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Coverage Policy Number **IP0387**

Alpha$_1$-Proteinase Inhibitors

Table of Contents

Related Coverage Resources

Genetic Testing for Hereditary and Multifactorial Conditions – (0052)

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. 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

This policy supports medical necessity review for the following alpha$_1$-proteinase inhibitor products:

- Aralast NP® (alpha$_1$-proteinase inhibitor [human] intravenous infusion)
- Glassia® (alpha$_1$-proteinase inhibitor [human] intravenous infusion)
- Prolastin®-C and Prolastin®-C Liquid (alpha$_1$-proteinase inhibitor [human] intravenous infusion)
- Zemaira® (alpha$_1$-proteinase inhibitor [human] intravenous infusion)

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

Medical Necessity Criteria

Alpha$_1$-proteinase inhibitor products are considered medically necessary when ONE of the following is met:

1. **Alpha$_1$-Antitrypsin Deficiency with Emphysema (or Chronic Obstructive Pulmonary Disease).** Individual meets **ALL** of the following criteria:
    A. Age 18 years or older
    B. Documentation of **ALL** of the following:
        i. 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. 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, documentation of **ONE** of the following:
            a. Forced expiratory volume in 1 second (FEV_1) less than 65% of predicted
            b. **ONE** of the following:
                1. 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. Supplemental oxygen required at rest or with exertion
        iv. Current non-smoker
    C. Medication is prescribed by, or in consultation with, a pulmonologist

    Dosing. 60 mg/kg intravenously once weekly

2. **Alpha$_1$-Antitrypsin Deficiency-Associated Panniculitis.** Individual meets **ALL** of the following criteria:
    A. Age 18 years or older
    B. Documented diagnosis of panniculitis confirmed by skin biopsy
    C. Documentation of **ONE** of the following:
        i. Mild panniculitis and **ONE** of the following:
            a. Experienced inadequate efficacy or significant intolerance with dapsone
            b. According to the prescriber, dapsone is contraindicated
        ii. Moderate to severe panniculitis
    D. Documentation of **BOTH** of the following:
        i. 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. 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

    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.

Reauthorization Criteria

Continuation of alpha$_1$-proteinase inhibitor products is considered medically necessary for **ALL** covered diagnoses when the above medical necessity criteria are met AND there is documentation of beneficial response.

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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 2022) 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.[14] 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

Experimental/Investigational/Unproven/Not Covered when used to report the inhalation form of alpha 1-proteinase inhibitor (human):

HCPCS Codes	Description
J7699	NOC drugs, inhalation solution administered through DME

Background

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] 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 Canadian Thoracic Society updated its guidelines (2012) regarding AAT deficiency testing and augmentation therapy.[11] 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 ≤ 11 mcM). 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.[12] 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.[13]

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]

References

1. Aralast NP® intravenous infusion [prescribing information]. Lexington, MA: Shire; December 2022.

2. Zemaira® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2022.
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 2022.
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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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. 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;19:109-116.
12. 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.
13. 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.
14. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2023. Available at: https://goldcopd.org/2024-gold-report/. Accessed on November 28, 2023.