Drug Coverage Policy

Effective Date.....06/01/2025
Coverage Policy Number.....IP0387
Policy Title.....Alpha$_1$-Proteinase Inhibitor Products

Alpha$_1$-Proteinase Inhibitor Products

- Aralast NP® (alpha1-proteinase inhibitor [human] intravenous infusion – Shire)
- Glassia® (alpha1-proteinase inhibitor [human] intravenous infusion – Shire)
- Prolastin® - C and Prolastin® - C Liquid (alpha1-proteinase inhibitor [human] intravenous infusion – Grifols Therapeutics)
- Zemaira® (alpha1-proteinase inhibitor [human] intravenous infusion – CSL Behring)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support

medical necessity and other coverage determinations.

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 mcM (mcmol/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 mcM.

Guidelines
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
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]

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]

Coverage Policy

Policy Statement
Prior Authorization is required 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.

Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, and/or other information.

FDA-Approved Indication

Alpha$_1$-proteinase inhibitor products (e.g., Aralast NP, Glassia, Prolastin-C, Prolastin-C Liquid, Zemaira) are considered medically necessary when ONE of the following is met (1 or 2):

1. **Alpha$_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease).** Approve for 1 year if the patient meets **ALL** of the following criteria (A, B, C, D, and E):
    A. Patient is ≥ 18 years of age
    B. Patient meets ALL of the following (i, ii, and iii):
        i. Documentation is provided the patient has a baseline (pretreatment) alpha$_1$-antitrypsin serum concentration of < 11 mcM (11 mcmol/L) [< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry]
        ii. Documentation is provided that genotyping or phenotyping demonstrates **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 mcmol/L
        iii. At baseline, the patient meets **ONE** of the following (a or b):
            a. Documentation is provided of a forced expiratory volume in 1 second (FEV_1) less than 65% of predicted
            b. Patient meets **ONE** of the following (1 or 2):
                1. Documentation is provided of an accelerated decline in lung function (accelerated decline in lung function includes FEV_1 decline greater than 100 mL/year or a decline in diffusing capacity of the lungs for carbon monoxide [DLCO] greater than 15% per year)
                2. Documentation is provided that supplemental oxygen required at rest or with exertion

C. According to the prescriber, the patient is a current non-smoker
D. Medication is prescribed by, or in consultation with, a pulmonologist
E. Preferred product criteria is met for the product(s) as listed in the below table(s)

Dosing. 60 mg/kg intravenously once weekly

Other Uses with Supportive Evidence

2. **Alpha$_1$-Antitrypsin Deficiency-Associated Panniculitis.** Approve for 1 year if the patient meets **ALL** of the following (A, B, C, D, E, and F):
   A. Patient is ≥ 18 years of age
   B. Documentation is provided that the diagnosis of panniculitis confirmed by skin biopsy
   C. Patient meets **ONE** of the following (i or ii):
      i. Documentation is provided of the patient has Mild panniculitis and **ONE** of the following (a or b):
         a. Documentation is provided the patient experienced inadequate efficacy or significant intolerance with dapsone
         b. According to the prescriber, dapsone is contraindicated
      ii. Documentation is provided of the patient has Moderate to severe panniculitis
   D. Patient meets **BOTH** of the following (i and ii):
      i. Documentation is provided of the patient has a baseline alpha$_1$-antitrypsin serum concentration of less than 11 mcmol/L (less than 80 mg/dL if measured by radial immunodiffusion or less than 57 mg/dL if measured by nephelometry)
      ii. Documentation is provided that genotyping or phenotyping demonstrates **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 mcmol/L
   E. Medication is prescribed by, or in consultation with, a dermatologist or pulmonologist
   F. Preferred product criteria is met for the product(s) as listed in the below table(s)

Dosing. 60 mg/kg intravenously once weekly

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Employer Plans:

Product	Criteria
Aralast NP (alpha1-proteinase inhibitor [human] intravenous infusion)	**EFFECTIVE 7/1/2025** Documentation is provided that the patient has tried and cannot take BOTH of the following (1 and 2): 1. Glassia 2. Prolastin-C (powder or liquid)
Zemaira	**EFFECTIVE 7/1/2025**

Product	Criteria
(alpha1-proteinase inhibitor [human] intravenous infusion)	Documentation is provided that the patient has tried and cannot take BOTH of the following (1 and 2): 1. Glassia 2. Prolastin-C (powder or liquid)

Individual and Family Plans:

Product	Criteria
Aralast NP (alpha1-proteinase inhibitor [human] intravenous infusion)	**EFFECTIVE 7/1/2025** Documentation is provided that the patient has tried and cannot take BOTH of the following (1 and 2): 1. Glassia 2. Prolastin-C (powder or liquid)
Zemaira (alpha1-proteinase inhibitor [human] intravenous infusion)	**EFFECTIVE 7/1/2025** Documentation is provided that the patient has tried and cannot take BOTH of the following (1 and 2): 1. Glassia 2. Prolastin-C (powder or liquid)

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Alpha$_1$-proteinase inhibitor products for any other use is considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

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 2023) 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.

Coding Information

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.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0256	Injection, alpha 1-proteinase inhibitor (human), not otherwise specified, 10 mg
J0257	Injection, alpha 1 proteinase inhibitor (human), (glassia), 10 mg
J7699	NOC drugs, inhalation solution administered through DME

References

1. Aralast NP® intravenous infusion [prescribing information]. Lexington, MA: Shire; October 2024.
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 2021.
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; September 2023.
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).
7. Brantly ML, Lascano JE, Shahmohammadi A. Intravenous alpha-1 antitrypsin therapy for alpha-1 antitrypsin deficiency: the current state of the evidence. *Chronc Obstr Pulm Dis.* 2018;6(1):100-114.
8. Stoller JK, Lacbawan FL, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. 2006 Oct 27 [Updated 2023 June 01]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1519. Accessed on December 6, 2024.
9. Miravitlles M, Herr C, Ferrarotti I, et al. Laboratory testing of individuals with severe alpha1-antitrypsin deficiency in three European centres. *Eur Respir J*. 2010 May;35(5):960-968.
10. American Thoracic Society and the European Respiratory Society. Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. *Am J Respir Crit Care Med.* 2003;168:818-900.

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.
12. Sabbagh DK, Barmayehvar B, Nguyen T, Edgar RG, Turner AM. Managing panniculitis in alpha-1 antitrypsin deficiency: systematic review of evidence behind treatment. *World J Dermatol.* 2018;7(1):1-8.
13. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2024. Available at: https://goldcopd.org/2024-gold-report/. Accessed on December 6, 2024.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes	03/15/2025
Selected Revision	**Added** Aralast-NP and Zemaira preferred product requirements for both Employer Plans and Individual and Family Plans, effective 7/1/2025.	06/01/2025

The policy effective date is in force until updated or retired.