# ALPHA$_{1}$-PROTEINASE INHIBITORS

**Policy Number:** PHARMACY 304.4 T2  
**Effective Date:** March 1, 2019

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## 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$^{1,3}$

All$^{2,3}$

**Applicable Site(s) of Service**

(If site of service is not listed, Medical Director review is required)

1.Precertification with review by a Medical Director or their designee through Oxford’s Medical Management is required.

2.**Participating Providers in the Office Setting:** Precertification is required for services performed in the office of a participating provider.

3.**Non-Participating/Out-of-Network Providers in the 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.

4. Additional precertification requirements apply to requests for hospital outpatient facility infusion of alpha$_{1}$-proteinase inhibitors (Aralast N, Glassia, Prolastin-C and Zemaira). Refer to the policy titled [Specialty Medication Administration - Site of Care Review Guidelines](Related_Policy).

**Special Considerations**
Alpha₁-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 alpha₁-proteinase inhibitor (A₁-PI), also known as alpha₁-antitrypsin (AAT) deficiency.¹⁻⁴

Alpha₁-proteinase inhibitors (Aralast NP™, Glassia™, Prolastin®-C and Zemaira®) are medically necessary for the treatment of emphysema due to congenital deficiency of alpha₁-proteinase inhibitor (A₁-PI) in patients who meet all of the following criteria:¹⁻⁴,⁷⁻⁹,¹⁹

- **For initial therapy, all** of the following:
  - Diagnosis of congenital alpha₁-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 alpha₁-antitrypsin (AAT) level <11 µmol/L [e.g., Pi(Malton, Malton)]
  - 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 alpha₁-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 alpha₁-antitrypsin (AAT) level <11 µmol/L [e.g., Pi(Malton, Malton)]
  - Submission of medical records (e.g., chart notes, laboratory values) documenting a positive clinical response from pretreatment baseline to alpha1-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.

**Alpha₁-proteinase inhibitor is unproven and not medically necessary for:**
- Conditions other than emphysema associated with alpha₁-antitrypsin deficiency
- Cystic fibrosis

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

Aralast NP, Prolastin-C, Glassia and Zemaira are all alpha₁-proteinase inhibitors (human) FDA-labeled for chronic augmentation therapy in patients having congenital deficiency of alpha₁-proteinase inhibitor (A₁-PI), also known as alpha₁-antitrypsin (AAT) deficiency, with clinically evident emphysema.¹⁻⁴

- 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 alpha₁-proteinase inhibitors are not available.
- Alpha₁-proteinase inhibitors are not indicated for treatment of lung disease in patients whom congenital A₁-PI deficiency has not been established.
- Alpha₁-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.
Deficiency of alpha₁-proteinase inhibitor (A₁-PI), also known as alpha₁-antitrypsin deficiency, is characterized by reduced levels of A₁-PI in the blood and lungs. A₁-PI deficiency is an autosomal, co-dominant, hereditary disorder. Patients with severe A₁-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. A₁-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.1-6

**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.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>J0257</td>
<td>Injection, alpha 1 proteinase inhibitor (human), (Glassia), 10 mg</td>
</tr>
<tr>
<td>J0256</td>
<td>Injection, alpha 1-proteinase inhibitor, human, 10 mg, not otherwise specified</td>
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<table>
<thead>
<tr>
<th>ICD-10 Diagnosis Code</th>
<th>Description</th>
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<tr>
<td>E88.01</td>
<td>Alpha-1-antitrypsin deficiency</td>
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**BENEFIT CONSIDERATIONS**

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 the policy titled **Acquired Rare Disease Drug Therapy Exception Process**.

**CLINICAL EVIDENCE**

**Proven**

**Alpha₁-Proteinase Inhibitor (A₁-PI) Deficiency [i.e., Alpha₁-Antitrypsin (AAT) Deficiency]**

Tonellis et al. examined the effect of alpha-1 antitrypsin augmentation therapy on FEV₁ decline in patients with alpha₁ antitrypsin deficiency (AATD) related lung disease enrolled in the Alpha-1 Foundation DNA and Tissue Bank study.13 Patients were included if they had a proven PI ZZ genotype and at least two recorded post-bronchodilator FEV₁ 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 FEV₁ at baseline was 1.7 L and the mean FEV₁ % 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 FEV₁ % of predicted, the mean overall change in FEV₁ reported was 47.6 mL/year, favoring the augmented group (decline in FEV₁ 10.6 +/- 21.4 mL/year) in comparison with the non-augmented group (decline in FEV₁ -36.96 +/- 12.1 mL/year) (p=0.05). Beneficial change in FEV₁ were observed in ex-smokers and the group with initial FEV₁ % 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 FEV₁ below 50% of predicted.

A multicenter, retrospective cohort study evaluated evaluate the progression of emphysema in patients with alpha₁-protease inhibitor (alpha₁-PI) deficiency before and during a period in which they received treatment with alpha₁-Pi augmentation therapy.14 Ninety-six patients with severe alpha₁-PI deficiency receiving weekly treatment with human alpha₁-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$_1$ was compared during non-treatment and treatment periods. The reported decline in FEV$_1$ 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$_1$ > 65%, IV alpha$_1$-Pi treatment reduced the decline in FEV$_1$ by 73.6 mL/yr (p=0.045). Seven individuals had a rapid decline of FEV$_1$ before treatment, and the loss in FEV$_1$ 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 alpha$_1$-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$_1$-antitrypsin (alpha$_1$-AT) levels ≤11 microM or PiZZ genotype were followed for 3.5 to 7 years with spirometry measurements every 6 to 12 months. 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$_1$-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$_1$ 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$_1$ 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.

Seershholm et al. conducted a non-randomized study which evaluated the effect of alpha$_1$-antitrypsin augmentation (alpha$_1$-AT) therapy on patients with alpha$_1$-antitrypsin deficiency (alpha$_1$-ATD) by comparing the annual decline in FEV$_1$ in a treated group of ex-smokers in Denmark and an untreated group of ex-smokers in Denmark. From the files of the Danish alpha$_1$-ATD register, 97 ex-smokers were included with the following criteria: PiZZ phenotype or having a alpha$_1$-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 alpha$_1$-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$_1$ 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$_1$ as fixed parameters, and the individual patients as random effects parameters. The reported decline in FEV$_1$ 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$_1$% predicted, however, gender did not have any influence on FEV$_1$ decline. Stratification by initial FEV$_1$% predicted showed a significant effect of the treatment only in the group of patients with an initial FEV$_1$% predicted of 31-65%, and FEV1 decline was reduced by 21 mL/year. Researchers concluded that this nonrandomized study suggested that weekly infusion of human alpha$_1$-antitrypsin in patients with moderately reduced lung function may slow the annual decline in FEV$_1$.

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. Patients were administered intravenous doses of 60 milligrams/kilogram/week alpha$_1$-protease 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

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**Alpha$_1$-Protease Inhibitors**

UnitedHealthcare Oxford Clinical Policy

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fibrosis have shown some promise; however larger studies with relevant clinical endpoints are needed to validate efficacy.\textsuperscript{10-11}

**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.\textsuperscript{12}

**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]

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right 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. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

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