

# ALPHA<sub>1</sub>-PROTEINASE INHIBITORS

**Policy Number:** PHARMACY 304.3 T2

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## Related Policy

- [Specialty Medication Administration - Site of Care Review Guidelines](#)

## INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

## CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General Benefits Package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes
Precertification with Medical Director Review Required	Yes <sup>1,3</sup>
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	All <sup>2,3</sup>
Special Considerations	<p><sup>1</sup>Precertification with review by a Medical Director or their designee through Oxford's Medical Management is required.</p> <p><sup>2</sup><b>Participating Providers in the Office Setting:</b> Precertification is required for services performed in the office of a participating provider.</p> <p><b>Non-Participating/Out-of-Network Providers in the</b></p>

Special Considerations  
(continued)

**Office Setting:** Precertification is not required, but encouraged for out-of-network services performed in the office. If precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered.

<sup>3</sup>Additional precertification requirements apply to requests for hospital outpatient facility infusion of alpha<sub>1</sub>-proteinase inhibitors (Aralast N, Glassia, Prolastin-C and Zemaira). Refer to the policy titled [Specialty Medication Administration - Site of Care Review Guidelines](#).

## BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member-specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to: [Acquired Rare Disease Drug Therapy Exception Process](#) policy.

### **Essential Health Benefits for Individual and Small Group**

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits ("EHBs"). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

## COVERAGE RATIONALE

**Alpha<sub>1</sub>-proteinase inhibitors (Aralast NP™, Glassia™, Prolastin®-C and Zemaira®) are proven for chronic augmentation and maintenance therapy of patients with emphysema due to congenital deficiency of alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI), also known as alpha<sub>1</sub>-antitrypsin (AAT) deficiency.<sup>1-4</sup>**

**Alpha<sub>1</sub>-proteinase inhibitors (Aralast NP™, Glassia™, Prolastin®-C and Zemaira®) are medically necessary for the treatment of emphysema due to congenital deficiency of alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI) in patients who meet all of the following criteria:<sup>1-4,7-9,19</sup>**

- For **initial therapy**, **all** of the following:
  - Diagnosis of congenital alpha<sub>1</sub>-antitrypsin deficiency confirmed by **one** of the following:
    - Pi\*ZZ, Pi\*Z(null) or Pi\*(null)(null) protein phenotypes (homozygous); **or**
    - Other rare AAT deficiency disease-causing alleles associated with serum alpha<sub>1</sub>-antitrypsin (AAT) level <11 µmol/L [e.g., Pi(Malton, Malton)]
  - and**
  - Circulating serum concentration of AAT level <11 µmol/L (which corresponds to <80 mg/dl if measured by radial immunodiffusion or <57 mg/dl if measured by nephelometry); **and**
  - Continued optimal conventional treatment for emphysema (e.g., bronchodilators, supplemental oxygen if necessary); **and**
  - Current nonsmoker; **and**
  - Diagnosis of emphysema confirmed with pulmonary function testing; **and**
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling: dosage is 60 mg/kg body weight administered once weekly; **and**
  - Initial authorization will be for no more than 12 months.
- For **continuation therapy**, **all** of the following:
  - Diagnosis of congenital alpha<sub>1</sub>-antitrypsin deficiency confirmed by **one** of the following:
    - Pi\*ZZ, Pi\*Z(null) or Pi\*(null)(null) protein phenotypes (homozygous); **or**

- Other rare AAT deficiency disease-causing alleles associated with serum alpha<sub>1</sub>-antitrypsin (AAT) level <11 µmol/L [e.g., Pi(Malton, Malton)]

**and**

- Submission of medical records (e.g., chart notes, laboratory values) documenting a positive clinical response from pretreatment baseline to alpha<sub>1</sub>-proteinase inhibitor treatment; **and**
- Current nonsmoker; **and**
- Diagnosis of emphysema confirmed with pulmonary function testing; **and**
- Dosing is in accordance with the United States Food and Drug Administration approved labeling: dosage is 60 mg/kg body weight administered once weekly; **and**
- Reauthorization will be for no more than 12 months.

**Alpha<sub>1</sub>-proteinase inhibitor is unproven and not medically necessary for:**

- Conditions other than emphysema associated with alpha<sub>1</sub>-antitrypsin deficiency
- Cystic fibrosis

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Aralast NP, Prolastin-C, Glassia and Zemaira are all alpha<sub>1</sub>-proteinase inhibitors (human) FDA-labeled for chronic augmentation therapy in patients having congenital deficiency of alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI), also known as alpha<sub>1</sub>-antitrypsin (AAT) deficiency, with clinically evident emphysema.<sup>1-4</sup>

- Effects on pulmonary exacerbations and on the progression of emphysema in AAT deficiency has not been demonstrated in randomized, controlled clinical trials.
- Clinical data demonstrating the long-term effects of chronic augmentation or replacement therapy of individuals treated with alpha<sub>1</sub>-proteinase inhibitors are not available.
- Alpha<sub>1</sub>-proteinase inhibitors are not indicated for treatment of lung disease in patients whom congenital A<sub>1</sub>-PI deficiency has not been established.
- Alpha<sub>1</sub>-proteinase inhibitors are derived from pooled human plasma and may carry a risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent.
- Aralast NP, Glassia, Prolastin-C and Zemaira are contraindicated in IgA deficient patients with antibodies against IgAt.

**BACKGROUND**

Deficiency of alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI), also known as alpha<sub>1</sub>-antitrypsin deficiency, is characterized by reduced levels of A<sub>1</sub>-PI in the blood and lungs. A<sub>1</sub>-PI deficiency is an autosomal, co-dominant, hereditary disorder. Patients with severe A<sub>1</sub>-PI deficiency have increased levels of neutrophil and neutrophil elastase levels in lung epithelial lining fluid which results in unopposed destruction of the connective tissue framework of the lung parenchyma. A<sub>1</sub>-PI (human) therapy augments the level of the deficient protein and theoretically corrects the imbalance between neutrophil elastase and protease inhibitors, which may protect the lower respiratory tract.<sup>1-6</sup>

**APPLICABLE CODES**

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

HCPCS Code	Description
J0257	Injection, alpha 1 proteinase inhibitor (human), (Glassia), 10 mg
J0256	Injection, alpha 1-proteinase inhibitor, human, 10 mg, not otherwise specified

ICD-10 Diagnosis Code	Description
E88.01	Alpha-1-antitrypsin deficiency

**CLINICAL EVIDENCE**

**Proven**

**Alpha<sub>1</sub>-Proteinase Inhibitor (A<sub>1</sub>-PI) Deficiency [i.e., Alpha<sub>1</sub>-Antitrypsin (AAT) Deficiency]**

Tonellis et al. examined the effect of alpha-1 antitrypsin augmentation therapy on FEV<sub>1</sub> decline in patients with alpha-1 antitrypsin deficiency (AATD) related lung disease enrolled in the Alpha-1 Foundation DNA and Tissue Bank study.<sup>13</sup> Patients were included if they had a proven PI ZZ genotype and at least two recorded post-bronchodilator FEV<sub>1</sub>

measurements, 6 months apart or more. The 164 patients were then divided into 2 groups: 1) "augmented" (patients who were receiving augmentation therapy at time of the inclusion in the study), 2) "nonaugmented"(patients who were not receiving augmentation therapy at the time of the inclusion in the study). Mean age of the included patients was 60 years, 52% were females, 94% were white and 78% ex-smokers. Researchers reported a mean FEV<sub>1</sub> at baseline was 1.7 L and the mean FEV<sub>1</sub> % of predicted was 51.3%. The mean follow-up time was 41.7 months. Of the 164 patients, 124 (76%) patients received augmentation therapy (augmented group) while 40 patients (24%) did not (non-augmented group). When adjusted by age at baseline, sex, smoking status, baseline FEV<sub>1</sub> % of predicted, the mean overall change in FEV<sub>1</sub> reported was 47.6 mL/year, favoring the augmented group (decline in FEV<sub>1</sub> 10.6 +/- 21.4 mL/year) in comparison with the non-augmented group (decline in FEV<sub>1</sub> -36.96 +/- 12.1 mL/year) (p=0.05). Beneficial change in FEV<sub>1</sub> were observed in ex-smokers and the group with initial FEV<sub>1</sub> % of predicted of <50%. There were no differences were observed in mortality. Researchers concluded that augmentation therapy improves lung function in subjects with AATD when adjusted by age, gender, smoking status and baseline FEV % of predicted. Additionally, the beneficial effects were observed in ex-smoker subjects with FEV<sub>1</sub> below 50% of predicted.

A multicenter, retrospective cohort study evaluated evaluate the progression of emphysema in patients with alpha<sub>1</sub>-protease inhibitor (alpha<sub>1</sub>-Pi) deficiency before and during a period in which they received treatment with alpha<sub>1</sub>-Pi augmentation therapy.<sup>14</sup> Ninety-six patients with severe alpha<sub>1</sub>-Pi deficiency receiving weekly treatment with human alpha<sub>1</sub>-Pi (60 mg/kg of body weight). A minimum of two lung function measurements before and two lung function measurements after augmentation therapy was started was performed. Lung function data were followed up for a minimum of 12 months both before and during treatment (mean, 47.5 months and 50.2 months, respectively). Patients were grouped according to the severity of their lung function impairment. A majority of patients had PiZ phenotypes and frequency did not differ between male and female patients. Change in FEV<sub>1</sub> was compared during non-treatment and treatment periods. The reported decline in FEV<sub>1</sub> was significantly lower during the treatment period (49.2 mL/yr vs. 34.2 mL/yr, p = 0.019) in all 96 patients. In patients with FEV<sub>1</sub> > 65%, IV alpha<sub>1</sub>-Pi treatment reduced the decline in FEV<sub>1</sub> by 73.6 mL/yr (p=0.045). Seven individuals had a rapid decline of FEV<sub>1</sub> before treatment, and the loss in FEV<sub>1</sub> could be reduced from 256 mL/yr to 53 mL/yr (p=0.001). This study showed a significant reduction in the loss of lung function during the period in which patients with α<sub>1</sub> -Pi deficiency received augmentation therapy, which reflected a slower progress of their lung emphysema. Patients with well-maintained lung function and a rapid decline profited most from augmentation therapy. Researchers concluded that early diagnosis and early start of augmentation therapy may prevent accelerated loss of lung tissue.

As part of a National Heart, Lung, and Blood Institute Registry of Patients with Severe Deficiency of Alpha-1-Antitrypsin, patients ≥ 18 years of age with a serum alpha<sub>1</sub>-antitrypsin (alpha<sub>1</sub>-AT) levels ≤11 microM or PiZZ genotype were followed for 3.5 to 7 years with spirometry measurements every 6 to 12 months.<sup>15</sup> Of the 1,129 patients enrolled in the observational study, 382 (34%) never received augmentation therapy, 390 (35%) always received therapy, and 357 (32%) were partly receiving therapy while in the Registry. Results showed that those patients that had received alpha<sub>1</sub>-antitrypsin augmentation therapy had decreased mortality [risk ratio (RR) = 0.64, 95% CI: 0.43 to 0.94, p=0.02] as compared with those not receiving therapy. Furthermore, use of augmentation therapy was associated with lower mortality in the subgroup with initial FEV<sub>1</sub> values of 35 to 49% predicted (ATS Stage II) (RR 5 0.21, 95% CI 5 0.09 to 0.50, p<0.001). FEV<sub>1</sub> decline was not different between augmentation-therapy groups (p=0.40). Researchers concluded that patients that received augmentation therapy have a better survival than do patients not on therapy, although these differences may have been due to other factors.

Seersholm et al. conducted a non-randomized study which evaluated the effect of α<sub>1</sub>-antitrypsin augmentation (α<sub>1</sub>-AT) therapy on patients with α<sub>1</sub>-antitrypsin deficiency (α<sub>1</sub>-ATD) by comparing the annual decline in FEV<sub>1</sub> in a treated group of ex-smokers in Germany and an untreated group of ex-smokers in Denmark.<sup>16</sup> From the files of the Danish α<sub>1</sub>-ATD register, 97 ex-smokers were included with the following criteria: PiZZ phenotype or having a α<sub>1</sub>-AT serum level of less than 12 μmol/L.; age > 25 years at entry; and have results of two or more spirometries at least 1 year apart available. German patients (n=198) utilized in the analysis met the following inclusion criteria: have the PiZZ phenotype; be ex-smokers before entering the surveillance study; have received weekly infusions of α<sub>1</sub>-AT 60 mg/kg augmentation therapy for at least 1 year; and have had two or more spirometries at least 1 year apart performed during the treatment period. The decline in FEV<sub>1</sub> was compared between the two treatment groups by random effects modeling which included age at entry and follow-up time as covariates, treatment (Denmark versus Germany), gender, and initial FEV<sub>1</sub> as fixed parameters, and the individual patients as random effects parameters. The reported decline in FEV<sub>1</sub> in the treated group was significantly lower than in the untreated group, with annual declines of 53 mL/year (95%CI 48-58 mL/year) and 75 mL/year (95% CI 63-87 mL/year), respectively (p=0.02). Both groups differed with respect to gender and initial FEV<sub>1</sub>% predicted, however, gender did not have any influence on FEV<sub>1</sub> decline. Stratification by initial FEV<sub>1</sub>% predicted showed a significant effect of the treatment only in the group of patients with an initial FEV<sub>1</sub>% predicted of 31-65%, and FEV<sub>1</sub> decline was reduced by 21 mL/year. Researchers concluded that this nonrandomized study suggested that weekly infusion of human α<sub>1</sub>-antitrypsin in patients with moderately reduced lung function may slow the annual decline in FEV<sub>1</sub>.

The treatment of 21 patients with alpha-1 antitrypsin deficiency with plasma-derived alpha-1 proteinase inhibitor for 6 months demonstrated the safety and effectiveness of the drug in producing elevations in serum and lung fluid levels of AAT.<sup>17</sup> Patients were administered intravenous doses of 60 milligrams/kilogram/week alpha-1 proteinase inhibitor (alpha-1 PI) at a rate of 2 mg/kg/min. Samples of serum and alveolar fluid were obtained prior to treatment and at various intervals after the infusions. Following administration of alpha-1 PI, trough serum AAT levels were 126 mg/dL compared to 30 mg/dL at baseline. The AAT level in the fluid from the epithelial lining of the lungs was measured at 1.89 micromoles (mcmol) 6 days after the infusion compared to a baseline level of 0.46 mcmol. Alpha-1 PI infusions resulted in an improved capacity to inhibit neutrophil elastase in the lower respiratory tract for the patients as demonstrated by an increase in the average anti-neutrophil elastase capacity in the lung fluid to 1.65 mcmol, compared to a baseline of 0.81 mcmol prior to therapy. Additionally, patients also demonstrated an increase in serum anti-neutrophil elastase capacity to 13.3 mcmol, as compared to 5.4 mcmol at baseline. No changes in pulmonary function tests were detected after 6 months of treatment. Adverse reactions were limited to 4 episodes of self-limited fever, 3 of which were related to contamination of the product with endotoxin. No evidence for formation of antibodies or immune complexes to treatment could be demonstrated. Researchers concluded that the study effectively demonstrated the reversibility of the alpha-1 antitrypsin deficiency in the blood and lung fluid of the patients treated with alpha-1 PI therapy.

## **Unproven**

### **Cystic Fibrosis**

A randomized controlled trial of alpha-1 proteinase inhibitor administration for 4 weeks to patients with cystic fibrosis (CF) showed reduction in a variety of pulmonary inflammatory mediators, including neutrophil elastase, although lung function itself was unchanged. Clinical studies of treatment with aerosolized alpha-1 proteinase inhibitor in cystic fibrosis have shown some promise; however larger studies with relevant clinical endpoints are needed to validate efficacy.<sup>10-11</sup>

### **Miscellaneous**

For conditions associated with alpha-1 proteinase inhibitor deficiency other than chronic obstructive lung disease, a review found only case reports of patients treated with alpha-1 proteinase inhibitor on a compassionate basis for refractory bronchial asthma, fibromyalgia, panniculitis, and vasculitis. Although all patients experienced a positive response to treatment, the authors concluded that further laboratory studies in animal and humans as well as larger clinical trials are warranted in order to determine efficacy of augmentation therapy in these conditions.<sup>12</sup>

## **REFERENCES**

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy, Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee. [2018D0067B]

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**POLICY HISTORY/REVISION INFORMATION**

Date	Action/Description
11/01/2018	<ul style="list-style-type: none"> <li>• Updated conditions of coverage/special considerations; modified notation to clarify:               <ul style="list-style-type: none"> <li>○ For <b>participating providers in the office setting</b>: Precertification is required for services performed in the office of a participating provider</li> <li>○ For <b>non-participating/out-of-network providers in the office setting</b>: Precertification is not required, but is encouraged for out-of-network services performed in the office; if precertification is not obtained, Oxford will review for out-of-network benefits and medical necessity after the service is rendered</li> </ul> </li> <li>• Updated coverage rationale:               <ul style="list-style-type: none"> <li>○ Reformatted coverage statements; separated content addressing “proven” and “medically necessary” guidelines/criteria</li> </ul> </li> <li>• Updated supporting information to reflect the most current references</li> <li>• Archived previous policy version PHARMACY 304.2 T2</li> </ul>