

**POLICY:** Alpha<sub>1</sub>-Proteinase Inhibitor Products

- Aralast NP™ (alpha<sub>1</sub>-proteinase inhibitor [human] lyophilized powder – Shire)
- Glassia™ (alpha<sub>1</sub>-proteinase inhibitor [human] solution – Shire)
- Prolastin®-C and Prolastin®-C Liquid (alpha<sub>1</sub>-proteinase inhibitor [human] lyophilized powder and solution – Grifols Therapeutics)
- Zemaira® (alpha<sub>1</sub>-proteinase inhibitor [human] lyophilized powder – CSL Behring)

**APPROVAL DATE:** 10/09/2019

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**OVERVIEW**

Alpha<sub>1</sub>-proteinase inhibitor (also known as alpha<sub>1</sub>-antitrypsin [AAT]), is indicated for use as a chronic replacement or augmentation therapy for individuals with a congenital deficiency of AAT with clinically demonstrable emphysema.<sup>1-5</sup> In the scientific literature, the disorder is referred to as AAT deficiency whereas the deficiency or replacement protein is referred to as alpha<sub>1</sub>-proteinase inhibitor. The following products are available commercially in the US: Prolastin-C (also available as Prolastin-C Liquid), Aralast NP, Zemaira, and Glassia. The products vary in their availability and in some of their purification and viral inactivation processes.

AAT deficiency is a rare, chronic, hereditary, autosomal co-dominant disorder marked by low concentrations of AAT which leads to progressive, severe emphysema that often does not manifest until the third to fourth decades of life.<sup>1</sup> One of the principal functions of AAT is the inhibition of neutrophil elastase, which is responsible for proteolytic degradation of matrix proteins.<sup>6</sup> When AAT is deficient, neutrophil elastase predominates and leads to breakdown of tissues, particularly in the parenchyma of the lungs. AAT can also predispose to liver disease since the protein is synthesized and can accumulate in hepatocytes. A large number of phenotypic variants exist, which have different clinical consequences.<sup>6,7</sup> This disease is most severe in those with null phenotypes (with no detectable circulating AAT in the plasma) or the PI\*ZZ variant (AAT levels typically < 35% of normal).<sup>1,7</sup>

The goal of treatment is to increase AAT levels in the lungs to provide adequate anti-elastase activity. Treatment is aimed at raising serum levels of AAT above a theoretical protective threshold of 11 µM, which is equivalent to the tenth percentile of the AAT range of PI\*SZ individuals; epidemiological data suggest lower probability of COPD above this level.<sup>6</sup> Of note, older laboratory techniques (e.g., radial immunodiffusion) measured non-purified levels of AAT, which tend to overestimate the concentration by 35% to 40%. To distinguish between non-purified and purified standards, the former are expressed in mg/dL and the latter are expressed in µM. An AAT level of 80 mg/dL measured by radial immunodiffusion corresponds to a plasma AAT level of 11 µM. Alpha<sub>1</sub>-proteinase inhibitor is the only treatment approved to correct AAT deficiency. The approved dosage regimen to achieve adequate concentrations in the lung is 60 mg/kg of body weight administered intravenously (IV) once weekly.

**Guidelines**

A European Respiratory Society (ERS) statement addresses diagnosis and treatment of pulmonary disease in alpha<sub>1</sub>-antitrypsin deficiency (2017).<sup>8</sup> It is noted that augmentation therapy has been shown to reduce progression of emphysema in severe AATD deficiency. There is no evidence to support efficacy of AAT augmentation therapy for current smokers of any phenotype. These guidelines support earlier American Thoracic Society (ATS)/ERS guidelines (2003) which state that intravenous augmentation therapy is recommended for individuals with established airflow obstruction from AAT deficiency.<sup>7</sup>

The Canadian Thoracic Society updated its guidelines (2012) regarding AAT deficiency testing and augmentation therapy.<sup>9</sup> The guidelines state that evidence supports the consideration of AAT augmentation therapy in non-smoking or ex-smoking patients with COPD due to emphysema and a documented AAT deficiency (level  $\leq 11$   $\mu\text{mol/L}$ ). Patients should also be receiving other pharmacological and non-pharmacologic therapies, including comprehensive case management and pulmonary rehabilitation.

The Medical and Scientific Advisory Committee of the Alpha-1 Foundation guidelines (2016) provide similar recommendations.<sup>10</sup> Intravenous alpha<sub>1</sub>-antitrypsin augmentation is strongly recommended in non-smoking or ex-smoking patients with forced expiratory volume (FEV<sub>1</sub>) 30 to 65% of predicted due to well-documented benefit in this group. Weaker recommendations also support treatment of patients with FEV<sub>1</sub> below 30% of predicted or above 65% of predicted. Usual management of COPD should also be provided, with strong emphasis on facilitating tobacco cessation. Of note, AAT replacement therapy is not recommended for patients who continue to smoke.

### **Other Uses with Supportive Evidence**

Although not indicated for this use, alpha<sub>1</sub>-proteinase inhibitor therapy has been utilized for AAT-associated panniculitis, a rare complication characterized by erythematous nodules and plaques located on subcutaneous (skin) tissue in wide areas of the lower extremities, arms, trunk, and/or face.<sup>11-16</sup> The literature mainly documents case reports.<sup>11-19</sup> In the American Thoracic Society (ATS) and ERS standards for the diagnosis and management of individuals with AAT deficiency (updated in 2003), it is stated that AAT replacement therapy is a reasonable option for AAT deficiency-associated panniculitis.<sup>7</sup> Although no controlled trials provide a clear treatment recommendation, augmentation therapy with purified human alpha<sub>1</sub>-proteinase inhibitor or fresh frozen plasma to restore plasma and local tissue levels of AAT appears to be rational, safe, and effective. In a review of treatment options for panniculitis in AAT deficiency, augmentation therapy with alpha<sub>1</sub>-proteinase inhibitor was noted to be the most successful medical treatment.<sup>20</sup>

### **Dosing Considerations**

For AAT deficiency-associated panniculitis, limited dosing is available. A standard dose of 60 mg/kg once weekly is recommended in product labeling for all alpha<sub>1</sub>-proteinase inhibitors for the labeled indication.<sup>1-5</sup>

### **POLICY STATEMENT**

Prior authorization is recommended for medical benefit coverage of alpha<sub>1</sub>-proteinase inhibitor. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below.

**Automation:** None.

### **RECOMMENDED AUTHORIZATION CRITERIA**

#### **FDA-Approved Indications**

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- 1. Alpha<sub>1</sub>-Antitrypsin Deficiency with Emphysema (or COPD).** Approve for 1 year in patients meeting the following criteria (A and B):

- A) The patient has a baseline (pretreatment) AAT serum concentration of < 80 mg/dL or 11 μM (11 μmol/L); AND
- B) According to the prescriber, the patient is a current non-smoker.

**Dosing.** Approve a dose of 60 mg/kg intravenously once weekly.

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### Other Uses with Supportive Evidence

- 2. **Alpha<sub>1</sub>-Antitrypsin Deficiency-Associated Panniculitis.** Approve for 1 year.

**Dosing.** Approve a dose of 60 mg/kg intravenously once weekly.

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### CONDITIONS NOT RECOMMENDED FOR APPROVAL

Alpha<sub>1</sub>-proteinase inhibitor has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

- 1. **Alpha<sub>1</sub>-Antitrypsin Deficiency without Lung Disease, even if Deficiency-Induced Hepatic Disease is Present.** The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency (2003) state that the pathophysiology of liver disease in AAT deficiency is different from that of lung disease, and the use of alpha<sub>1</sub>-proteinase inhibitor is not discussed for these patients.<sup>8</sup> There is an absence of information that suggests alpha<sub>1</sub>-proteinase inhibitor is useful in patients with AAT deficiency-related liver disease.
- 2. **Bronchiectasis (without alpha<sub>1</sub>-antitrypsin deficiency).** Studies have not demonstrated alpha<sub>1</sub> proteinase inhibitor to be effective for this condition. The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency (2003) state that despite the well-recognized association between AAT deficiency and the early development of emphysema, only a limited number of studies have assessed the association between AAT deficiency and bronchiectasis.<sup>8</sup> Studies suggest that bronchiectasis is more a result of emphysematous changes in the parenchyma than of AAT deficiency.
- 3. **Chronic Obstructive Pulmonary Disease (COPD) without Alpha<sub>1</sub>-Antitrypsin Deficiency.** The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the diagnosis management and prevention of COPD, updated in 2017, state that never or ex-smokers with an FEV<sub>1</sub> of 35 to 60% of predicted may be most suitable for AAT deficiency augmentation therapy.<sup>23</sup> However, this therapy is not recommended for COPD that is unrelated to AAT deficiency.
- 4. **Cystic Fibrosis.** The use of alpha<sub>1</sub>-proteinase inhibitor is considered investigational due to the lack of literature available regarding use of the agent for this disease state and many studies utilized an investigational aerosolized AAT delivery mechanism.<sup>24-25</sup>
- 5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

### REFERENCES

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- 2. Zemaira<sup>®</sup> [prescribing information]. Kankakee, IL: CSL Behring; April 2019.

3. Prolastin<sup>®</sup>-C [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics; June 2018.
4. Prolastin<sup>®</sup>-C Liquid [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics; August 2018.
5. Glassia<sup>®</sup> [prescribing information]. Lexington, MA: Shire; June 2017.
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## HISTORY

Type of Revision	Summary of Changes	Approval Date
New policy	--	11/21/2018
Annual revision	Dosing for all indications clarified to note that alpha1-proteinase inhibitors are given by intravenous route.	10/09/2019