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Policy Number: C8797-A

## Alpha-1 Antitrypsin (AAT) Deficiency Enzyme

### PRODUCTS AFFECTED

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

### 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:**

for the treatment of long-term augmentation and maintenance therapy in adults with severe 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.*

#### **A. ALPHA 1-PROTEINASE INHIBITOR DEFICIENCY**

1. Documented diagnosis of emphysema due to alpha<sub>1</sub> antitrypsin (AAT) deficiency  
AND
2. Documentation that Severe AAT deficiency is confirmed by serum concentration AAT level below 11 micromol/L [which corresponds to 57 mg/dl (nephelometry) or 80 mg/dl (radial immunodiffusion)]  
AND

## Drug and Biologic Coverage Criteria

3. Documentation of a severe, increased-risk alpha 1-antitrypsin deficient homozygous phenotype as determined by an isoelectric focusing lab test [ONE] [DOCUMENTATION REQUIRED]
  - a. PiZZ
  - b. PiZ (null)
  - c. Pi (null)(null)AND
4. Documentation of clinical evidence of emphysema as defined by one of the following: [ONE]
  - a. A forced expiratory volume in one second (FEV<sub>1</sub>) of 35% to 65% of predicted value, post-bronchodilatorOR
  - b. FEV<sub>1</sub> from > 65% to < 80% of predicted, post-bronchodilator, and a rapid decline in lung function showing a change in FEV<sub>1</sub> > 100 mL/yearAND
5. Documentation of symptomatic panacinar/panlobular emphysema as evidenced by one or more of the following: [AT LEAST ONE]
  - a. Chronic productive cough
  - b. Unusual frequency of lower respiratory infection
  - c. Airflow obstruction
  - d. Accelerated decline of FEV<sub>1</sub>
  - e. Chest radiograph
  - f. CT scan evidence of emphysemaAND
6. Prescriber attests that member is a non-smoker or smoker who has been counseled on the importance of smoking cessation.  
AND
7. Prescriber attests there is no evidence of alpha1-proteinase-associated liver disease and member has not undergone a liver transplant  
AND
8. Prescriber attests that member does not have antibodies to IgA.  
AND
9. Prescriber attests that member is receiving optimal pharmacological and non- pharmacological management for obstructive lung disease, including ONE of the following [AT LEAST ONE]
  - a. Inhaled bronchodilators, inhaled steroids
  - 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 malnutritionAND
10. 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 severe immediate hypersensitivity reactions, including anaphylaxis, to Alpha1-PI products]  
AND
11. For post-lung transplant and lung volume reduction patients ONLY: Refer to 'Coverage Exclusions' section. Exceptions on a case-by-case basis only. Peer Review and additional supporting information may be required.  
AND
12. Documentation of member's current weight (within the last 30 days)

## CONTINUATION OF THERAPY:

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## Drug and Biologic Coverage Criteria

### 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 and therapeutic response in slowing progression of lung function indicated by ALL of the following documentation [DOCUMENTATION REQUIRED]:
  - a. Assessment of therapeutic efficacy: Follow-up evaluations from specialist indicating disease stability or improvement
  - b. Positive response to treatment as evidenced by:
    - i. Elevation of AAT levels
    - ii. Reduction in rate of deterioration of lung function: reduction in FEV1 rate of decline
  - c. Pulmonary function test to evaluate the member's pulmonary function status required every 6 monthsAND
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. Documentation of member's current weight (within the last 30 days)

### **DURATION OF APPROVAL:**

Initial authorization: 6 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. NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually

### **AGE RESTRICTIONS:**

18 years of age or older

### **QUANTITY:**

60 mg/kg IV infusion once weekly

**Maximum Quantity Limits** – Dose does not exceed 60 mg/kg/week

### **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 \(molinamarketplace.com\)](https://www.molinamarketplace.com/specialty-medication-administration-site-of-care-coverage-criteria)

## **DRUG INFORMATION**

### **ROUTE OF ADMINISTRATION:**

Intravenous

### **DRUG CLASS:**

Alpha-Proteinase Inhibitor (Human)

**FDA-APPROVED USES:**

Alpha<sub>1</sub>-proteinase inhibitor deficiency Long-term augmentation and maintenance therapy in adults with severe hereditary deficiency of alpha<sub>1</sub>-antitrypsin (AAT) with clinically evident emphysema

*Limitations of use*

Not indicated as therapy for patients with lung disease in whom hereditary AAT deficiency has not been established; the long-term effects of chronic augmentation or maintenance therapy of individuals with alpha<sub>1</sub>-proteinase inhibitors are not available. The effect of augmentation therapy with any alpha<sub>1</sub>-proteinase inhibitor on pulmonary exacerbations has not been demonstrated in clinical trials. However, one randomized controlled trial showed a reduction in emphysema progression with alpha<sub>1</sub>-proteinase inhibitor augmentation therapy when CT lung density was measured at total lung capacity.

**COMPENDIAL APPROVED OFF-LABELED USES:**

None

**APPENDIX**

**APPENDIX:**

Alpha<sub>1</sub>-antitrypsin: a plasma α<sub>1</sub>-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 (FEV<sub>1</sub>): 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 alpha<sub>1</sub>-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. AAT 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 of A1-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

## Drug and Biologic Coverage Criteria

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.

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### 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 Prolastin, Glassia, Aralast NP and Zemaira Include: IgA deficient patients with antibodies against IgA, PiMZ or PiMS phenotypes, Emphysema not due to AAT deficiency, Associated liver disease; members who have undergone a liver transplant (COPD Foundation 2016), Treatment of cystic fibrosis, PiMZ heterozygotes or other AAT deficiencies (i.e., PiMM), Dosing exceeding package labeling, Frequency exceeding once weekly infusions, Non-compliance with therapy

Evidence for the use of alpha1-antitrypsin augmentation in patients after lung transplantation for alpha1-antitrypsin deficiency is insufficient (Stoller, JK UpToDate 2020). 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  $\alpha$ 1-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).

### OTHER SPECIAL CONSIDERATIONS:

None

## CODING/BILLING INFORMATION

*Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement*

HCPSC 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:

Prolastin-C SOLN1000MG/20ML

Prolastin-C SOLR 1000MG

Glassia SOLN 1000MG/50ML

Aralast NP SOLR 500MG

Aralast NP SOLR 1000MG

Zemaira SOLR 1000MG

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Prescriber Requirements References	Quarter 3 2022
Q2 2022 Established tracking in new format	Historical changes on file