of the post-approval process. Phase IV clinical studies, required by the FDA, are currently being conducted. The FDA has required that studies of randomized, controlled, parallel, masked design be conducted to determine the effect of regular administration of alpha₁-PI (human) on one or more clinically meaningful endpoints (e.g., pulmonary exacerbations, serial pulmonary functions, and serial quantitative computerized axial tomographic [CT] lung scans).

Intravenous administration of alpha₁-PI (human) can increase lung concentrations of alpha₁-PI, but there are few data describing improved clinical outcomes. Most trials address surrogate outcomes such as lung function tests or lung volume. One trial is available comparing Prolastin[®] and Aralast[™] which showed equivalent results. An observational report of 1129 patients with AATD shows better survival rates for patients receiving alpha₁-PI (human) therapy than those who did not receive treatment (RR 0.64, 95% CI 0.43, 0.94, p = 0.02). This report outlined the greatest benefit for patients with an initial FEV₁ of 35–49% of predicted (RR 0.21, 95% CI 0.09–0.5, p < 0.001). An observational report of German patients with AATD shows that the rate of FEV₁ decline in patients with an initial FEV₁ of 30–65% of predicted is much less with treatment than without (64 mL/year vs. ~100 mL/year for historical controls, P=not reported). No published trials are available comparing Zemaira to another alpha₁-PI (human) product; however, data contained within FDA product labeling describes a comparison of Zemaira and Prolastin which showed equivalent results.

While there are few efficacy data, patients with an initial FEV₁ of 30–65% seem to benefit the most from augmentation therapy, with improved survival rates and a slower decline in FEV₁. Current guidelines support the use of augmentation therapy in this group of patients. No data are available regarding switching between brands of alpha₁-PI (human) products. There are no comparative trials assessing adverse effects between the alpha₁-PI (human) products.

One unpublished, randomized, controlled study compared Glassia to Prolastin, another purified human API. Fifty patients with congenital API deficiency and clinical signs and symptoms of emphysema were randomized to receive either Glassia (n = 33) or Prolastin (n = 17) at a dose of 60 mg/kg IV once weekly for 12 weeks. The primary objective was to assess API trough antigenic and functional levels over weeks 7 – 12 of the study. The 95% CI for the mean difference in antigenic trough levels (-0.08 to 2.67 micromoles) and functional trough levels (-1.04 to 1.63 micromoles) between groups met prespecified criteria for noninferiority. No clinical endpoints were assessed.

Ongoing Studies/Investigational Uses

There are limited data available regarding the inhalation of alpha₁-PI (human) products. Brand et al. (2003) showed that nebulizer systems varied in their ability to deposit product consistently. A nebulizer that is individualized to use an optimized breathing pattern provides the best product disposition. There are no data regarding the efficacy of inhalation therapy in patients with AATD.

Therapy continues to be studied for use in cystic fibrosis and emerging information regarding recruiting for studies for use in new onset diabetes.

Adverse Reactions/Contraindications

Relatively few patients have been treated with these agents. The product labeling for the agents reports that adverse effects generally occur in < 2% of patients and include fever, light-headedness, dizziness, somnolence, cough, pain at the infusion site, headache, and pruritus.

Alpha₁-PI (human) is contraindicated in individuals with selective IgA deficiencies (i.e., IgA concentrations less than 15 mg/dL) who have known antibodies against IgA, because they may experience severe adverse reactions, including anaphylaxis, to IgA which may be present. Alpha₁-PI (human) is made from human plasma and may contain infectious agents that can cause disease, such as viruses. Although many measures have been taken to reduce the risk that this product will transmit an infectious agent, this product can still potentially transmit disease.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

HCPCS Codes	Description
J0256	Injection, alpha a-proteinase inhibitor, human, 10 mg

ICD-9-CM Diagnosis Codes	Description
273.4	Alpha 1-antitrypsin deficiency
491.20- 491.22	Obstructed chronic bronchitis
492.8	Other emphysema
493.21- 493.22	Chronic obstructed asthma

Experimental/Investigational/Unproven/Not Covered:

HCPCS Codes	Description
J7699 [†]	NOC drugs, inhalation solution administered through DME

†Note: Experimental/Investigational/Unproven/Not Covered when used to report the inhalation form of alpha 1-proteinase inhibitor (human).

ICD-9-CM Diagnosis Codes	Description
249.00- 249.91	Secondary diabetes mellitus
250.00- 250.93	Diabetes mellitus
270.00- 270.09	Cystic fibrosis

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Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	7/15/2008	4037	Alpha ₁ -Proteinase Inhibitor (Human) (Aralast NP™, Aralast™, Prolastin®, Zemaira®)
Great-West Healthcare			

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