Medical Drug Clinical Criteria

Subject:	Alpha-1 Proteinase Inhibitor Therapy		
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Overview

This document addresses the use of alpha-1 proteinase inhibitor therapy for chronic augmentation in adults with clinically evident emphysema due to severe congenital alpha-1 proteinase inhibitor deficiency (alpha-1 antitrypsin deficiency). Alpha-1 proteinase inhibitors approved by the Food and Drug Administration include:

- Aralast NP (alpha-1 proteinase inhibitor)
- Glassia (alpha-1 proteinase inhibitor)
- Prolastin-C (alpha-1 proteinase inhibitor)
- Zemaira (alpha-1 proteinase inhibitor)

Alpha-1 antitrypsin deficiency (AATD) is a hereditary disease characterized by deficient serum and lung concentrations of alpha-1 antitrypsin (AAT). This deficiency creates an imbalance between serine proteases like neutrophil elastase and AAT in the lungs. Neutrophil elastase destroys elastin while AAT protects against elastin degradation. The imbalance leads to destruction of pulmonary connective tissue and development of early-onset emphysema. AATD can also affect the liver cells and cause liver injury, cirrhosis or liver failure.

Severe AATD is highly under recognized and known to affect approximately 100,000 Americans. A diagnosis of AATD relies on laboratory assessment of the individual's serum levels of AAT. AAT can be assessed by radial immunodiffusion, rocket immunoelectrophoresis or nephelometry. The different tests have slightly different normal ranges, and the cut-off point for detecting AAT deficiency varies by test.

Chronic augmentation therapy with intravenous alpha-1 proteinase inhibitors is used to manage individuals with congenital AATD and clinically evident emphysema to slow the progression of the disease. The goal of therapy is to correct the imbalance of neutrophil elastase by raising the level of AAT above the protective threshold. Neutrophil elastase levels increase in the lungs in response to irritants including infection and cigarette smoke. A significant risk factor impacting the decline in lung function is current smoking. Therefore, use of augmentation therapy is recommended only for individuals who are former smokers or non-smokers.

Safety and efficacy data for augmentation therapy in AAT is of poor quality and report no significant differences in outcomes or, in some instances, a decline in lung function. However, the American Thoracic Society/European Respiratory Society (2003) and Canadian Thoracic Society (2012) have released guidance recommending augmentation therapy for individuals with moderate airflow obstruction (FEV_1 of 30-65% of the predicted value) and individuals with a rapid decline of lung function (change in FEV_1 > 120 mL/year). These guidelines did not recommend augmentation therapy for individuals with AATD without emphysema or individuals with mild or severe airway obstruction.

Alpha-1 proteinase inhibitors are derived from pooled human plasma and may contain trace amounts of IgA. Individuals with known antibodies to IgA, which can be present in individuals with selective or severe IgA deficiency, have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. Alpha-1 proteinase inhibitors are contraindicated in individuals with antibodies against IgA due to the risk of severe hypersensitivity.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Alpha-1 Proteinase Inhibitors (Aralast, Glassia, Prolastin-C, Zemaira)

Requests for alpha-1 proteinase inhibitor therapy may be approved if the following criteria are met:

I. Individual has a diagnosis of congenital alpha-1 antitrypsin deficiency (alpha-1 proteinase inhibitor deficiency); **AND**
II. Documentation is provided that individual's alpha-1 antitrypsin level less than or equal to 11 µmol/L (approximately equivalent to 80 mg/dL measured by radial immunodiffusion or 57 mg/dL measured by nephelometry) (ATS/ERS, 2003; Stoller, 2017); **AND**
III. Individual has clinically evident emphysema (or chronic obstructive pulmonary disease [COPD]); **AND**
IV. Individual is currently a non-smoker (ATS/ERS, 2003; CTS, 2012); **AND**
V. One of the following:
    A. Documentation is provided that individual has moderate airflow obstruction evidenced by a forced expiratory volume (FEV_1) of 30-65% of predicted value prior to initiation of therapy (ATS/ERS, 2003); **OR**
    B. Documentation is provided that individual has a rapid decline in lung function as measured by a change in FEV_1 greater than 120 ml/year (ATS/ERS, 2003); **AND**
VI. Individual meets one of the following:
    A. Individual is not IgA deficient; **OR**
    B. Individual is IgA deficient and does not have antibodies to IgA.

Continuation requests for alpha-1 proteinase inhibitor therapy may be approved if the following criteria are met:

I. Documentation is provided that there is clinically significant improvement or stabilization in clinical signs and symptoms of disease (including but not limited to decreased frequency of exacerbations, slowed rate of FEV_1 decline, preservation of CT scan lung density or improvement in symptom burden); **AND**
II. Individual remains a non-smoker.

Alpha-1 proteinase inhibitor therapy

I. My not be approved when the above criteria are not met and for all other indications.

Quantity Limits

Alpha-1 Proteinase Inhibitors (Aralast, Glassia, Prolastin-C, Zemaira) Quantity Limits

Drug	Limit
Aralast (alpha$_1$-proteinase inhibitor) 500 mg, 1000 mg vial	60 mg/kg once a week
Prolastin (alpha$_1$-proteinase inhibitor) 500 mg, 1000 mg vial	60 mg/kg once a week
Glassia (alpha$_1$-proteinase inhibitor) 1000 mg vial	60 mg/kg once a week
Zemaira (alpha$_1$-proteinase inhibitor) 1000 mg, 4000 mg, 5000 mg vial	60 mg/kg once a week

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

J0256	Injection, alpha 1-proteinase inhibitor (human), not otherwise specified, 10 mg [Aralast NP, Prolastin-C, Zemaira]
J0257	Injection, alpha 1 proteinase inhibitor (human), (Glassia), 10 mg

ICD-10 Diagnosis

E88.01	Alpha-1-antitrypsin deficiency
J43.0-J43.9	Emphysema

Document History

Revised: 2/21/2025
Document History:

- 2/21/2025 – Select Review: Move criteria for antibodies to IgA to initial request section. Coding Reviewed: No changes.
- 11/15/2024 – Annual Review: Add new vial strengths for Zemaira to quantity limit. Coding Reviewed: No changes.
- 11/17/2023 – Annual Review: Wording and formatting changes. Coding Reviewed: No changes.
- 11/18/2022 – Annual Review: Clarify clinically evident emphysema. Align may not approve criteria for individuals with IgA antibodies to labeled contraindication. Wording and formatting changes. Coding Reviewed: No changes.
- 11/19/2021 – Annual Review: No changes. Coding reviewed: No changes.
- 08/01/2021 – Administrative update to add documentation.
- 11/20/2020 – Annual Review: Add continuation criteria. Remove obsolete Prolastin-C vial size. Coding Reviewed: Removed HCPCS S9346.
- 11/15/2019 – Annual Review: Wording and formatting changes. Coding reviewed: No changes
- 09/23/2019 - Administrative update to add drug specific quantity limits.
- 11/16/2018 – Annual Review: Initial P&T review of ING-CC-0073 Alpha-1 Proteinase Inhibitor Therapy. Remove age criteria. Move alternative values for the alpha-1 antitrypsin level from a note at the end to a parenthetical comment in RN2. Add references for non-label-based criteria elements. Wording updates for clarity and consistency. Coding Review: Added HCPCS S9346.

References

1. American Thoracic Society(ATS)/European Respiratory Society (ERS) Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency. Am J Respir Crit Care Med. 2003; 168(7):818-900.
2. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: January 15, 2025.
3. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
4. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc. Updated periodically.
5. Marciniuk DD, Hernandez P, Balter M, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline. Can Respir J. 2012; 19(2):109-116.
6. Stoller JK. Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency. Updated: October 1, 2024. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed: January 14, 2025.
7. Stoller JK. Treatment of emphysema from alpha-1 antitrypsin deficiency. Updated: April 16, 2024. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. Accessed: January 14, 2025.
8. Stoller JK, Hupertz V, Aboussouan LS. Alpha-1 Antitrypsin Deficiency. GeneReviews (online). University of Washington, Seattle. Updated: June 1, 2023. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1519/?report=classic. Accessed: January 15, 2025.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.