

## MEDICAL POLICY – 5.01.624

## Alpha-1 Proteinase Inhibitors

Effective Date: **Feb. 1, 2025\***  
Last Revised: Jan. 27, 2025  
Replaces: N/A

\*This policy has been revised. View upcoming changes here.

## RELATED MEDICAL POLICIES:

11.01.523 Site of Service: Infusion Drugs and Biologic Agents

The Site of Service Medical Necessity criteria within this policy DOES NOT apply to Alaska fully-insured members; refer to the infusion drug Medical Necessity criteria only.


Site of Service *and* the infusion drug Medical Necessity criteria apply to all other plan members.

Please contact Customer Service for more information.

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Select a hyperlink below to be directed to that section.

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[RELATED INFORMATION](#) | [EVIDENCE REVIEW](#) | [REFERENCES](#) | [HISTORY](#)

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## Introduction

Alpha<sub>1</sub>-antitrypsin (AAT) deficiency is a rare, inherited disease that is caused by a change (mutation) in the SERPINA1 gene. The SERPINA1 gene provides instructions to create alpha<sub>1</sub>-antitrypsin which prevents the destruction of elastin in the lungs, liver, and skin. In the lungs this elastin deficiency can cause early onset chronic obstructive pulmonary disease (COPD) (i.e., emphysema). Cigarette smoke can rapidly accelerate damage to the lungs in individuals with AAT deficiency. Standard treatment includes exercise programs, nutritional support, drugs, and avoidance of cigarette smoke. When the AAT deficiency becomes severe drugs called alpha<sub>1</sub>-proteinase inhibitors can be used to increase the AAT levels which may slow the decline in lung function and delay any further damage. There are currently four Food and Drug Administration (FDA) approved alpha<sub>1</sub>-proteinase inhibitors available which are Aralast NP, Glassia, Prolastin-C,

and Zemaira. This policy describes when drugs used to treat emphysema due to severe AAT deficiency may be considered medically necessary.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

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**Site of Service (SOS) Medical Necessity criteria applies ONLY to medical benefit reviews. SOS Medical Necessity criteria does NOT apply to Alaska fully-insured members; refer to the infusion drug Medical Necessity criteria only. Please contact Customer Service for more information.**

We will review specific intravenous (IV) and injectable drugs for medical necessity for all ages.

For those age 13 and older, we also will review the site of service for medical necessity. Site of service is defined as the location where the drug is administered, such as a hospital-based outpatient setting, an infusion center, a physician's office, or at home. Click [here](#) to be directed to the site of service review criteria.

**Drugs subject to site of service review addressed in this policy are:**

- **First-line products:**
  - Aralast NP (alpha<sub>1</sub>-proteinase inhibitor [human]) IV
  - Prolastin-C (alpha<sub>1</sub>-proteinase inhibitor [human]) IV
  - Zemaira (alpha<sub>1</sub>-proteinase inhibitor [human]) IV
- **Second-line product:**
  - Glassia (alpha<sub>1</sub>-proteinase inhibitor [human]) IV



Site of Service Administration	Medical Necessity
<b>Medically necessary sites of service</b> <ul style="list-style-type: none"> <li>• Physician's office</li> <li>• Infusion center</li> <li>• Home infusion</li> </ul>	<p><b>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site:</b></p> <ul style="list-style-type: none"> <li>• These are the preferred <b>medically necessary</b> sites of service for specified drugs.</li> </ul>
<b>Hospital-based outpatient setting</b> <ul style="list-style-type: none"> <li>• Outpatient hospital IV infusion department</li> <li>• Hospital-based outpatient clinical level of care</li> </ul>	<p><b>IV infusion therapy of various medical or biologic agents will be covered in the most appropriate, safe and cost-effective site.</b></p> <p><b>This site is considered medically necessary for the first 90 days for the following:</b></p> <ul style="list-style-type: none"> <li>• The initial course of infusion of a pharmacologic or biologic agent</li> </ul> <p><b>OR</b></p> <ul style="list-style-type: none"> <li>• Re-initiation of an agent after 6 months or longer following discontinuation of therapy*</li> </ul> <p><b>Note:</b> *This does not include when standard dosing between infusions is 6 months or longer</p> <p><b>This site is considered medically necessary when there is no outpatient infusion center within 50 miles of the individual's home and there is no contracted home infusion agency that will travel to their home, or a hospital is the only place that offers infusions of this drug.</b></p> <p><b>This site is considered medically necessary only when the individual has a clinical condition which puts him or her at increased risk of complications for infusions, including any 1 of the following:</b></p> <ul style="list-style-type: none"> <li>• Known cardiac condition (e.g., symptomatic cardiac arrhythmia) or pulmonary condition (e.g., significant respiratory disease, serious obstructive airway disease, %FVC less than or equal to 40%) that may increase the risk of an adverse reaction</li> </ul>



Site of Service Administration	Medical Necessity
	<ul style="list-style-type: none"> <li>• Unstable renal function which decreases the ability to respond to fluids</li> <li>• Difficult or unstable vascular access</li> <li>• Acute mental status changes or cognitive conditions that impact the safety of infusion therapy</li> <li>• A known history of severe adverse drug reactions and/or anaphylaxis to prior treatment with a related or similar drug</li> </ul> <p><b>This site is considered medically necessary when the individual has cytokine release syndrome (CRS) and all the following are met:</b></p> <ul style="list-style-type: none"> <li>• CRS is grade 3 or 4 as evidenced by ALL the following: <ul style="list-style-type: none"> <li>○ Temperature at least 38 °C</li> <li>○ Hypotension that requires 1 or more vasopressors</li> <li>○ Hypoxia that requires oxygen through a high-flow nasal cannula, face mask, non-rebreather mask, or Venturi mask OR positive pressure (continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, or mechanical ventilation)</li> </ul> </li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>• The individual will be admitted into an inpatient setting as soon as possible</li> </ul>
<p><b>Hospital-based outpatient setting</b></p> <ul style="list-style-type: none"> <li>• Outpatient hospital IV infusion department</li> <li>• Hospital-based outpatient clinical level of care</li> </ul>	<p><b>These sites are considered not medically necessary for infusion and injectable therapy services of various medical and biologic agents when the site-of-service criteria in this policy are not met.</b></p>



Drug	Medical Necessity
<p><b>Aralast NP (alpha<sub>1</sub>-proteinase inhibitor [human]) IV</b></p> <ul style="list-style-type: none"> <li>First-line</li> </ul> <p><b>Prolastin-C (alpha<sub>1</sub>-proteinase inhibitor [human]) IV</b></p> <ul style="list-style-type: none"> <li>First-line</li> </ul> <p><b>Zemaira (alpha<sub>1</sub>-proteinase inhibitor [human]) IV</b></p> <ul style="list-style-type: none"> <li>First-line</li> </ul>	<p><b>Aralast NP (alpha<sub>1</sub>-proteinase inhibitor (PI) [human]), Prolastin-C (alpha<sub>1</sub>-PI [human]), and Zemaira (alpha<sub>1</sub>-PI [human]) are subject to review for site of service administration.</b></p> <p><b>Aralast NP (alpha<sub>1</sub>-proteinase inhibitor (PI) [human]), Prolastin-C (alpha<sub>1</sub>-PI [human]), and Zemaira (alpha<sub>1</sub>-PI [human]) may be considered medically necessary for the treatment of adult individuals with clinically evident emphysema due to severe hereditary deficiency of alpha<sub>1</sub>-PI (alpha<sub>1</sub>-antitrypsin deficiency) when the following criteria are met:</b></p> <ul style="list-style-type: none"> <li>The individual is aged 18 years or older</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Genetic testing documents mutation in the SERPINA1 gene</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Serum alpha<sub>1</sub>-antitrypsin is less than 11 micromole/L (approximately 57 mg/dL by nephelometry)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Forced expiratory volume in one second (FEV<sub>1</sub>) is 30-65% of predicted</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Is receiving treatment for emphysema with a long-acting inhaled bronchodilator and/or corticosteroid</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Is a non-smoker or is enrolled in a smoking cessation program</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Medication is prescribed by or in consultation with a pulmonologist or geneticist</li> </ul>
<p><b>Glassia (alpha<sub>1</sub>-proteinase inhibitor [human]) IV</b></p> <ul style="list-style-type: none"> <li>Second-line</li> </ul>	<p><b>Glassia (alpha<sub>1</sub>-PI [human]) is subject to review for site of service administration.</b></p> <p><b>Glassia (alpha<sub>1</sub>-PI [human]) may be considered medically necessary for the treatment of adult individuals with clinically evident emphysema due to severe hereditary deficiency of alpha<sub>1</sub>-PI (alpha<sub>1</sub>-antitrypsin deficiency) when the following criteria are met:</b></p> <ul style="list-style-type: none"> <li>The individual is aged 18 years or older</li> </ul>

Drug	Medical Necessity
	<p><b>AND</b></p> <ul style="list-style-type: none"> <li>Genetic testing documents mutation in the SERPINA1 gene</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Serum alpha<sub>1</sub>-antitrypsin is less than 11 micromole/L (approximately 57 mg/dL by nephelometry)</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Forced expiratory volume in one second (FEV<sub>1</sub>) is 30-65% of predicted</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Is receiving treatment for emphysema with a long-acting inhaled bronchodilator and/or corticosteroid</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Is a non-smoker or is enrolled in a smoking cessation program</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Medication is prescribed by or in consultation with a pulmonologist or geneticist</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Has had an inadequate response or intolerance to Aralast NP (alpha1-proteinase inhibitor (PI) [human]), Prolastin-C (alpha1-PI [human]), or Zemaira (alpha1-PI [human])</li> </ul>

Drug	Investigational
<b>As listed</b>	<p><b>The medications listed in this policy are subject to the product's US Food and Drug Administration (FDA) dosage and administration prescribing information.</b></p> <p><b>All other uses of the drugs for conditions not outlined in this policy are considered investigational.</b></p>

Length of Approval	
Approval	Criteria
<b>Initial authorization</b>	<b>Non-formulary exception reviews for all drugs listed in the policy may be approved up to 12 months.</b>



Length of Approval	
Approval	Criteria
	All other reviews for all drugs listed in policy may be approved up to 6 months.
Re-authorization criteria	<p>Non-formulary exception reviews and all other reviews for all drugs listed in policy may be approved up to 12 months as long as the drug-specific coverage criteria are met and chart notes at the time of re-authorization show:</p> <ul style="list-style-type: none"> <li>An increase from baseline of alpha<sub>1</sub>-antitrypsin levels</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>Slowing of decline in lung function</li> </ul>

Documentation Requirements
<p>The individual's medical records submitted for review for all conditions should document that medical necessity criteria are met. The record should include the following:</p> <ul style="list-style-type: none"> <li>Office visit notes that contain the diagnosis, relevant history, physical evaluation, and medication history</li> </ul>

## Coding

Code	Description
<b>HCPCS</b>	
J0256	Injection, alpha 1-proteinase inhibitor, human, 10 mg, not otherwise specified (Aralast NP, Prolastin-C, Zemaira)
J0257	Injection, alpha 1 proteinase inhibitor (human), (Glassia), 10 mg

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## Related Information



## Consideration of Age

The ages stated in this policy for which Aralast NP, Glassia, Prolastin-C, and Zemaira are considered medically necessary are based on the ages approved in the US Food and Drug Administration (FDA) labeling.

## Benefit Application

This policy is managed through the medical benefit.

## Evidence Review

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### Background

Alpha<sub>1</sub>-antitrypsin (AAT) deficiency is a chronic, autosomal, co-dominant hereditary disorder characterized by reduced levels of AAT in the blood and lungs. Smoking is an important risk factor for the development of emphysema in individuals with AAT deficiency. Because emphysema affects many, but not all individuals with the more severe genetic variants of AAT deficiency, augmentation therapy with alpha<sub>1</sub>-proteinase inhibitor (human) is indicated only in individuals with severe AAT deficiency who have clinically evident emphysema.

A large number of phenotypic variants of AAT deficiency exist, not all of which are associated with the clinical disease. Approximately 95% of identified AAT deficient individuals have the PiZZ variant, typically characterized by AAT serum levels less than 35% of normal. Individuals with the Pi(null)(null) variant have no AAT protein in their serum. Individuals with the lack of, or low, endogenous serum levels of AAT (i.e., below 11 µM) manifest a significantly increased risk for development of emphysema above the general population background risk. In addition, PiSZ individuals, whose serum AAT levels range from approximately 9 to 23 µM are considered to have moderately increased risk for developing emphysema, regardless of whether their serum AAT levels are above or below 11 µM.

Augmenting the levels of functional protease inhibitor by intravenous infusion is an approach to therapy for individuals with AAT deficiency. However, the efficacy of augmentation therapy in affecting the progression of emphysema has not been demonstrated in randomized, controlled clinical trials. The intended theoretical goal is to provide protection to the lower respiratory tract by correcting the imbalance between neutrophil elastase and protease inhibitors. Whether



augmentation therapy with any alpha<sub>1</sub>-proteinase inhibitor product actually protects the lower respiratory tract from progressive emphysematous changes has not been conclusively demonstrated in adequately powered, randomized controlled clinical trials. Although the maintenance of blood serum levels of AAT (antigenically measured) above 11 µM has been historically postulated to provide therapeutically relevant antineutrophil elastase protection, this has not been proven. Individuals with severe AAT deficiency have been shown to have increased neutrophil and neutrophil elastase concentrations in lung epithelial lining fluid compared to normal PiMM individuals, and some PiSZ individuals with AAT above 11 µM have emphysema attributed to AAT deficiency. These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of AAT during augmentation therapy.

## **Summary of Evidence**

### **Aralast NP (alpha1-proteinase inhibitor [human])**

#### **Description**

Aralast NP contains approximately 2% alpha<sub>1</sub>-PI with truncated C-terminal lysine (removal of Lys394). Aralast NP is a sterile, lyophilized preparation of purified human alpha<sub>1</sub>-proteinase inhibitor. Aralast NP is prepared from large pools of human plasma by using the cold ethanol fractionation process, followed by purification steps including polyethylene glycol and zinc chloride precipitations and ion exchange chromatography.

#### **Dosage and Administration**

Administer 60 mg/kg body weight of Aralast NP once weekly by intravenous infusion. The infusion rate of Aralast NP should not exceed 0.2 mL/kg/min, and as determined by the response and comfort of the individual.

#### **Efficacy**

A clinical trial (Aralast versus Prolastin trial) was conducted to compare the predecessor product Aralast to a commercially available preparation of alpha<sub>1</sub>-PI (Prolastin) in 28 subjects with congenital alpha<sub>1</sub>-PI deficiency and emphysema, who had not received alpha<sub>1</sub>-PI augmentation therapy within the preceding six months.



Subjects were randomized to receive either Aralast or Prolastin, 60 mg/kg intravenously per week for 10 consecutive weeks. Following their first 10 weekly infusions, the subjects who were receiving Prolastin were switched to Aralast while those who already were receiving Aralast continued to receive it.

Following weekly augmentation therapy with Aralast or Prolastin, a gradual increase in peak and trough serum alpha<sub>1</sub>-PI levels was noted, with stabilization after several weeks. The metabolic half-life of Aralast was 5.9 days. Serum anti-neutrophil elastase capacity (ANEC) trough levels rose substantially in all subjects by Week 2, and by Week 3, serum ANEC trough levels exceeded 11 µM in the majority of subjects. With few exceptions, levels in both treatment groups remained above this level in individual subjects for the duration of the period Weeks 3 through 24. Although only five of fourteen subjects (35.7%) receiving Aralast had BALs meeting acceptance criteria for analysis at both baseline and Week 7, a statistically significant increase in the antigenic level of alpha<sub>1</sub>-PI in epithelial lining fluid (ELF) was observed. No statistically significant increase in the ANEC in the ELF was detected. It was concluded that at a dose of 60 mg/kg administered intravenously once weekly, Aralast and Prolastin had similar effects in maintaining target serum alpha<sub>1</sub>-PI trough levels and increasing antigenic levels of alpha<sub>1</sub>-PI in the ELF with maintenance augmentation therapy.

### **Adverse Reactions**

The most common adverse reactions occurring in greater than or equal to 5% of infusions in clinical studies were headache, musculoskeletal discomfort, vessel puncture site bruise, nausea, and rhinorrhea.

## **Glassia (alpha1-proteinase inhibitor [human])**

### **Description**

Glassia is a sterile, ready to use, liquid preparation of purified human alpha<sub>1</sub>-proteinase inhibitor (PI). The solution contains 2% active alpha<sub>1</sub>-PI in a phosphate-buffered saline solution. The specific activity of Glassia is greater than or equal to 0.7 mg functional alpha<sub>1</sub>-PI per mg of total protein. No less than 90% of the alpha<sub>1</sub>-PI in Glassia is of the monomeric form as measured by size-exclusion chromatography. Glassia is prepared from human plasma obtained from US-licensed plasma collection centers by a modified version of the cold ethanol fractionation process and the alpha<sub>1</sub>-PI is then purified using chromatographic methods.



## Dosage and Administration

Administer 60 mg/kg body weight of Glassia once weekly by intravenous infusion. The infusion rate of Glassia should not exceed 0.2 mL/kg/min, and as determined by the response and comfort of the individual. The recommended dosage of 60 mg/kg at a rate of 0.2 mL/kg/min will take approximately 15 minutes to infuse.

## Efficacy

A randomized, double-blind trial with a partial cross-over was conducted to compare Glassia to a commercially available preparation of  $\alpha_1$ -PI (Prolastin) in 50  $\alpha_1$ -PI deficient subjects. The trial objectives were to demonstrate that the pharmacokinetics of antigenic and/or functional  $\alpha_1$ -PI in Glassia were not inferior to those of the control product, to determine whether Glassia maintained antigenic and/or functional plasma levels of at least 11  $\mu$ M (57 mg/dL) and to compare  $\alpha_1$ -PI trough levels (antigenic and functional) over 6 infusions.

For inclusion in the trial, subjects were required to have lung disease related to  $\alpha_1$ -PI deficiency and 'at-risk' alleles associated with  $\alpha_1$ -PI plasma levels less than 11  $\mu$ M. Subjects already receiving  $\alpha_1$ -PI therapy were required to undergo a 5-week wash-out period of exogenous  $\alpha_1$ -PI prior to dosing.

Fifty subjects received either Glassia (33 subjects) or the comparator product (17 subjects) at a dose of 60 mg/kg intravenously per week for 12 consecutive weeks. From Week 13 to Week 24 all subjects received open-label weekly infusions of Glassia at a dose of 60 mg/kg.

Trough levels of functional and antigenic  $\alpha_1$ -PI were measured prior to treatment, at baseline and throughout the trial until Week 24. The median trough  $\alpha_1$ -PI values for Weeks 7-12 for subjects receiving Glassia were 14.5  $\mu$ M (range: 11.6 to 18.5  $\mu$ M) for antigenic and 11.8  $\mu$ M (range: 8.2 to 16.9  $\mu$ M) for functional  $\alpha_1$ -PI. Eleven of 33 subjects (33.3%) receiving Glassia had mean steady-state functional  $\alpha_1$ -PI levels below 11  $\mu$ M. Glassia was shown to be non-inferior to the comparator product.

Serum  $\alpha_1$ -PI trough levels rose substantially in all subjects by Week 2 and were comparatively stable during Weeks 7 to 12. All subjects receiving Glassia had mean serum trough antigenic  $\alpha_1$ -PI levels greater than 11  $\mu$ M during Weeks 7-12.

A subset of subjects in both treatment groups (n = 7 for subjects receiving Glassia) underwent broncho-alveolar lavage (BAL) and were shown to have increased levels of antigenic  $\alpha_1$ -PI



and alpha<sub>1</sub>-PI - neutrophil elastase complexes in the epithelial lining fluid at Week 10-12 over levels found at baseline, demonstrating the ability of the product to reach the lung.

The clinical efficacy of Glassia in influencing the course of pulmonary emphysema or the frequency, duration, or severity of pulmonary exacerbations has not been demonstrated in randomized, controlled clinical trials.

### **Adverse Reactions**

The most common adverse reactions (greater than 0.5% of infusions) in clinical trials were headache and upper respiratory infection.

## **Prolastin-C (alpha<sub>1</sub>-proteinase inhibitor [human])**

### **Description**

Prolastin-C is a sterile, white to beige-colored concentrate of alpha<sub>1</sub>-PI in lyophilized powder form for reconstitution for intravenous infusion. Each vial contains approximately 1,000 mg of functionally active alpha<sub>1</sub>-PI as determined by capacity to neutralize porcine pancreatic elastase. The specific activity of Prolastin-C is greater than or equal to 0.7 mg functional alpha<sub>1</sub>-PI per mg of total protein. Prolastin-C has a purity of greater than or equal to 90% alpha<sub>1</sub>-PI (alpha<sub>1</sub>-PI protein/total protein). When reconstituted with 20 mL of Sterile Water for Injection, USP, Prolastin-C has a pH of 6.6–7.4, a sodium content of 100–210 mM, a chloride content of 60–180 mM and a sodium phosphate content of 13–25 mM. Prolastin-C contains no preservative. Prolastin-C is produced from pooled human plasma through modifications of the Prolastin process using purification by polyethylene glycol (PEG) precipitation, anion exchange chromatography, and cation exchange chromatography.

### **Dosage and Administration**

Administer 60 mg/kg body weight of Prolastin-C once weekly by intravenous infusion. The infusion rate of Prolastin-C should not exceed 0.08 mL/kg/min, and as determined by the response and comfort of the individual.

### **Efficacy**



The clinical efficacy of Prolastin-C in influencing the course of pulmonary emphysema or pulmonary exacerbations has not been demonstrated in adequately powered, randomized, controlled clinical trials.

A total of 23 subjects with the PiZZ variant and documented emphysema were studied in a single-arm, open label clinical trial with Prolastin, the predecessor product. Nineteen of the subjects received Prolastin, 60 mg/kg, once weekly for up to 26 weeks (average 24 weeks). Blood levels of  $\alpha_1$ -PI were maintained above 11  $\mu$ M. Bronchoalveolar lavage studies demonstrated statistically significant increased levels of  $\alpha_1$ -PI and functional anti-neutrophil elastase capacity (ANEC) in the epithelial lining fluid of the lower respiratory tract of the lung, as compared to levels prior to dosing.

### **Adverse Reactions**

The most common adverse reaction during clinical trials in > 5% of subjects was upper respiratory tract infection.

## **Zemaira ( $\alpha_1$ -proteinase inhibitor [human])**

### **Description**

Zemaira is a sterile, white to off-white, lyophilized preparation of purified  $\alpha_1$ -proteinase inhibitor (human) ( $\alpha_1$ -PI), also known as  $\alpha_1$ -antitrypsin, to be reconstituted and administered by the intravenous route. The specific activity of Zemaira is greater than or equal to 0.7 mg of functional  $\alpha_1$ -PI per milligram of total protein. The purity (total  $\alpha_1$ -PI/total protein) is greater than or equal to 90%  $\alpha_1$ -PI. Each vial contains approximately 1000 mg, 4000 mg, or 5000 mg of functionally active  $\alpha_1$ -PI. The measured amount per vial of functionally active  $\alpha_1$ -PI as determined by its capacity to neutralize human neutrophil elastase (NE) is printed on the vial label and carton. Following reconstitution with 20 mL, 76 mL, or 95 mL of Sterile Water for Injection, USP, the Zemaira solution contains 73 to 89 mM sodium, 33 to 42 mM chloride, 15 to 20 mM phosphate, and 121 to 168 mM mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH. Zemaira contains no preservative.

### **Dosage and Administration**



Administer 60 mg/kg body weight of Zemaira once weekly by intravenous infusion. The infusion rate of Zemaira should not exceed 0.08 mL/kg/min, and as determined by the response and comfort of the individual. The recommended dosage of 60 mg/kg body weight will take approximately 15 minutes to infuse.

## **Efficacy**

Clinical trials were conducted pre-licensure with Zemaira in 89 subjects (59 males and 30 females). The subjects ranged in age from 29 to 68 years (median age 49 years). Ninety-seven percent of the treated subjects had the PiZZ phenotype of  $\alpha_1$ -PI deficiency, and 3% had the M phenotype. At screening, serum  $\alpha_1$ -PI levels were between 3.2 and 10.1  $\mu$ M (mean of 5.6  $\mu$ M). The objectives of the clinical trials were to demonstrate that Zemaira augments and maintains serum levels of  $\alpha_1$ -PI above 11  $\mu$ M (80 mg/dL) and increases  $\alpha_1$ -PI levels in epithelial lining fluid (ELF) of the lower lung.

In a double-blind, controlled clinical trial to evaluate the safety and efficacy of Zemaira, 44 subjects were randomized to receive 60 mg/kg of either Zemaira or Prolastin once weekly for 10 weeks. After 10 weeks, subjects in both groups received Zemaira for an additional 14 weeks. Subjects were followed for a total of 24 weeks to complete the safety evaluation. The mean trough serum  $\alpha_1$ -PI levels at steady state (Weeks 7-11) in the Zemaira-treated subjects were statistically equivalent to those in the Prolastin treated subjects within a range of  $\pm 3$   $\mu$ M. Both groups were maintained above 11  $\mu$ M. The mean (range and standard deviation [SD]) of the steady state trough serum antigenic  $\alpha_1$ -PI level for Zemaira-treated subjects was 17.7  $\mu$ M (range 13.9 to 23.2, SD 2.5) and for Prolastin-treated subjects was 19.1  $\mu$ M (range 14.7 to 23.1, SD 2.2). The difference between the Zemaira and the Prolastin groups was not considered clinically significant and may be related to the higher specific activity of Zemaira.

The clinical efficacy of Zemaira or any  $\alpha_1$ -PI product in influencing the course of pulmonary emphysema or pulmonary exacerbations has not been demonstrated in adequately powered, randomized, controlled clinical trials.

## **Adverse Reactions**

The most common adverse reactions occurring in at least 5% of subjects in all pre-licensure clinical trials were headache, sinusitis, upper respiratory infection, bronchitis, asthenia, cough increased, fever, injection site hemorrhage, rhinitis, sore throat, and vasodilation



## 2022 Update

Reviewed prescribing information for all drugs listed in policy and information on the management of adults with clinically evident emphysema due to severe hereditary deficiency of alpha<sub>1</sub>-PI (alpha<sub>1</sub>-antitrypsin deficiency). No new information was identified that would require changes to this policy.

## 2023 Update

Reviewed prescribing information for all drugs listed in policy. No new evidence found that would require changes to the policy. Removed trademarks from the brand products for the process of standardization.

## 2024 Update

Reviewed prescribing information for all drugs listed in policy. Added site of service review for Aralast NP, Glassia, Prolastin-C, and Zemaira. Changed Glassia to a non-preferred product and updated Glassia coverage criteria to require the individual had an inadequate response or intolerance to Aralast NP, Prolastin-C, or Zemaira.

## 2025 Update

Reviewed prescribing information for all drugs listed in policy. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members pursuant to [Alaska HB 226](#) (accessed January 3, 2025). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS).

## References

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1. Aralast NP (alpha1-proteinase inhibitor (PI) [human]) Prescribing Information. Baxalta US Inc., Lexington, MA. Revised October 2024.
2. Glassia (alpha1-proteinase inhibitor (PI) [human]) Prescribing Information. Baxalta US Inc., Lexington, MA. Revised September 2024.
3. Prolastin-C (alpha1-proteinase inhibitor (PI) [human]) Prescribing Information. Grifols Therapeutics LLC, Research Triangle Park, NC. Revised May 2020.
4. Zemaira (alpha1-proteinase inhibitor (PI) [human]) Prescribing Information. CSL Behring LLC, Kankakee, IL. Revised January 2024.
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## History

Date	Comments
06/01/21	New policy, approved May 11, 2021, effective for dates of service on or after September 3, 2021, following 90-day provider notification. Add to Prescription Drug section. Added criteria for Aralast NP (alpha <sub>1</sub> -proteinase inhibitor (PI) [human]), Glassia (alpha <sub>1</sub> -PI [human]), Prolastin-C (alpha <sub>1</sub> -PI [human]), and Zemaira (alpha <sub>1</sub> -PI [human]) for the treatment of emphysema due to severe alpha <sub>1</sub> -antitrypsin deficiency. Added HCPC code J0256 for Aralast NP, Prolastin-C, Zemaira and HCPC code J0257 for Glassia.
01/01/23	Annual Review, approved December 23, 2022. No changes to policy statements. Changed the wording from "patient" to "individual" throughout the policy for standardization.
09/01/23	Annual Review, approved August 7, 2023. Reviewed prescribing information for all drugs listed in policy. No new evidence found that would require changes to the policy.
08/01/24	Annual Review, approved July 9, 2024. The following policy changes are effective November 1, 2024, following 90-day provider notification. Added site of service review for Aralast NP, Glassia, Prolastin-C, and Zemaira.
10/01/24	Interim Review, approved September 10, 2024. The following policy changes are effective January 3, 2025, following a 90-day provider notification. Changed Glassia to a non-preferred product and updated Glassia coverage criteria to require the





Date	Comments
	individual had an inadequate response or intolerance to Aralast NP, Prolastin-C, or Zemaira.
02/01/25	Annual Review, approved January 27, 2025. Policy updated to indicate that Site of Service Medical Necessity criteria does not apply to Alaska fully-insured members; only Medical Necessity criteria for the infusion drug applies pursuant to Alaska HB 226 (link added). Clarified that the medications listed in this policy are subject to the product's FDA dosage and administration prescribing information. Clarified that non-formulary exception review authorizations for all drugs listed in this policy may be approved up to 12 months. Added an exception to the site-of-service requirements for certain individuals receiving treatment for cytokine release syndrome (CRS).

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2025 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

