



Drug Coverage Policy

Effective Date 10/15/2026

Coverage Policy Number.....IP0387

Policy Title.....Alpha₁-Proteinase
Inhibitor Products

Alpha₁-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

Alpha₁-proteinase inhibitor (also known as alpha₁-antitrypsin [AAT]) is indicated for **alpha₁-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 (FEV₁) 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 (FEV₁) 30 to 65% of predicted due to well-documented benefit in this group. Weaker recommendations also support treatment of patients with FEV₁ 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 alpha₁-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 alpha₁-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 alpha₁-proteinase inhibitors for the labeled indication.¹⁻⁵

Coverage Policy

POLICY STATEMENT

Prior Authorization is required for benefit coverage of alpha₁-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 as **[documentation required]**. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, prescription receipts and/or other information. All documentation must include patient-specific identifying information.

FDA-Approved Indication

Alpha₁-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. Alpha₁-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, vi, and vii):

- i. Patient is ≥ 18 years of age; AND
- ii. Patient has a baseline (pretreatment) alpha₁-antitrypsin serum concentration of < 11 micromol/L (< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry) **[documentation required]**; 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 alpha₁-antitrypsin (AAT) level < 11 micromol/L **[documentation required]**; 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; AND
 - vii. Preferred product criteria is met for the product(s) as listed in the below table(s); OR
- B) Patient is Currently Receiving an Alpha₁-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. According to the prescriber, the patient is a current non-smoker; AND
 - iii. Preferred product criteria is met for the product(s) as listed in the below table(s)

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

Other Uses with Supportive Evidence

2. Alpha₁-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, v, and vi):
- i. Patient is ≥ 18 years of age; AND
 - ii. Patient has a diagnosis of panniculitis confirmed by skin biopsy [**documentation required**]; AND
 - iii. Patient has a baseline (pretreatment) alpha₁-antitrypsin serum concentration of < 11 micromol/L (< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry) [**documentation required**]; 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 alpha₁-antitrypsin (AAT) level < 11 micromol/L [**documentation required**]; AND
 - v. The medication is prescribed by or in consultation with a dermatologist or pulmonologist; AND
 - vi. Preferred product criteria is met for the product(s) as listed in the below table(s); OR
- B) Patient is Currently Receiving an Alpha₁-Proteinase Inhibitor Product.** Approve for 1 year if the patient meets ALL of the following (i and ii):
- i. Patient is ≥ 18 years of age; AND
 - ii. Preferred product criteria is met for the product(s) as listed in the below table(s)

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

Employer Plans:

Product	Criteria
Aralast NP (alpha1-proteinase inhibitor [human] intravenous infusion)	Patient has tried and cannot take BOTH of the following (1 <u>and</u> 2) [documentation required]: 1. Glassia 2. Prolastin-C
Zemaira (alpha1-proteinase inhibitor [human] intravenous infusion)	Patient has tried and cannot take BOTH of the following (1 <u>and</u> 2) [documentation required]: 1. Glassia 2. Prolastin-C

Individual and Family Plans:

Product	Criteria
Aralast NP (alpha1-proteinase inhibitor [human] intravenous infusion)	Patient has tried and cannot take BOTH of the following (1 <u>and</u> 2) [documentation required] : 1. Glassia 2. Prolastin-C
Zemaira (alpha1-proteinase inhibitor [human] intravenous infusion)	Patient has tried and cannot take BOTH of the following (1 <u>and</u> 2) [documentation required] : 1. Glassia 2. Prolastin-C

Conditions Not Covered

Alpha₁-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. Alpha₁-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 alpha₁-proteinase inhibitor is not discussed for these patients.¹⁰ There is an absence of information that suggests alpha₁-proteinase inhibitor is useful in patients with AAT deficiency-related liver disease.
- 2. Bronchiectasis (without alpha₁-antitrypsin deficiency).** Studies have not demonstrated alpha₁ 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 Alpha₁-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 FEV₁ of 35 to 60% of predicted may be most suitable for AAT deficiency augmentation therapy; newer evidence suggests that individuals with higher FEV₁ values may also be candidates.¹³ However, this therapy is not recommended for COPD that is unrelated to AAT deficiency.

Coding 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.

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

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. Miravittles 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 March 27, 2026.
9. Miravittles 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 2026. Available at: <https://goldcopd.org/2026-gold-report-and-pocket-guide/>. Accessed on April 1, 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.

Revision Details

Summary of Changes	Review Date	Effective Date
No criteria changes	1/9/2025	03/15/2025
Added Aralast-NP and Zemaira preferred product requirements for both Employer Plans and Individual and Family Plans, effective 7/1/2025.	4/10/2025	06/01/2025
Updated documentation statement from "Documentation: Documentation is required where noted in the criteria. Documentation may include, but not limited to, chart notes,	4/2/2026	6/1/2026

laboratory tests, claims records, and/or other information.” to “Documentation: Documentation is required where noted in the criteria as [documentation required]. Documentation may include, but not limited to, chart notes, laboratory tests, claims records, prescription receipts and/or other information. All documentation must include patient-specific identifying information.” Alpha₁-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease). Criteria were divided into initial therapy and continuation of therapy. For <u>initial</u> therapy: Updated from “Documentation is provided the patient has a baseline (pretreatment) alpha₁-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]” to “Patient has a baseline (pretreatment) alpha₁-antitrypsin serum concentration of < 11 micromol/L (< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry) [documentation required].” Updated from “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 alpha₁-antitrypsin (AAT) level less than 11 mcmol/L” to “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 alpha₁-antitrypsin (AAT) level < 11 micromol/L [documentation required].” Added “According to the prescriber, the patient has clinical evidence of emphysema or chronic obstructive pulmonary disease.” Removed “At baseline, the patient meets ONE of the following: Documentation is provided of a forced expiratory volume in 1 second (FEV1) less than 65% of predicted OR 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 FEV1 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.” For Patient is <u>Currently Receiving</u> an Alpha₁-Proteinase Inhibitor Product: Added “Approve for Approve for 1 year if the patient meets ALL of the following (i, ii, and iii): i. Patient is ≥ 18 years of		
---	--	--

age; ii. According to the prescriber, the patient is a current non-smoker; iii. Preferred product criteria is met for the product(s) as listed in the below table(s)." Alpha₁-Antitrypsin Deficiency-Associated Panniculitis. Criteria were divided into initial therapy and continuation of therapy. For initial therapy: Updated from "Documentation is provided that the diagnosis of panniculitis confirmed by skin biopsy" to "Patient has a diagnosis of panniculitis confirmed by skin biopsy [documentation required]." Updated from "Documentation is provided of the patient has a baseline alpha₁-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)" to "Patient has a baseline (pretreatment) alpha₁-antitrypsin serum concentration of < 11 micromol/L (< 80 mg/dL if measured by radial immunodiffusion or < 57 mg/dL if measured by nephelometry) [documentation required]." Updated from "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 alpha₁-antitrypsin (AAT) level less than 11 mcmol/L" to "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 alpha₁-antitrypsin (AAT) level < 11 micromol/L [documentation required]." Removed "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 OR b. According to the prescriber, dapsone is contraindicated; OR ii. Documentation is provided of the patient has Moderate to severe panniculitis." For Patient is Currently Receiving an Alpha₁-Proteinase Inhibitor Product: Added "Approve for Approve for 1 year if the patient meets ALL of the following (i and ii): i. Patient is ≥ 18 years of age; ii. Preferred product criteria is met for the product(s) as listed in the below table(s)." Preferred Product Criteria – Employer Plans and Individual and Family Plans.		
--	--	--

Aralast NP and Zemaira: Updated from "Documentation is provided that the patient has tried and cannot take BOTH of the following (1 and 2): 1. Glassia AND 2. Prolastin-C (powder or liquid)" to "Patient has tried and cannot take BOTH of the following (1 and 2) [documentation required]: 1. Glassia AND 2. Prolastin-C" Coding Information: Removed HCPCS code: J7699		
No criteria changes.	10/01/2026	10/15/2026

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