Alpha$_1$-Proteinase Inhibitors

Policy Number: CS2020D0067E
Effective Date: December 1, 2020

Instructions for Use

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Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Indiana	Alpha$_1$-Proteinase Inhibitors (for Indiana Only)
Kansas	Refer to the state's Medicaid clinical policy
Kentucky	Alpha$_1$-Proteinase Inhibitors (for Kentucky Only)
Louisiana	Alpha$_1$-Proteinase Inhibitors (for Louisiana Only)
North Carolina	None

Coverage Rationale

Alpha$_1$-proteinase inhibitors (Aralast NP™, Glassia™, Prolastin®-C and Zemaira®) are proven and medically necessary for chronic augmentation and maintenance therapy of patients with emphysema due to congenital deficiency of alpha$_1$-proteinase inhibitor (A$_1$-PI), also known as alpha$_1$-antitrypsin (AAT) deficiency.[1-4]

- The treatment of emphysema due to congenital deficiency of alpha$_1$-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 alpha$_1$-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 AAT level < 11 μmol/L [e.g., Pi(Malton, Malton)];

      and
    - Circulating serum concentration of AAT < 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; and
        - Initial authorization will be for no more than 12 months
    - For continuation of therapy, all of the following:
        - Diagnosis of congenital alpha$_1$-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 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$_1$-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; and
        - Reauthorization will be for no more than 12 months

Alpha$_1$-proteinase inhibitors are unproven for:
- Conditions other than emphysema associated with alpha$_1$-antitrypsin deficiency
- Cystic fibrosis

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 federal, state, or contractual requirements 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 and Guidelines may apply.

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

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

Background

Deficiency of alpha$_1$-proteinase inhibitor (A$_1$-PI), also known as alpha$_1$-antitrypsin (AAT) deficiency, is characterized by reduced levels of A$_1$-PI in the blood and lungs. A$_1$-PI deficiency is an autosomal, co-dominant, hereditary disorder. Patients with severe A$_1$-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$_1$-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]

Clinical Evidence

Proven

Alpha$_1$-Proteinase Inhibitor (A$_1$-PI) Deficiency [i.e., Alpha$_1$-Antitrypsin (AAT) Deficiency]

Tonellis et al. examined the effect of alpha-1 antitrypsin augmentation therapy on FEV$_1$ decline in patients with AAT deficiency 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 FEV$_1$ 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_1 at baseline was 1.7 L and the mean FEV_1 % 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_1 % of predicted, the mean overall change in FEV_1 reported was 47.6 mL/year, favoring the augmented group (decline in FEV_1 10.6 +/- 21.4 mL/year) in comparison with the non-augmented group (decline in FEV_1 -36.96 +/- 12.1 mL/year) (p=0.05). Beneficial change in FEV_1 were observed in ex-smokers and the group with initial FEV_1 % of predicted of <50%. There were no differences were observed in mortality. Researchers concluded that augmentation therapy improves lung function in subjects with AAT deficiency when adjusted by age, gender, smoking status and baseline FEV % of predicted. Additionally, the beneficial effects were observed in ex-smoker subjects with FEV_1 below 50% of predicted.

A multicenter, retrospective cohort study evaluated evaluate the progression of emphysema in patients with alpha$_1$-protease inhibitor (alpha$_1$-Pi) deficiency before and during a period in which they received treatment with alpha$_1$-Pi augmentation therapy. [14] Ninety-six patients with severe alpha$_1$-Pi deficiency receiving weekly treatment with human alpha$_1$-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_1could 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 α1 -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.[15] 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 α_1-antitrypsin augmentation (α1-AT) therapy on patients with α_1-antitrypsin deficiency (α_1-ATD) by comparing the annual decline in FEV_1 in a treated group of ex-smokers in Germany and an untreated group of ex-smokers in Denmark.[16] From the files of the Danish α_1-ATD register, 97 ex-smokers were included with the following criteria:. PiZZ phenotype or having a α1-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 α1-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 α_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.[17] 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.[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.[12]

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Aralast NP, Prolastin-C, Glassia and Zemaira are all alpha$_1$-proteinase inhibitors (human) FDA-labeled for chronic augmentation therapy in patients having congenital deficiency of alpha$_1$-proteinase inhibitor (A_1-PI), also known as 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 alpha$_1$-proteinase inhibitors are not available.
- Alpha$_1$-proteinase inhibitors are not indicated for treatment of lung disease in patients whom congenital A_1-PI deficiency has not been established.
- Alpha$_1$-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.

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) specifically for Alpha-1-Proteinase Inhibitors (Aralast NP®, Glassia®, Prolastin®-C and Zemaira®) used to treat alpha1-antitrypsin (AAT) deficiency. Local Coverage Determinations (LCDs)/Local Coverage Articles (LCAs) do not exist at this time.

In general, Medicare may cover outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual, Chapter 15, §50 - Drugs and Biologicals. (Accessed October 2, 2020)

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Policy History/Revision Information

Date	Summary of Changes
08/01/2021	**Application** • Added language to indicate this policy does not apply to the states of Indiana and North Carolina
02/01/2021	**Application** • Reformatted content • Added language to indicate this policy does not apply to the state of Kentucky; refer to the state-specific policy version
12/01/2020	**Application** • Added instruction for the state of Kansas to refer to the state's Medicaid clinical policy • Added language to indicate this policy does not apply to the state of Louisiana; refer to the state-specific policy version **Coverage Rationale** • Removed specific dosage requirements for the use of alpha$_1$-proteinase inhibitors; refer to the applicable US FDA approved labeling **Supporting Information** • Updated *CMS* and *References* sections to reflect the most current information • Archived previous policy version CS2019D0067D

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies 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.