

Corporate Medical Policy

Alpha 1-Antitrypsin Inhibitor Therapy

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Description of Procedure or Service

Alpha₁-antitrypsin deficiency

Deficiency of alpha₁-proteinase inhibitor (A₁-PI), also known as alpha₁- antitrypsin (AAT) deficiency is a chronic, hereditary disorder, characterized by reduced levels of A₁-PI in the blood and lungs. A low concentration of AAT is associated with slowly progressive, moderate-to-severe panacinar emphysema that most often manifests in the third to fourth decades of life, resulting in significantly reduced life expectancy. Individuals with 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. Alpha₁- antitrypsin inhibitor therapy augments the level of the deficient protein and therefore may correct the imbalance between neutrophil elastase and protease inhibitors, protecting the lower respiratory tract.

A large number of phenotypic variants of AAT deficiency exists. The most severely affected individuals are those with the PiZZ variant, characterized by A₁-PI serum levels <35% normal. Individuals with these low serum A₁-PI levels, i.e., less than 11µmol (80 mg/dL), have an unknown risk of developing emphysema over their lifetimes. Studies of the various phenotypes of A₁-PI deficiency have demonstrated that individuals with endogenous serum levels of A₁-PI ≤50 mg/dl have a risk of >80% of developing emphysema over a lifetime. However, individuals with endogenous A₁-PI levels >80 mg/dl, in general, do not manifest an increased risk for development of emphysema above the general population background risk. Therefore, the “threshold” level of A₁-PI in the serum required to provide adequate anti-elastase activity in the lung of individuals with alpha₁-antitrypsin deficiency is about 80 mg/dL.

Alpha₁-proteinase inhibitors approved by the U.S. Food & Drug Administration (FDA) include: Aralast NP™ (Baxter Healthcare, Westlake Village, CA), Glassia® (Baxter Healthcare, Westlake Village, CA), Prolastin-C® (Talecris Biotherapeutics, Inc., Research Triangle Park, NC) and Zemaira® (CSL Behring, LLC, Kankakee, IL).

Related Policies:

Place of Service for Medical Infusion
Genetic Testing for Alpha-1 Antitrypsin Deficiency

*****Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

Policy

BCBSNC will provide coverage for alpha₁-antitrypsin inhibitor therapy (Aralast NP™, Glassia™, Prolastin®-C and Zemaira®) for alpha₁-antitrypsin deficiency in adults when the medical necessity criteria and guidelines shown below are met.

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Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Alpha₁-Antitrypsin Inhibitor Therapy for Alpha₁-Antitrypsin Deficiency is covered

Alpha₁-antitrypsin inhibitor therapy (Aralast NP™, Glassia™, Prolastin®-C and Zemaira ®) is medically necessary for adults with emphysema due to congenital deficiency of alpha₁-antitrypsin (AAT) when the following criteria have been met.

A. For **initial therapy**, **all** of the following:

1. Diagnosis of emphysema; and
2. Current nonsmoker; and
3. Low serum concentration of AAT < 80 mg/dL by radial immunodiffusion (or less than 50 mg/dL if measured by nephelometry) or < 11µmol/L (35% of normal); and
4. Diagnosis of congenital alpha₁-antitrypsin deficiency confirmed by one of the following:
 - a. PiZZ, PiZ(null) or Pi(null)(null) protein phenotypes (homozygous); or
 - b. Other rare AAT disease-causing alleles associated with serum alpha₁-antitrypsin (AAT) level <11µmol/L; and
5. Individual is not IgA antibody deficient with antibodies to IgA.

B. For **continuation therapy**, **all** of the following:

1. Items 1-5 above, and
2. Documentation of a positive clinical response from pretreatment baseline to alpha₁-antitrypsin inhibitor therapy

When Alpha₁-Antitrypsin Inhibitor Therapy for Alpha₁-Antitrypsin Deficiency is not covered

Alpha₁-antitrypsin inhibitor therapy is considered **investigational** for any other indication not listed above.

Alpha₁-antitrypsin inhibitor therapy is considered **investigational** for treatment of cystic fibrosis.

Inhaled alpha₁-antitrypsin therapy is considered **investigational** because its effectiveness has not been established.

Because panacinar emphysema does not develop in some individuals who have AAT deficiency, replacement therapy with AAT inhibitor is of no proven value in affected individuals without clinical evidence of emphysema and is therefore considered **investigational** for these individuals

Policy Guidelines

Alpha₁-antitrypsin is an antiprotease found in human plasma that inhibits the neutrophil elastase enzyme from degrading elastin tissues in the lung. Alpha₁-antitrypsin (AAT) deficiency is a hereditary disorder associated with the early onset of severe pulmonary emphysema in adults. Although alpha₁-antitrypsin inhibitor therapy has not been shown to prevent or reverse emphysema in these patients affected by AAT deficiency, there is reason to believe that maintenance of antitrypsin serum levels may be compatible with decrease in the progression of emphysema.

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Dosing is in accordance with the United States FDA approved labeling: dosage is 60mg/kg body weight administered intravenously once weekly.

Once initiated, therapy will usually be continued for the remainder of the patient's life. Recipients of alpha₁-antitrypsin inhibitor therapy should be immunized against hepatitis B. It is also recommended that this medication not be used in patients with immunoglobulin antibody IgA deficiency that is known to have antibodies against IgA (anti-IgA antibody). These patients may experience severe reactions, including anaphylaxis to IgA, which may be present in human alpha₁-antitrypsin inhibitor.

As part of a National Heart, Lung, and Blood Institute Registry of Patients with Severe Deficiency of Alpha₁-Antitrypsin, patients ≥ 18 years of age with serum alpha₁-antitrypsin levels $\leq 11\mu\text{mol/L}$ 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 alpha₁-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 FEV1 values of 35 to 49% predicted (ATS Stage II) (RR 5 0.21, 95% CI 5 0.09 to 0.50, $p < 0.001$). FEV1 decline was not different between augmentation therapy groups ($p=0.40$). Researchers concluded that patients that receive augmentation therapy have a better survival than do patients not on therapy, although these differences may have been due to other factors.

Tonellis and colleagues examined the effect of alpha₁-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. Patients were included if they had a proven PiZZ 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 the time of 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 1.7L 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 observed in mortality. Researchers concluded that augmentation therapy improves lung function in subject with AAT deficiency when adjusted by age, gender, smoking status and baseline FEV1 % of predicted. Additionally, the beneficial effects were observed in ex-smoker with FEV1 below 50% of predicted.

A multicenter, retrospective cohort study evaluated the progression of emphysema in patients with alpha₁-protease inhibitor (A₁-Pi) deficiency before and during a period in which they received treatment with alpha₁-Pi augmentation therapy. Ninety-six patients with severe alpha₁-Pi deficiency receiving weekly treatment with human alpha₁-antitrypsin inhibitor (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 FEV1 was compared during non-treatment and

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treatment periods. The reported decline in FEV1 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 FEV1 >65%, IV A₁-PI treatment reduced the decline in FEV1 by 73.6 mL/yr ($p=0.045$). Seven individuals had a rapid decline of FEV1 before treatment, and the loss in FEV1 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 A₁-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.

A randomized controlled trial of alpha₁-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 alpha₁-proteinase inhibitor in cystic fibrosis have shown some promise; however larger studies with relevant clinical endpoints are needed to validate efficacy.

For conditions associated with alpha₁ proteinase inhibitor deficiency other than chronic obstructive lung disease, a review found only case reports of patients treated with alpha₁ 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 as well as larger clinical trials are warranted in order to determine efficacy of augmentation therapy in these conditions.

Alpha₁-Antitrypsin Inhibitor Therapy for Alpha₁-antitrypsin Deficiency - Site of Care Eligibility

1. Alpha₁-Antitrypsin Inhibitor Therapy administration may be given in an inpatient setting if the inpatient setting is medically necessary. An inpatient admission for the sole purpose of Alpha₁-Antitrypsin Inhibitor Therapy infusion is not medically necessary.
2. Alpha₁-Antitrypsin Inhibitor Therapy administration in a hospital outpatient setting is considered medically necessary if the following criteria are met:
 - a. History of mild adverse events that have not been successfully managed through mild pre-medication (diphenhydramine, acetaminophen, steroids, fluids, etc.),
OR
 - b. Inability to physically and cognitively adhere to the treatment schedule and regimen complexity, OR
 - c. First infusion, OR
 - d. Less than 3 months since first Alpha₁-Antitrypsin Inhibitor infusion, OR
 - e. First infusion after six months of no Alpha₁-Antitrypsin Inhibitor infusions, OR
 - f. Requirement of a change in Alpha₁-Antitrypsin Inhibitor product.
3. Members who do not meet the criteria above are appropriate for Alpha₁-Antitrypsin Inhibitor Therapy administration in a **home-based** or physician office setting with or without supervision by a certified healthcare professional. Inpatient and hospital outpatient infusion, in the absence of the criteria in #1 or #2 above is considered not medically necessary.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: J0256, J0257, S9346; Codes are effective for PPA as of 4/1/2018.

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BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

U.S. Food and Drug Administration (FDA), Aralast NP package insert. Available at <https://www.fda.gov>: (Accessed 11/2017)

U.S. Food and Drug Administration (FDA), Glassia package insert. Available at <https://www.fda.gov>: (Accessed 11/2017)

U.S. Food and Drug Administration (FDA), Prolastin-C package insert. Available at <https://www.fda.gov>: (Accessed 11/2017)

U.S. Food and Drug Administration (FDA), Zemaira package insert. Available at <https://www.fda.gov>: (Accessed 11/2017)

The Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. *Am J Respir Crit Care Med*. 1998 Jul;158(1):49-59.

Tonelli AR, Rouhani F, Li N, et al. Alpha-1-antitrypsin augmentation therapy in deficient individuals enrolled in the Alpha-1 Foundation DNA and Tissue Bank. *Int J Chron Obstruct Pulmon Dis*. 2009;4:443-52.

Griese M, et al. alpha1-Antitrypsin inhalation reduces airway inflammation in cystic fibrosis patients. *European Respiratory Journal* 2007;29(2):240-50.

Griese M, Kappler M, Gaggar A, Hartl D. Inhibition of airway proteases in cystic fibrosis lung disease. *European Respiratory Journal* 2008;32(3):783-95.

Blanco I, Lara B, de Serres F. Efficacy of alpha1-antitrypsin augmentation therapy in conditions other than pulmonary emphysema. *Orphanet Journal of Rare Diseases* 2011;6:14.

Medical Director review 11/2017

Specialty Matched Consultant Advisory Panel review 11/2018

Specialty Matched Consultant Advisory Panel review 3/2019

Policy Implementation/Update Information

- 12/29/17 New Policy developed titled, "Alpha 1-Antitrypsin Inhibitor Therapy" with policy statement, "BCBSNC will provide coverage for Alpha₁-Antitrypsin Inhibitor Therapy (Aralast NP™, Glassia™, Prolastin®-C and Zemaira®) for alpha₁-antitrypsin deficiency in adults when the medical necessity criteria and guidelines shown below are met." Medical Director review 11/2017. Notification given 12/29/17 for policy effective date 4/1/18. (jd)
- 12/14/18 Minor revisions made to policy for clarity. Specialty Matched Consultant Advisory Panel review 11/28/2018. No change to policy intent. (krc)
- 4/16/19 Specialty Matched Consultant Advisory Panel review 3/20/2019. No change to policy statement. (krc)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.