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Alpha 1-Antitrypsin Inhibitor Therapy [Medicare]

Clinical Policy Bulletins | Medical Clinical Policy Bulletins

Number: 0145m

Commercial CPB (0145.html) | Medicare CPB

Medicare Part B Step Therapy Criteria

Aralast NP, Glassia and **Zemaira**, for the indications listed below:

- Clinically evident emphysema due to hereditary deficiency of Alpha-1 PI (alpha-1 antitrypsin deficiency)

  Are not covered for new starts, unless the member meets ANY of the following:

  1. Inadequate response to a trial of Prolastin-C
  2. Intolerable adverse event to Prolastin-C
  3. Prolastin-C is contraindicated for the member.

Policy

Note: Requires Precertification:

Policy History

Effective: 01/01/2022

Next Review: 01/13/2022

Definitions

Additional Information

Clinical Policy Bulletin Notes

Precertification of alpha 1-antitrypsin (AAT) inhibitors (Aralast NP, Glassia, Prolastin-C, and Zemaira) is required of all Aetna participating providers and members in applicable plan designs. For precertification of alpha 1-antitrypsin (AAT) inhibitors, call (866) 752-7021 or fax (888) 267-3277.

Note: Site of Care Utilization Management Policy applies. For information on site of service for alpha 1-antitrypsin inhibitors see Utilization Management Policy on Site of Care for Specialty Drug Infusions (https://www.aetna.com/health-care-professionals/utilization-management/drug-infusion-site-of-care-policy.html).

I. Criteria for Initial Approval

Aetna considers alpha 1-antitrypsin (AAT) inhibitor therapy (e.g., Aralast NP, Glassia, Prolastin-C, and Zemaira) medically necessary for the treatment of emphysema due to AAT deficiency when *all* of the following criteria are met:

A. The member's pretreatment serum AAT level is less than 11 micromol/L (80 mg/dL by radial immunodiffusion or 50 mg/dL by nephelometry); *and*
B. The member's pretreatment post-bronchodilation forced expiratory volume in 1 second (FEV_1) is greater than or equal to 25% and less than or equal to 80% of the predicted value; *and*
C. The member has a documented PiZZ, PiZ (null), or Pi (null, null) phenotype (homozygous) AAT deficiency or other phenotype associated with serum AAT concentrations of less than 11 micromol/L (80 mg/dL by radial immunodiffusion or 50 mg/dL by nephelometry); *and*
D. The member does not have the PiMZ or PiMS phenotype AAT deficiency.

Aetna considers all other indications as experimental and investigational (for additional information, see 'Experimental and Investigational' and 'Background' sections).

II. Continuation of Therapy

Aetna considers continuation of AAT inhibitors (Aralast NP, Glassia, Prolastin-C, and Zemaira) medically necessary for treatment of emphysema due to AAT deficiency when the member is experiencing beneficial clinical response from therapy.

III. Other

Note: If the member is a current smoker, they should be counseled on the harmful effects of smoking on pulmonary conditions and available smoking cessation options.

Dosage and Administration

Aralast NP

- Available as lyophilized powder in single dose vials containing 0.5 gram or 1 gram of functional Alpha1-PI
- Recommended dosage is 60 mg/kg body weight administered once weekly by intravenous infusion
- Administer at a rate not to exceed 0.2 mL/kg body weight/minute, and as determined by the response and comfort of the individual

Source: Baxalta US, 2018

Glassia

- Available for injection: aproximately 1 gram of functional alpha1-PI in 50 mL of ready to use solution in a single use vial
- The recommended dosage is 60 mg/kg body weight administered once weekly by intravenous infusion
- Administer at a rate not to exceed 0.2 mL/kg body weight per minute, depending on individual's response and comfort

Source: Baxalta US, 2017

Prolastin-C

- Available for injection: approximately 1,000 mg in a single-use vial containing 20 mL of solution for injection
- The recommended dosage is 60 mg/kg body weight administered once weekly by intravenous infusion
- Dose ranging studies using efficacy endpoints have not been performed with any Alpha1-PI product
- Administration: 0.08 mL/kg/min as determined by individual's response and comfort

Source: Grifols Therapeutics, 2018

Zemaira

- Zemaira is supplied in a single-use vial containing approximately 1000 mg, 4000 mg, or 5000 mg of functionally active A1-PI as a white to off-white lyophilized powder for reconstitution with 20 mL, 76 mL, or 95 mL of Sterile Water for Injection, USP
- The recommended weekly dose of Zemaira is 60 mg/kg body weight. Dose ranging studies using efficacy endpoints have not been performed with Zemaira or any A1 -PI product
- Administer at a rate of approximately 0.08 mL/kg/min as determined by the response and comfort of the individual

Source: CSL Behring, 2019

Experimental and Investigational

I. 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 experimental and investigational for these individuals.

II. Aetna considers AAT inhibitor experimental and investigational for treatment of the following (not an all-inclusive list):

- Acute respiratory distress syndrome in persons undergoing mechanical ventilation;

- Cystic fibrosis;
- Inflammatory and autoimmune diseases (e.g., acute myocardial infarction, colitis-associated colon cancer, connective tissue/rheumatoid diseases including rheumatoid arthritis, diabetes mellitus, graft-versus-host disease, inflammatory bowel disease);
- Ischemia-reperfusion injury in organ transplantation.

III. Aetna considers alpha-1 antitrypsin deficiency gene therapy experimental and investigational because its effectiveness has not been established.

IV. Aetna considers inhaled alpha-1 antitrypsin therapy experimental and investigational because its effectiveness has not been established.

Background

U.S. Food and Drug Administration (FDA)-Approved Indications

- *Aralast NP*

  Chronic augmentation therapy in adults with clinically evident emphysema due to severe congenital deficiency of alpha1-proteinase inhibitor (alpha1-antitrypsin deficiency)

- *Glassia*

  Chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe hereditary deficiency of alpha1-proteinase inhibitor (alpha1-antitrypsin deficiency)

- *Prolastin-C*

  Chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of alpha1-proteinase inhibitor (alpha1-antitrypsin

deficiency)

- *Zemaira*

  Chronic augmentation and maintenance therapy in adults with alpha1-proteinase inhibitor deficiency and clinical evidence of emphysema

Alpha 1-antitrypsin is an antiprotease found in human plasma that inhibits the neutrophil elastase enzyme from degrading elastin tissues in the lung. Alpha-1-antitrypsin (AAT) deficiency is a hereditary disorder associated with the early onset of severe pulmonary emphysema in adults. Although alpha 1-antitrypsin inhibitor therapy (Prolastin, Aralast) 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 retardation of the progression of emphysema.

Once initiated, therapy will usually be continued for the remainder of the patient's life. Recipients of alpha 1-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 alpha 1-antitrypsin inhibitor.

According to American Thoracic Society (2003) guidelines, a "protective" threshold plasma AAT level of 11 mol/L corresponds to 80 mg/dl if measured by radial immunodiffusion and to 50 mg/dl if measured by nephelometry. This protective threshold has evolved from the observation that patients with heterozygote phenotypes whose levels of AAT exceed this level are usually free from emphysema.

Alpha-1 Proteinase inhibitors are contraindicated in IgA deficient patients with antibodies against IgA, since these products may contain trace amounts of IgA and cause an increased risk for severe hypersensitivity.

Abboud and colleagues (2005) stated that AAT replacement therapy has not yet been proven to be clinically effective in reducing the progression of disease in AAT-deficient patients. There was a suggestion of a slower progression of emphysema by computed tomography scan in a small randomized trial. Two non-randomized studies comparing AAT-deficient patients already receiving replacement therapy with those not receiving it, and a retrospective study evaluating a decline in forced expiratory volume in 1 second (FEV1) before and after replacement therapy, suggested a possible benefit for selected patients. Because of the lack of definitive proof of the clinical effectiveness of AAT replacement therapy and its cost, these investigators recommended reserving AAT replacement therapy for deficient patients with impaired FEV1 (35 to 65 % of predicted value), who have quit smoking and are on optimal medical therapy but continue to show a rapid decline in FEV1 after a period of observation of at least 18 months.

An assessment by the Canadian Agency for Drugs and Technologies in Health (Chen et al, 2007) concluded that evidence showing health improvement from alpha-1 antitrypsin inhibitor therapy is inconclusive. The assessment found that, in controlled trials, augmentation therapy has not shown reduced lung function impairment in patients with AAT deficiency and chronic obstructive pulmonary disease (COPD), compared with normal care. Conversely, the assessment reported that in observational studies, alpha-1 antitrypsin inhibitor therapy is associated with outcomes suggestive of therapeutic benefit in patients with severe AAT deficiency and moderate airflow obstruction. The assessment found that severe adverse events from treatment have been reported in approximately 1 % of study populations.

The assessment concluded that use of alpha-1 antitrypsin inhibitor therapy in patients without COPD is experimental (Chen et al, 2007). The assessment found no evidence evaluating the use of alpha-1 antitrypsin inhibitor therapy in patients with AAT deficiency and no lung function impairment.

On July 1, 2010, Kamada, Ltd., (Beit Kama, Israel) received approval from the Food and Drug Administration for manufacturing Glassia (alpha-1-proteinase inhibitor [human]), which is an intravenously administered

biologic product indicated for chronic augmentation and maintenance therapy in individuals with emphysema due to congenital deficiency of alpha-1-proteinase inhibitor, also known as AAT deficiency.

McElvaney and colleagues (2017) noted that purified alpha 1 proteinase inhibitor (A1PI) slowed emphysema progression in patients with severe alpha 1 antitrypsin deficiency in a randomized controlled trial (RAPID-RCT), which was followed by an open-label extension trial (RAPID-OLE). These researchers examined the prolonged treatment effect of A1PI on the progression of emphysema as assessed by the loss of lung density in relation to RAPID-RCT. Patients who had received either A1PI treatment (Zemaira or Respreeza; early-start group) or placebo (delayed-start group) in the RAPID-RCT trial were included in this 2-year open-label extension trial (RAPID-OLE). Patients from 22 hospitals in 11 countries outside of the USA received 60 mg/kg per week A1PI. The primary end-point was annual rate of adjusted 15th percentile lung density loss measured using CT in the intention-to-treat population with a mixed-effects regression model. Between March 1, 2006, and October 13, 2010, a total of 140 patients from RAPID-RCT entered RAPID-OLE: 76 from the early-start group and 64 from the delayed-start group. Between day 1 and month 24 (RAPID-RCT), the rate of lung density loss in RAPID-OLE patients was lower in the early-start group (-1.51 g/L per year [SE 0.25] at total lung capacity [TLC]; -1.55 g/L per year [0.24] at TLC plus functional residual capacity [FRC]; and -1.60 g/L per year [0.26] at FRC) than in the delayed-start group (-2.26 g/L per year [0.27] at TLC; -2.16 g/L per year [0.26] at TLC plus FRC, and -2.05 g/L per year [0.28] at FRC). Between months 24 and 48, the rate of lung density loss was reduced in delayed-start patients (from -2.26 g/L per year to -1.26 g/L per year), but no significant difference was seen in the rate in early-start patients during this time period (-1.51 g/L per year to -1.63 g/L per year), thus in early-start patients the efficacy was sustained to month 48. The authors concluded that RAPID-OLE supported the continued efficacy of A1PI in slowing disease progression during 4 years of treatment. Lost lung density was never recovered, highlighting the importance of early intervention with A1PI treatment.

Alpha-1 Antitrypsin Deficiency Gene Therapy

Guo et al (2014) noted that AAT is a serum protease inhibitor that belongs to the serpin superfamily. Mutations in AAT are associated with AATD, a rare genetic disease with 2 distinct manifestations: AATD lung disease and AATD liver disease. The former is caused by loss-of-function of AAT and can be treated with plasma-derived AAT; the latter is due to the aggregation and retention of mutant AAT protein in the liver. The only treatment available for AATD liver disease is liver transplantation. These researchers demonstrated that anti-sense oligonucleotides (ASOs) targeting human AAT efficiently reduced levels of both short and long human AAT transcript in-vitro and in transgenic mice, providing a novel therapy for AATD liver disease. In addition, ASO-mediated depletion of mouse AAT may offer a useful animal model for the investigation of AATD lung disease.

Wozniak et al (2015) stated that a number of identified mutations in the SERPINA1 gene encoding this protein result in AATD. A decrease in AAT serum concentration or reduced biological activity causes considerable risk of chronic respiratory and liver disorders. As a monogenic disease, AATD appears to be an attractive target for gene therapy, particularly for patients with pulmonary dysfunction, where augmentation of functional AAT levels in plasma might slow down respiratory disease development. The short AAT coding sequence and its activity in the extracellular matrix would enable an increase in systemic serum AAT production by cellular secretion. In-vitro and in-vivo experimental AAT gene transfer with gamma-retroviral, lentiviral, adenoviral, and adeno-associated viral (AAV) vectors has resulted in enhanced AAT serum levels and a promising safety profile. Human clinical trials using intramuscular viral transfer with AAV1 and AAV2 vectors of the AAT gene demonstrated its safety, but did not achieve a protective level of AAT greater than 11 μM in serum. These researchers provided an in-depth critical analysis of current progress in AATD gene therapy based on viral gene transfer. The factors affecting transgene expression levels, such as site of administration, dose and type of vector, and activity of the immune system, were discussed further as crucial variables for optimizing the clinical effectiveness of gene therapy in AATD subjects.

Chiuchiolo and Crystal (2016) described the various strategies for AAT gene therapy for the pulmonary manifestations of AATD and the state of

the art in bringing AAT gene therapy to the bedside. These researchers noted that the pre-clinical safety and efficacy studies with the AAVrh.10 vector supported the Food and Drug Administration (FDA)'s approval for a phase I/II clinical trial Investigational New Drug (IND) application. The aim of the clinical trial (NCT02168686) is to assess the hypothesis that a single intra-pleural administration of a serotype AAVrh.10 vector expressing the normal M1-type AAT (AAVrh.10hAAT) to individuals with AATD is safe and results in persistent therapeutic serum and alveolar ELF levels of AAT. The study will compare 2 doses: (i) $8 \times 10(12)$, and (ii) $8 \times 10(13)$ genome copy, administered to individuals (n = 5) with a ZZ or Z null genotype and serum AAT levels of less than 11 μM. Individuals will receive the vector as one 50-ml dose, administered directly into the intra-pleural space using a needle attached to a central line catheter, and fluoroscopic guidance. As a comparator to the intra-pleural route, 5 individuals with AATD will be administered the AAVrh.10hAAT vector at each dose level by the intravenous route. In addition to the normal safety parameters, the goal of the therapy will be to reach a sustained concentration of more than 1.2 μM AAT in epithelial lining fluid (ELF), the lung "protective level". The completion of this study will provide critical safety and preliminary efficacy data to determine whether to proceed to a phase II/III efficacy study for eventual FDA approval.

AAT Inhibitor Therapy for Acute Respiratory Distress Syndrome in Persons Undergoing Mechanical Ventilation

Zhu and colleagues (2018) stated that mechanical ventilation is extensively used to treat patients with lung injury but may result in ventilator-induced lung injury (VILI). These investigators examined the protective effect of AAT on VILI. Adult male rats were subjected to sham, ventilation + saline, or ventilation + AAT treatment and lung injuries were evaluated. Peripheral blood and broncho-alveolar lavage fluid (BALF) were obtained to assess systemic and local inflammatory responses, respectively. Mechanical ventilation resulted in lung injury, as evidenced by histological abnormalities as well as elevations in PaO2/FiO2 ratio, the wet-to-dry weight ratio, and the BALF level of proteins. The intravenous administration of AAT significantly improved these parameters of lung function, suggesting a protective role of AAT in VILI. Mechanistically, ventilator-induced inflammation was effectively reduced by AAT, as evidenced by decreases in BALF neutrophil counts, BALF cytokines, and

serum adhesion factors. In contrast, anti-inflammatory interleukin-10 (IL-10) in BALF was increased in response to AAT; and AAT treatment also inhibited the expression of nuclear factor-κB, Bax, and cleaved caspase-3 while promoting Bcl-2 expression in ventilator-injured lung tissues. These researchers noted that AAT treatment could ameliorate VILI by inhibiting inflammatory mediator production and apoptosis. The authors concluded that the findings of the present study demonstrated that AAT inhibited the development of VILI by modulating inflammation- and apoptosis-related protein expression; thus, AAT may be a novel therapeutic agent for acute respiratory distress syndrome patients undergoing mechanical ventilation.

AAT Inhibitor Therapy for Inflammatory and Autoimmune Diseases

Kim and colleagues (2018) noted that genetic deficiency of AAT can present as several neutrophilic diseases associated with emphysema, liver cirrhosis, panniculitis, and systemic vasculitis. Animal and human studies have shown that AAT could control inflammatory, immunological, and tissue-protective responses. In addition, AAT therapy could prevent overt hyperglycemia, increase insulin secretion, and reduce cytokine-mediated apoptosis of pancreatic β-cells in diabetes. These multi-functional roles of AAT drew attention to the glycoprotein's therapeutic potential for many inflammatory and autoimmune diseases beyond AAT deficiency. As underlying mechanisms, studies have suggested the importance of serine protease inhibitory activity of AAT in obesity-associated insulin resistance, chronic obstructive pulmonary disease, and CF. These researchers explored the multiple functions of AAT, in particular, the anti-inflammatory and serine protease inhibitory functions, and AAT's therapeutic potential in a variety of human diseases through published literature. In particular, ongoing studies continue to investigate the association of AAT with and its potential for treating diabetes mellitus, especially type 1 diabetes (T1D). The beneficial effects of AAT on insulitis, glycemic control, and pancreatic islet allografts have been confirmed in animal studies. The authors noted that AAT is also currently being used in clinical trials for diabetes. Based on these valuable findings on AAT, it may prove to be an alternative to various disease treatments and should be evaluated in further prospective human studies focused on long-term safety and efficacy.

These investigators stated that graft-versus-host disease (GVHD), which remains a major problem in allogeneic hematopoietic cell transplantation, is ameliorated by the inhibition of IL-1 production/activity, inhibition of proteinase 3-related IL-32 activation, and increased release of IL-1 receptor antagonist and IL-10 in animal models. In a human study, AAT was well-tolerated and demonstrated efficacy in the treatment of steroid-refractory severe acute GVHD. The injection of human AAT or the production of adenoviral plasmid-derived, circulating human AAT could delay rheumatoid arthritis (RA) development in a mouse model via the inhibition of IL-6, IL-1β, and TNF-α along with the neutralization of serine proteinases and aggrecanase-1 from neutrophils. Published pre-clinical and clinical reports have shown that AAT is related not only to infectious diseases, but also to inflammatory bowel disease (IBD), acute myocardial infarction, and connective tissue/rheumatoid diseases. In addition, animal studies using the colitis-associated colon cancer mouse model demonstrated that AAT therapy resulted in a significant inhibition of tumor incidence accompanying amelioration of colonic inflammation compared with controls, strongly suggesting therapeutic potential of AAT in colitis-associated colon cancer.

In an open-label, multi-center, phase-I clinical trial, Weir and colleagues (2018) determined the safety and pharmacokinetics of AAT in adults and children with new-onset T1D (n = 16). These researchers studied the safety and pharmacokinetics of Aralast NP (AAT). This open-label, dose-escalation study enrolled 8 adults aged 16 to 35 years and 8 children aged 8 to 15 years within 100 days of diagnosis, to receive 12 infusions of AAT: a low dose of 45 mg/kg weekly for 6 weeks, followed by a higher dose of 90 mg/kg for 6 weeks; C-peptide secretion during a mixed meal, hemoglobin A1c (HbA1c), and insulin usage remained relatively stable during the treatment period. At 72 hours after infusion of 90 mg/kg, mean levels of AAT fell below 2.0 g/L for 7 of 15 subjects. To identify a plasma level of AAT likely to be therapeutic, pharmacodynamic ex-vivo assays were performed on fresh whole blood from adult subjects. Polymerase chain reaction (PCR) analyses were performed on inhibitor of IKBKE, NOD1, TLR1, and TRAD gene expression, which are important for activation of nuclear factor-κB (NF-κB) and apoptosis pathways; AAT suppressed expression dose-dependently; 50 % inhibition was achieved

in the 2.5 to 5.0 mg/ml range. The authors concluded that AAT was safe and well-tolerated in subjects with new-onset T1D; weekly doses of AAT greater than 90 mg/kg may be necessary for an optimal therapeutic effect.

Brener and co-workers (2018) stated that promising findings of AAT intervention in mice models of T1D led researchers to examine AAT as a therapeutic modality for β-cell preservation in recent-onset T1D patients. This prospective, open-label, phase I/II extension study demonstrated that the administration of multiple repeated AAT infusions (up to 36) to AAT-sufficient pediatric T1D patients was safe and well-tolerated. Long-term surveillance of participants (up to 5 years) from diabetes onset revealed normal growth and pubertal progression through adolescence to attainment of full puberty and near adult height. No serious adverse events (AEs), clinical or laboratory abnormalities were reported. The authors concluded that given its safety profile, AAT may be an individualized-tailored innovative immunotherapy in AAT-sufficient pediatric patients with diverse immune-related medical conditions.

AAT Inhibitor Therapy for Ischemia-Reperfusion Injury in Organ Transplantation

Berger and associates (2018) noted that limited availability of donor organs and risk of ischemia-reperfusion injury (IRI) seriously restrict organ transplantation. Therapeutics that could prevent or reduce IRI could potentially increase the number of transplants by increasing use of borderline organs and decreasing discards; and AAT is an acute phase reactant and serine protease inhibitor that limits inflammatory tissue damage. Purified plasma-derived AAT has been well-tolerated in more than 30 years of use to prevent emphysema in AAT-deficient individuals. Accumulating evidence suggested that AAT has additional anti-inflammatory and tissue-protective effects including improving mitochondrial membrane stability, inhibiting apoptosis, inhibiting nuclear factor kappa B activation, modulating pro-inflammatory versus anti-inflammatory cytokine balance, and promoting immunologic tolerance. Cell culture and animal studies have shown that AAT limited tissue injury and promoted cell and tissue survival; AAT could promote tolerance in animal models by down-regulating early inflammation and favoring induction and stabilization of regulatory T cells. The diverse intracellular and immune-modulatory effects of AAT and its well-established tolerability

in patients suggested that it might be useful in transplantation. The authors concluded that clinical trials, planned and/or in progress, should help determine whether the promise of the animal and cellular studies would be fulfilled by improving outcomes in human organ transplantation.

Inhaled Human Alpha-1 Antitrypsin Therapy

Franciosi et al (2015) stated that alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant condition characterized by low circulating levels of AAT. Significant work has been performed in the development of AAT augmentation therapy for AATD. While the majority of this activity has focused on intravenous (i.v.) augmentation, evidence of a significant clinical benefit is still debated and i.v. therapy is expensive, onerous and time consuming. Inhalation therapy offers the opportunity for easier and more efficient delivery of AAT directly to the lungs with some evidence of a reduction in local inflammatory and proteolytic activity, potentially offering an alternative therapeutic option to the i.v. route. There are, however, theoretical obstacles to the potential effectiveness of aerosol-delivered AAT and although there have been a number of short-term studies examining inhaled AAT and its effect on lung inflammation, there has only been 1 long-term study to date in AATD looking at clinical outcomes, which is as yet unpublished.

Gaggar et al (2016) noted that inhaled alpha-1 proteinase inhibitor (PI) is known to reduce neutrophil elastase burden in some patients with cystic fibrosis (CF). In a phase IIa, randomized, double-blind, placebo-controlled study, these researchers tested inhaled Aapha-1 HC, a new aerosolized alpha1-PI formulation, in CF patients. These investigators evaluated the safety of 100 or 200 mg of inhaled Alpha-1 HC once-daily for 3 weeks in subjects with CF. A total of 30 adult subjects were randomized in a 2:1 ratio to receive alpha-1 HC or placebo. Drug delivery was confirmed by a dose-dependent increase in the sputum alpha1-PI; 7 (20.0 %) of the 35 adverse events in the 100-mg dose group, 3 (13.0 %) of 23 in the 200-mg dose group, and 4 (14.3 %) of 28 in the placebo group were drug-related in these subjects. One serious adverse event occurred in 1 subject within each group. The authors concluded that alpha-1 HC inhalation was safe and well-tolerated. However, the effectiveness of inhaled alpha-1 antitrypsin therapy has yet to be established.

The current study was not powered to assess changes in FEV1 or sputum A1AT concentrations; however, subsequent phase II and phase III studies could be sufficiently powered to analyze these parameters. Other opportunities for further phase II and phase III studies include a longer duration safety evaluation period, inclusion of patients with more severe respiratory insufficiency, and the delivery of Alpha-1 HC via alternative delivery devices. The authors concluded that daily alpha-1 HC (100 mg or 200 mg) delivered for 3 weeks was safe, well-tolerated, and effective in raising the alpha1-PI levels in the sputum of subjects with CF. They stated that these promising results suggested that alpha-1 HC is effectively and safely delivered in patients with CF. However, future studies are needed to determine the effectiveness and potential use of alpha-1 HC for chronic therapy in CF lung disease.

Griese and Scheuch (2016) noted that treatment with exogenous AAT was developed originally for COPD associated with AAT deficiency; however, other lung conditions involving neutrophilic inflammation and proteolytic tissue injury related to neutrophil elastase and other serine proteases may also be considered for AAT therapy. These conditions include bronchiectasis caused by primary ciliary dyskinesia, CF, and other diseases associated with an increased free elastase activity in the airways. Inhaled AAT may be a viable option to counteract proteolytic tissue damage. This form of treatment requires efficient drug delivery to the targeted pulmonary compartment. Aerosol technology meeting this requirement is currently available and offers an alternative therapeutic approach to systemic AAT administration. To-date, early studies in humans have shown biochemical efficacy and have established the safety of inhaled AAT. The authors stated that to bring aerosol AAT therapy to patients, large phase III protocols in carefully selected patient populations (i.e., subgroups of patients with AAT deficiency, CF, or other lung diseases with bronchiectasis) will be needed with clinical end-points in addition to the measurement of proteolytic activity in the airway. They stated that the outcomes likely will have to include lung function, lung structure assessed by computed tomography imaging, disease exacerbations, health status, and mortality.

CPT Codes / HCPCS Codes / ICD-10 Codes

Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+".

Code	Code Description
CPT codes covered if selection criteria are met:	
Forced expiratory volume in 1 second (FEV1) - no specific code:	
CPT codes not covered for indications listed in the CPB:	
38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition [alpha-1 antitrypsin deficiency gene therapy]
Other CPT codes related to the CPB:	
82103	Alpha-1-antitrypsin; total
82104	phenotype
HCPCS codes covered if selection criteria are met:	
J0256	Injection, alpha 1 - proteinase inhibitor - (human), not otherwise specified, 10 mg
J0257	Injection, alpha 1 proteinase inhibitor - (human), (glassia), 10 mg
S9346	Home infusion therapy, alpha-1-proteinase inhibitor (e.g., Prolastin); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem
ICD-10 codes covered if selection criteria are met:	
E88.01	Alpha-1-antitrypsin deficiency [only covered when billed with panlobular emphysema]
J43.1	Panlobular emphysema [panacinar emphysema]
ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):	
D80.2	Selective deficiency of immunoglobulin A [IgA deficient with IgA antibodies]
E84.0 - E84.9	Cystic fibrosis
J80	Acute respiratory distress syndrome
T86.90 - T86.99	Complication of unspecified transplanted organ and tissue [ischemia-reperfusion injury]

The above policy is based on the following references:

1. Abboud RT, Ford GT, Chapman KR. Emphysema in alpha1-antitrypsin deficiency: Does replacement therapy affect outcome? Treat Respir Med. 2005;4(1):1-8.
2. 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;158(1):49-59.
3. American Thoracic Society/European Respiratory Society statement: standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. Am J Respir Crit Care Med. 2003;168:818-900.
4. Baxalta US, Inc. Aralast NP [alpha1-proteinase inhibitor (human)] for intravenous use. Lyophilized powder for solution for injection. Prescribing Information. Lexington, MA: Baxalta US; revised December 2018.
5. Baxalta US, Inc. Glassia [alpha1-proteinase inhibitor (human)] injection solution – for intravenous use only. Prescribing Information. Lexington, MA: Baxalta US; revised June 2017.
6. Berger M, Liu M, Uknis ME, Koulmanda M. Alpha-1-antitrypsin in cell and organ transplantation. Am J Transplant. 2018;18(7):1589-1595.
7. Brener A, Lebenthal Y, Interator H, et al. Long-term safety of α-1 antitrypsin therapy in children and adolescents with Type 1 diabetes. Immunotherapy. 2018;10(13):1137-1148.
8. Canadian Thoracic Society. Current status of alpha-1-antitrypsin replacement therapy: Recommendation for the management of patients with severe hereditary deficiency. Ad Hoc Committee on alpha-1-antitrypsin replacement therapy of the Standards Committee, Canadian Thoracic Society. CMAJ. 1992;146(6):841-844.
9. Chapman KR, Stockley RA, Dawkins C, et al. Augmentation therapy for alpha1 antitrypsin deficiency: A meta-analysis. J Chronic Obstruct Pulm Dis. 2009;6(3):177-184.
10. Chen S, Farahati F, Marciniuk D, et al. Human a1-proteinase inhibitor for patients with a1-antitrypsin deficiency. Technology Report No. 74. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); 2007.

11. Chiuchiolo MJ, Crystal RG. Gene therapy for alpha-1 antitrypsin deficiency lung disease. Ann Am Thorac Soc. 2016;13 Suppl 4:S352-S369.
12. Coakley RJ, Taggart C, O'Neill S, et al. Alpha1-antitrypsin deficiency: Biological answers to clinical questions. Am J Med Sci. 2001;321(1):33-41.
13. CSL Behring, LLC. Zemaira, alpha1-proteinase inhibitor (human) lyophilized powder for reconstitution for intravenous use. Prescribing Information. Kankakee, IL: CSL; revised April 2019.
14. Franciosi AN, McCarthy C, McElvaney NG. The efficacy and safety of inhaled human α-1 antitrypsin in people with α-1 antitrypsin deficiency-related emphysema. Expert Rev Respir Med. 2015;9(2):143-151.
15. Gaggar A, Chen J, Chmiel JF, et al. Inhaled alpha1-proteinase inhibitor therapy in patients with cystic fibrosis. J Cyst Fibros. 2016;15(2):227-233.
16. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Vancouver, WA: Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2011.
17. Gotzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. Cochrane Database Syst Rev. 2010;(7):CD007851.
18. Griese M, Scheuch G. Delivery of alpha-1 antitrypsin to airways. Ann Am Thorac Soc. 2016;13 Suppl 4:S346-S351.
19. Grifols Therapeutics, Inc. Prolastin-C liquid (alpha1-proteinase inhibitor (human) solution for intravenous injection. Prescribing Information. Research Triangle Park, NC: Grifols; revised August 2018.
20. Guo S, Booten SL, Watt A, et al. Using antisense technology to develop a novel therapy for α-1 antitrypsin deficient (AATD) liver disease and to model AATD lung disease. Rare Dis. 2014;2:e28511.
21. Hutchison DC, Hughes MD. Alpha-1-antitrypsin replacement therapy: Will its efficacy ever be proved? Eur Respir J. 1997;10(10):2191-2193.
22. Juvelekian GS, Stoller JK. Augmentation therapy for alpha(1)-antitrypsin deficiency. Drugs. 2004;64(16):1743-1756.

23. Kalsheker NA. alpha1-Antitrypsin deficiency: Best clinical practice. J Clin Pathol. 2009;62(10):865-869.
24. Kerstiens H, Postma D, ten Hacken N. Chronic obstructive pulmonary disease. In: Clincial Evidence. London, UK: BMJ Publishing Group; March 2005.
25. Kim M, Cai Q, Oh Y. Therapeutic potential of alpha-1 antitrypsin in human disease. Ann Pediatr Endocrinol Metab. 2018;23(3):131-135.
26. Kohnlein T, Welte T. Alpha-1 antitrypsin deficiency: Pathogenesis, clinical presentation, diagnosis, and treatment. Am J Med. 2008;121(1):3-9.
27. MacDonald JL, Johnson CE. Pathophysiology and treatment of alpha 1-antitrypsin deficiency. Am J Health Syst Pharm. 1995;52(5):481-489.
28. Marciniuk DD, Hernandez P, Balter M, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: A Canadian Thoracic Society clinical practice guideline. Can Respir J. 2012;19:109-116.
29. McElvaney NG, Burdon J, Holmes M, et al; RAPID Extension Trial Group. Long-term efficacy and safety of α1 proteinase inhibitor treatment for emphysema caused by severe α1 antitrypsin deficiency: An open-label extension trial (RAPID-OLE). Lancet Respir Med. 2017;5(1):51-60.
30. Miravitlles M, Vidal R, Torrella M, et al. Evaluation of replacement therapy in emphysema caused by alpha 1-antitrypsin deficiency. Arch Bronconeumol. 1994;30(10):479-484.
31. Mordwinkin NM, Louie SG. Aralast: An alpha 1-protease inhibitor for the treatment of alpha-antitrypsin deficiency. Expert Opin Pharmacother. 2007;8(15):2609-2614.
32. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004;59 Suppl 1:1-232 (Reviewed March 2008).
33. No authors listed. What is the pathophysiology, epidemiology and treatment of alpha-1 antitrypsin deficiency? What tests are required to make the diagnosis? ATTRACT Database. Gwent, Wales, UK: National Health Service; December 18, 2002.

34. Parfrey H, Mahadeva R, Lomas DA. Alpha(1)-antitrypsin deficiency, liver disease and emphysema. Int J Biochem Cell Biol. 2003;35(7):1009-1014.
35. Pierce JA. Alpha1-antitrypsin augmentation therapy. Chest. 1997;112(4):872-874.
36. Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. Chronic Obstr Pulm Dis. 2016;3(3):668-682.
37. Sandhaus RA. Alpha 1-antitrypsin augmentation therapy. Agents Actions Suppl. 1993;42:97-102.
38. Schwaiblmair M, Vogelmeier C, Fruhmann G. Long-term augmentation therapy in twenty patients with severe alpha-1-antitrypsin deficiency -- three-year follow-up. Respiration. 1997;64(1):10-15.
39. Schwaiblmair M, Vogelmeier C. Alpha 1-antitrypsin. Hope on the horizon for emphysema sufferers? Drugs Aging. 1998;12(6):429-440.
40. Seersholm N, Wencker M, Banik N, et al. Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. Eur Respir J. 1997;10(10):2260-2263.
41. Shah P, Ohlsson A. Alpha-1 proteinase inhibitor (a1PI) for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev. 2001;(3):CD002775.
42. Stocks JM, Brantly M, Pollock D, et al. Multi-center study: The biochemical efficacy, safety and tolerability of a new alpha1-proteinase inhibitor, Zemaira. COPD. 2006;3(1):17-23.
43. Stoller JK. Augmentation therapy for severe alpha 1-antitrypsin deficiency: Is the jury still out on a trial? Thorax. 1998;53(12):1007-1009.
44. U.S. Food and Drug Administration (FDA). Glassia -- Approval letter. Silver Spring, MD; FDA; July 1, 2010.
45. University of Michigan Health System. Chronic obstructive pulmonary disease. Ann Arbor, MI: University of Michigan Health System; May 2010.
46. Weir GC, Ehlers MR, Harris KM, et al. Alpha-1 antitrypsin treatment of new-onset type 1 diabetes: An open-label, phase I

clinical trial (RETAIN) to assess safety and pharmacokinetics. Pediatr Diabetes. 2018;19(5):945-954.

47. Work Loss Data Institute. COPD - Chronic obstructive pulmonary disease. In: Pulmonary (acute & chronic). San Diego, CA: Work Loss Data Institute; 2009.
48. World Health Organization (WHO). Alpha-1-antitrypsin deficiency: Memorandum from a WHO meeting. Bull World Health Organ. 1997;75(5):397-415.
49. Wozniak J, Wandtke T, Kopinski P, Chorostowska-Wynimko J. Challenges and prospects for alpha-1 antitrypsin deficiency gene therapy. Hum Gene Ther. 2015;26(11):709-718.
50. Zhu H, He J, Liu J, et al. Alpha 1-antitrypsin ameliorates ventilator-induced lung injury in rats by inhibiting inflammatory responses and apoptosis. Exp Biol Med (Maywood). 2018;243(1):87-95.