CARECONTINUUM™

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Alpha$_1$-Proteinase Inhibitor Products Utilization Management Medical Policy
- Aralast NP® (alpha$_1$-proteinase inhibitor [human] intravenous infusion – Shire)
- Glassia® (alpha$_1$-proteinase inhibitor [human] intravenous infusion – Shire)
- Prolastin®-C and Prolastin®-C Liquid (alpha$_1$-proteinase inhibitor [human] intravenous infusion – Grifols Therapeutics)
- Zemaira® (alpha$_1$-proteinase inhibitor [human] intravenous infusion – CSL Behring)

REVIEW DATE: 12/03/2025; selected revision 03/18/2026, 04/01/2026

OVERVIEW

Alpha$_1$-proteinase inhibitor (also known as alpha$_1$-antitrypsin [AAT]) is indicated for **alpha$_1$-proteinase deficiency** as a chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema.[1-5] 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.

Disease Overview

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.[1] Diagnosis of AAT deficiency begins with quantitative measurement of AAT levels in the plasma.[6] A serum AAT level below 80 mg/dL (11 micromol/L) is considered suggestive of AAT deficiency. Treatment is aimed at raising serum levels of AAT above a theoretical protective threshold of 11 microM (micromol/L), which is equivalent to the tenth percentile of the AAT range of PI*SZ individuals; epidemiological data suggest lower probability of chronic obstructive pulmonary disease (COPD) above this level.[7] A variety of techniques have been used to measure serum AAT concentration.[8] The most commonly used technique today is nephelometry. Using this technique, a serum AAT concentration < 57 mg/dL is usually associated with AAT deficiency with lung disease. 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%.[9] An AAT level of 80 mg/dL measured by radial immunodiffusion corresponds to a plasma AAT level of 11 microM.

Guidelines

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for the diagnosis, management, and prevention of COPD (2026) note that the World Health Organization recommends that all patients with a diagnosis of COPD should be screened once for AAT deficiency, especially in areas with a high prevalence.[13] With regard to the use of augmentation therapy, the GOLD guidelines state that never or ex-smokers with a forced expiratory volume in 1 second (FEV_1) of 35% to 60% predicted would be the most suitable for AAT deficiency augmentation therapy. However, they also note that based on CT scans providing evidence for an effect on preserving lung tissue in treated patients compared to placebo, therapy can be extended to include patients with evidence of progressive lung disease despite other optimal therapy (e.g., smoking cessation). It is noted that not all patients with AAT deficiency develop or continue to have rapid spirometric progression once smoking cessation has occurred, so AAT augmentation therapy should be reserved for patients with continued and rapid progression after smoking cessation. Furthermore, recent studies have suggested increased risk of COPD in heterozygotes for the Z gene, however unlike ZZ, do not develop COPD in the absence of smoking; therefore, augmentation therapy is not indicated or appropriate.

A European Respiratory Society (ERS) statement addresses diagnosis and treatment of pulmonary disease in AAT deficiency (2017).[6] It is noted that augmentation therapy has been shown to reduce progression of emphysema in severe AAT 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.[10]

The Medical and Scientific Advisory Committee of the Alpha-1 Foundation guidelines (2016) provide similar recommendations.[11] Intravenous AAT augmentation is strongly recommended in non-smoking or ex-smoking patients with forced expiratory volume (FEV_1) 30 to 65% of predicted due to well-documented benefit in this group. Weaker recommendations also support treatment of patients with FEV_1 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

Panniculitis is a histopathologic descriptor for inflammation of subcutaneous fat and is associated with a variety of disorders, including AAT deficiency.[14] A skin biopsy is taken during active inflammation that is deep enough to examine the subdermal fat. In the ATS/ERS 2003 guidelines, it is stated that AAT replacement therapy is a reasonable option for AAT deficiency-associated panniculitis.[10] Although no controlled trials provide a clear treatment recommendation, augmentation therapy with purified human alpha$_1$-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$_1$-proteinase inhibitor was noted to be the most successful medical treatment.[12,14]

Dosing Considerations

For AAT deficiency-associated panniculitis, limited dosing is available. A dose of 60 mg/kg once weekly is recommended in product labeling for all alpha$_1$-proteinase inhibitors for the labeled indication.[1-5]

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of alpha$_1$-proteinase inhibitor. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. 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

Coverage of alpha$_1$-proteinase inhibitor products (e.g., Aralast NP, Glassia, Prolastin-C, Prolastin-C Liquid, Zemaira) is recommended in those who meet one of the following criteria:

FDA-Approved Indication

1. **Alpha$_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease).** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, v, and vi):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a baseline (pretreatment) alpha$_1$-antitrypsin serum concentration of < 11 micromol/L (< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry); AND
     - **iii.** Patient had genotyping or phenotyping demonstrating ONE of the following types: PI*ZZ, PI*(null)(null), PI*Z(null), PI*SZ or other rare disease-causing alleles associated with serum alpha$_1$-antitrypsin (AAT) level < 11 micromol/L; AND
     - **iv.** According to the prescriber, the patient has clinical evidence of emphysema or chronic obstructive pulmonary disease; AND
     - **v.** According to the prescriber, the patient is a current non-smoker; AND
     - **vi.** The medication is prescribed by or in consultation with a pulmonologist; OR
   - **B)** Patient is Currently Receiving an Alpha$_1$-Proteinase Inhibitor Product. Approve for 1 year if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient had a baseline (pretreatment) alpha$_1$-antitrypsin serum concentration of < 11 micromol/L (< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry); AND
     - **iii.** According to the prescriber, the patient is a current non-smoker.

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

Other Uses with Supportive Evidence

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2. **Alpha$_1$-Antitrypsin Deficiency-Associated Panniculitis.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve for 1 year if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient has a diagnosis of panniculitis confirmed by skin biopsy; AND
     - **iii.** Patient has a baseline (pretreatment) alpha$_1$-antitrypsin serum concentration of < 11 micromol/L (< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry); AND
     - **iv.** Patient had genotyping or phenotyping demonstrating ONE of the following types: PI*ZZ, PI*(null)(null), PI*Z(null), PI*SZ or other rare disease-causing alleles associated with serum alpha$_1$-antitrypsin (AAT) level < 11 micromol/L; AND
     - **v.** The medication is prescribed by or in consultation with a dermatologist or pulmonologist; OR
   - **B)** Patient is Currently Receiving an Alpha$_1$-Proteinase Inhibitor Product. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** Patient is ≥ 18 years of age; AND
     - **ii.** Patient had a baseline (pretreatment) alpha$_1$-antitrypsin serum concentration of < 11 micromol/L (< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry).

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

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of alpha$_1$-proteinase inhibitor products is not recommended in the following situations:

1. **Alpha$_1$-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$_1$-proteinase inhibitor is not discussed for these patients.[10] There is an absence of information that suggests alpha$_1$-proteinase inhibitor is useful in patients with AAT deficiency-related liver disease.

2. **Bronchiectasis (without alpha$_1$-antitrypsin deficiency).** Studies have not demonstrated alpha$_1$ 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.[10] 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$_1$-Antitrypsin Deficiency.** The Global Initiative for Chronic Obstructive Lung Disease guidelines for the diagnosis, management, and prevention of COPD (updated 2026) state that never or ex-smokers with an FEV_1 of 35 to 60% of predicted may be most suitable for AAT deficiency augmentation therapy; newer evidence suggests that individuals with higher FEV_1 values may also be candidates.[13] However, this therapy is not recommended for COPD that is unrelated to AAT deficiency.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Aralast NP® intravenous infusion [prescribing information]. Lexington, MA: Shire; May 2025.
2. Zemaira® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; January 2024.
3. Prolastin®-C intravenous infusion [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics; January 2022.
4. Prolastin®-C Liquid intravenous infusion [prescribing information]. Research Triangle Park, NC: Grifols Therapeutics; May 2020.
5. Glassia® intravenous infusion [prescribing information]. Lexington, MA: Shire; February 2025.
6. Miravitlles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: diagnosis and treatment of pulmonary disease in alpha1-antitrypsin deficiency. *Eur Respir J.* 2017;50(5).
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11. 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.
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13. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2026. Available at: https://goldcopd.org/2026-gold-report-and-pocket-guide/. Accessed on March 11, 2026.
14. Franciosi AN, Ralph J, O'Farrell NJ, et al. Alpha-1 antitrypsin deficiency-associated panniculitis. *J Am Acad Dermatol*. 2022 Oct;87:825-832.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	12/06/2023
Annual Revision	No criteria changes.	12/11/2024
Annual Revision	No criteria changes.	12/03/2025
Selected Revision	**Alpha$_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease):** Criteria were divided into initial therapy and continuation of therapy. For initial therapy, requirements were added that the patient had genotyping or phenotyping demonstrating ONE of the following types: ZZ, (null)(null), Z(null), SZ or other rare disease-causing alleles associated with serum alpha$_1$-antitrypsin (AAT) level less than 11 mcM; and that according to prescriber, the patient has clinical evidence of emphysema or chronic obstructive pulmonary disease; and that the medication is prescribed by or in consultation with a pulmonologist. **Alpha$_1$-Antitrypsin Deficiency-Associated Panniculitis:** Criteria were divided into initial therapy and continuation of therapy. For initial therapy, requirements were added that the patient has a diagnosis of panniculitis confirmed by skin biopsy; and that the patient has a baseline (pretreatment) alpha$_1$-antitrypsin serum concentration of < 11 mcM (11 micromol/L) [< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry]; and that the patient had genotyping or phenotyping demonstrating ONE of the following types: ZZ, (null)(null), Z(null), SZ or other rare disease-causing alleles associated with serum alpha$_1$-antitrypsin (AAT) level less than 11 mcM; and that the medication is prescribed by or in consultation with a dermatologist or pulmonologist. For a patient currently receiving an alpha$_1$-proteinase inhibitor product, a requirement was added that the patient had a baseline (pretreatment) alpha$_1$-antitrypsin serum concentration of < 11 mcM (11 micromol/L) [< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry].	03/18/2026
Selected Revision	Throughout the policy, 11 mcM was removed and replaced with 11 micromol/L. **Alpha$_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease) and Alpha$_1$-Antitrypsin Deficiency-Associated Panniculitis:** The disease causing alleles associated with a serum alpha1-antitrypsin (AAT) level less than 11 micromol/L were modified from ZZ, (null)(null), Z(null), and SZ to PI*ZZ, PI*(null)(null), PI*Z(null), PI*SZ.	04/01/2026