Original Effective Date: 12/06/2007
Current Effective Date: 09/21/2025
Last P&T Approval/Version: 07/30/2025
Next Review Due By: 07/2026
Policy Number: C8797-A

Alpha-1 Antitrypsin (AAT) Deficiency Enzyme

PRODUCTS AFFECTED

Aralast NP [Alpha1-Proteinase Inhibitor (Human)], Glassia [Alpha1-Proteinase Inhibitor (Human)], Prolastin-C [Alpha1-Proteinase Inhibitor (Human)], Zemaira [Alpha1-Proteinase Inhibitor (Human)]

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Hereditary deficiency of alpha1-antitrypsin (AAT) with clinically evident emphysema

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. ALPHA 1-PROTEINASE INHIBITOR DEFICIENCY:
1. Documented diagnosis of alpha-1 antitrypsin (AAT) deficiency
   AND

2. Documentation of severe AAT deficiency confirmed by serum concentration AAT level less than 11 micromol/L [which corresponds to 50 mg/dl (nephelometry) or 80 mg/dl (radial immunodiffusion)]
   AND
3. Documentation of a severe, increased-risk alpha 1-antitrypsin deficient homozygous phenotype (i.e., Pi*ZZ, PiZ (null), Pi (null)(null) [PI QOQO]) as determined by an isoelectric focusing lab test [DOCUMENTATION REQUIRED]
   AND
4. Documentation of clinical evidence of emphysema as defined by one of the following:
   a. A forced expiratory volume in one second (FEV_1) of 35% to 65% of predicted value, post-bronchodilator
      OR
   b. FEV1 from > 65% to < 80% of predicted, post-bronchodilator, and a rapid decline in lung function showing a change in FEV1 > 100 mL/year

   AND
5. Documentation of symptomatic panacinar/panlobular emphysema as evidenced by one or more of the following:
   a. Chronic productive cough
   b. Unusual frequency of lower respiratory infection
   c. Airflow obstruction
   d. Accelerated decline of FEV1
   e. Chest radiograph
   f. CT scan evidence of emphysema

   AND
6. Prescriber attests that member is a non-smoker or smoker who has been counseled on the importance of smoking cessation.
   AND
7. Member is receiving optimal pharmacological and non- pharmacological management for obstructive lung disease, including ONE of the following:
   a. Inhaled bronchodilators, inhaled long-acting muscarinic antagonists
   b. Inhaled or oral corticosteroids (for asthmatic components or acute exacerbations)
   c. Early treatment with antibiotics if there is evidence of purulent exacerbations, bronchitis, or respiratory infections
   d. Preventive vaccines (influenza, pneumococcus)
   e. Supplemental oxygen, as indicated and during air travel
   f. Pulmonary rehabilitation (cardiovascular fitness, self-confidence, and stress control)
   g. Treatment, when necessary, of depression, panic disorder, weight loss, and malnutrition

   AND
8. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Alpha-1-proteinase inhibitor (A1-PI) products include: IgA deficient patients with antibodies against IgA, history of anaphylaxis or other severe systemic reaction to Alpha1-PI products]
   AND
9. For post-lung transplant and lung volume reduction patients ONLY: Refer to 'Other Special Considerations' section. Exceptions on a case-by-case basis only. Peer Review and additional supporting information may be required.

CONTINUATION OF THERAPY:

A. ALPHA 1-PROTEINASE INHIBITOR DEFICIENCY:

1. Prescriber attests to or clinical reviewer has found no evidence of severe adverse reactions or severe drug toxicity

AND

2. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms (e.g., reduction in FEV1 rate of decline) [DOCUMENTATION REQUIRED]
   AND
3. Prescriber attests smoking status has been assessed, member has continued non-smoking status or has been appropriately counseled on the importance of smoking cessation.
   AND
4. For post-lung transplant and lung volume reduction patients ONLY: Refer to 'Other Special Considerations' section. Exceptions on a case-by-case basis only. Peer Review and additional supporting information may be required.

DURATION OF APPROVAL:
Initial authorization: 12 months, Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by, or in consultation with, a board-certified pulmonologist, thoracic surgeon, or physician experienced in the treatment of alpha-1 antitrypsin (AAT) deficiency. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
60 mg/kg IV infusion once weekly

PLACE OF ADMINISTRATION:
The recommendation is that infused medications in this policy will be for pharmacy or medical benefit coverage administered in a place of service that is a non-hospital facility-based location as per the Molina Health Care Site of Care program.

Note: Site of Care Utilization Management Policy applies for Prolastin, Glassia, Aralast NP, and Zemaira. For information on site of care, see Specialty Medication Administration Site of Care Coverage Criteria (molinamarketplace.com)

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intravenous

DRUG CLASS:
Alpha-Proteinase Inhibitor (Human)

FDA-APPROVED USES:
Indicated for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of alpha$_1$-PI (alpha1-antitrypsin deficiency)
Limitations of Use: Not indicated as therapy for lung disease in patients in whom severe Alpha1-PI deficiency has not been established. The effect of augmentation therapy with any Alpha1-PI on pulmonary exacerbations and on the progression of emphysema in alpha1-antitrypsin deficiency has not been conclusively demonstrated in randomized, controlled clinical trials. Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with these agents are not available.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

Alpha1-antitrypsin: a plasma α1-globulin produced primarily in the liver; it inhibits the activity of elastase, cathepsin G, trypsin, and other proteolytic enzymes. Deficiency is associated with development of emphysema.

Alpha-1 protease inhibitor deficiency may also be referred to as:

- AAT
- AATD
- alpha-1 related emphysema
- genetic emphysema
- hereditary pulmonary emphysema
- inherited emphysema

Forced Expiratory Volume in One Second (FEV1): Represents the volume of air forcibly exhaled from the lungs in the first second of a forced expiratory effort. This important measure of obstruction is measured by spirometry during pulmonary function testing.

Panacinar emphysema refers to enlargement or destruction of all parts of the acinus. Diffuse panacinar emphysema is most commonly associated with alpha-1 antitrypsin deficiency, although it can be seen in combination with proximal emphysema in smokers. Panacinar emphysema generally is observed in patients with homozygous alpha1-antitrypsin (AAT) deficiency. In people who smoke, focal panacinar emphysema at the lung bases may accompany centriacinar emphysema.

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Alpha-1 Antitrypsin (AAT) Deficiency

- An autosomal recessive genetic disorder that results in decreased levels of the protease inhibitor alpha-1 antitrypsin. ATT deficiency is a chronic, hereditary, usually fatal, autosomal recessive disorder in which a low concentration of A1-PI (or ATT) is associated with slow progressive, severe panacinar emphysema that most often manifests itself in the third to fourth decades of life. AAT, produced by the liver, is a "lung protector." In the absence of AAT, emphysema is almost inevitable. There are many genetic variants of A1-PI deficiency, only some of which result in very low levels ofA1-PI. The more severe types are the PiZZ, PiZ(null) and Pi(null)(null) phenotypes.
- Condition is characterized by inappropriately low levels of AAT, which inhibits neutrophil elastase—a protease with elastolytic properties that can attack lung elastin and other structural components of the alveolar wall, leading to lung injury and parenchyma destruction. The disorder can affect multiple organ systems, but primarily affects the lungs and liver. Liver disease in patients with AATD is caused by an alternative mechanism, and is not related to active destruction as in lung disease.
- Treatment of AAT deficiency AATD is based on an individual's symptoms. There is currently no cure. The major goal of AATD management is preventing or slowing the progression of lung disease. Preventing or slowing the progression of lung disease is the major goal of AAT deficiency management. Decreasing any proinflammatory stimuli in the alveolus, including smoking, asthma, or respiratory infection, facilitates this goal. Alternatively, augmenting or replacing the deficient enzyme, and thereby moderating inflammatory stimuli, is also important. Most patients are identified only after they develop lung disease, and the goals of treating AATD emphysema are similar to those for treating

all forms of emphysema.

- Treatment involves smoking cessation, bronchodilation, and physical rehabilitation in a program similar to that designed for patients with smoking-related COPD. Organ transplantation is another option for patients with end-stage lung or liver disease. Lung transplantation is reserved for patients with advanced emphysema due to severe AAT deficiency. Similarly, liver transplantation is reserved for patients with end-stage hepatic disease. After liver transplantation, the AAT deficiency is corrected, because the normal phenotype donor liver produces and secretes AAT.
- Intravenous augmentation therapy is the only FDA-approved treatment specific for alpha1- antitrypsin deficiency. It is most clearly indicated for patients with moderate degrees of airflow obstruction (FEV1 35-65% of predicted). Currently available alpha-1 proteinase inhibitor products include Aralast NP, Glassia, Prolastin C and Zemaira.
- Augmentation or replacement therapy involves the restoration of normal levels of AAT by administering alpha1-PI purified from pooled human plasma through an intravenous infusion. The drug is given at a dose of 60 mg/kg every week and appears to work best for those with a moderate decline in lung function, rather than those with severe or only mild symptoms. Treatment is given at home, or in outpatient centers.
- Alpha1-proteinase inhibitors are indicated for chronic augmentation and maintenance therapy in individuals with A1-PI deficiency (also referred to as alpha1-antitrypsin deficiency) and clinical evidence of emphysema.

Alpha1-proteinase Inhibitors

- There are four augmentation therapy products FDA approved: Aralast NP, Prolastin-C, Zemaira, and Glassia.
- Prolastin has been marketed since 1988 and with an excellent safety record. Aralast NP and Zemaira were introduced to the marketplace in 2003 and Glassia was introduced in 2010. Each was approved by demonstrating that they were comparable to Prolastin in their safety and in augmenting blood and lung alpha-1 levels.
- Alpha1-proteinase inhibitors are not indicated for treatment of lung disease in patients whom congenital A1-PI deficiency has not been established.
- 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.
- Weekly IV infusions of alpha1-antitrypsin protein concentrates restore serum and alveolar alpha1-antitrypsin concentrations to protective levels. Although other dosing regimens have been used, only the weekly infusion schedule has US FDA approval.
- 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.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of Prolastin, Glassia, Aralast NP and Zemaira are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Alpha-1-proteinase inhibitor (A1-PI) products include: IgA deficient patients with antibodies against IgA, history of anaphylaxis or other severe systemic reaction, PiMZ or PiMS phenotypes, Treatment of cystic fibrosis, PiMZ heterozygotes or other AAT deficiencies (i.e., PiMM).

Exclusions/Discontinuation:

Do not use for emphysema not due to AAT deficiency.

Alpha-1-proteinase inhibitor was not studied in patients with evidence of alpha1-proteinase-associated

liver disease or patients who have undergone a liver transplant.

OTHER SPECIAL CONSIDERATIONS:
Evidence for the use of alpha1-antitrypsin augmentation in patients after lung transplantation for alpha1-antitrypsin deficiency is insufficient (Stoller, JK UpToDate 2024). Continuation of AAT augmentation therapy following lung transplantation is controversial because it is costly and lacks proven efficacy (European Respiratory Society statement: diagnosis and treatment of pulmonary disease in α1-antitrypsin deficiency, 2017). Augmentation therapy is generally not given to AAT deficient lung transplant recipients by most transplant centers since it is unknown whether it would improve outcomes or longevity during the patient's lifetime, and recurrent emphysema is unlikely to occur for 30 to 40 years in the absence of smoking (Banga A, et al. 2014). Cases have been reported of AAT augmentation being initiated if characteristic radiologic changes of emphysema were to develop in the absence of lung function decline, or if the patient has persistent lung function decline after transplant. This practice is supported by a report that two of four lung transplant recipients responded to weekly augmentation therapy after experiencing lung function decline refractory to the usual therapies for bronchiolitis obliterans syndrome (Teschler H. 2015).

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.*

HCPCS CODE	DESCRIPTION
J0256	Injection, alpha 1 proteinase inhibitor (human), not otherwise specified, 10 mg
J0257	Injection, alpha 1 proteinase inhibitor (human), (Glassia), 10 mg

AVAILABLE DOSAGE FORMS:
Aralast NP SOLR 500MG single dose vial
Aralast NP SOLR 1000MG single dose vial
Glassia SOLN 1000MG/50ML single-dose vial
Glassia SOLN 4GM/200ML single-dose vial
Glassia SOLN 5GM/250ML single-dose vial
Prolastin-C SOLN 1000MG/20ML single-dose vial
Prolastin-C SOLR 1000MG
Zemaira SOLR 1000MG single-dose vial

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Contraindications/Exclusions/Discontinuation Available Dosage Forms References	Q3 2025
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Contraindications/Exclusions/ Discontinuation References	Q3 2024
REVISION- Notable revisions: Products Affected Diagnosis Required Medical Information Continuation of Therapy Prescriber Requirements FDA-Approved Uses Other Special Considerations References	Q3 2023
REVISION- Notable revisions: Required Medical Information Prescriber Requirements References	Q3 2022
Q2 2022 Established tracking in new format	Historical changes on file