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Subject: Alpha1-Proteinase Inhibitors (Human)

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DESCRIPTION:

Alpha-1-proteinase inhibitor (A1-PI) is a sterile, parenteral preparation of purified human alpha-1-proteinase inhibitor, which is also known as alpha-1-antitrypsin (AAT). The product is derived from pooled human plasma of healthy donors and is used for the treatment of individuals with congenital AAT deficiency that have clinically evident emphysema. Several A1-PI products have been approved by the US Food and Drug Administration (FDA): Prolastin® was the first product approved in 1987; however, a more concentrated version, Prolastin-C®, is available as a powder for injection and Prolastin C liquid was approved in September 2017. Aralast-NP® was approved by the FDA in December 2002, Zemaira was approved in July 2003, and Glassia™ was approved in July 2010.

Deficiency of AAT is an autosomal, co-dominant genetic disorder and by itself is not a disease, but a predisposition to later development of a disease. Low serum levels of AAT, in conjunction with other genetically determined characteristics and environment influences, result in the development of a disease state (e.g., pulmonary). Evidence from epidemiologic studies suggests there is a serum threshold level above which the lung appears to be protected. The serum threshold level lies at 11 micromoles, about 35% of the average normal level. More than 30 genetic variants have been identified that lead to deficient levels of AAT. The most common allele is referred to as M; most individuals have a protein phenotype PI*MM. AAT genotypes that confer an increased risk for developing lung disease are those in which deficiency or null alleles, combined in homozygous or heterozygous states, encode AAT levels below the protective threshold. The null alleles (homozygotes designated as PI QOQO) are associated with the most severe deficiency, producing no active AAT, or less than 1% of the normal amount of plasma AAT. The most frequent deficient AAT allele is the Z variant and individuals who are PI*ZZ

homozygotes are at the greatest risk for developing AAT deficiency-associated lung disease. The remaining frequent types of AAT phenotypes include PI*SZ, PI*MS, and PI*MZ. Although evidence from the literature suggests that individuals with the SS, SZ, MS, or MZ phenotype are at an increased risk of developing AAT-deficiency-associated disease, individuals with PI*MZ or PI*MS phenotypes of AAT deficiency are at small risk of developing panacinar emphysema. Table 1 depicts the range of serum levels (measured using typical commercial standard [mg/dL] and the purified standard [micromoles] used in the US registry) of AAT according to phenotype. Of note, a level of less than 11 micromoles is associated with an increased risk of emphysema.

Table 1

Range of Serum Levels of Alpha-1 Antitrypsin According to Phenotype		
Phenotype	**Micromoles**	**mg/dL**
PI*MM	20-48	150-350
PI*MZ	17-33	90-210
PI*SS	15-33	100-200
PI*SZ	8-16	75-120
PI*ZZ	2.5-7	20-45

Based on recommendations from an expert Task Force, the American Thoracic Society/European Respiratory Society (ATS/ERS) published standards for the diagnosis and management of individuals with alpha-1-antitrypsin deficiency in 2003. The guideline reviews the role of augmentation therapy in the management of individuals with severe deficiency of AAT. The Task Force recommends intravenous augmentation therapy for individuals with established airflow obstruction from AAT deficiency (i.e., defined as serum concentration less than 80 mg/dL [11 micromoles/L] if measured by radial diffusion or less than 50 mg/dL if measured by nephelometry) and highlights that evidence that augmentation therapy confers benefit (e.g., slowed rate of FEV1 decline and decrease mortality) is stronger for individuals with moderate airflow obstruction (e.g., Forced expiratory volume in 1 second [FEV1] 30 – 65% predicted) or a rapid decline in lung function (change in FEV1 greater than 120 ml/year) than for those with severe airflow obstruction. The Task Force does not recommend augmentation therapy for individuals without emphysema, and recognizes that the evidence of benefits in severe or mild airflow obstruction are less clear. Of note, indication for treatment is independent of the phenotype and based on serum AAT level and presence of obstructive lung disease (e.g., emphysema).

POSITION STATEMENT:

I. Intravenous administration of alpha-1 proteinase inhibitors (Human) (e.g., Aralast-NP, Prolastin-C, Prolastin-C Liquid, Glassia, Zemaira) **meets the definition of medical necessity** when administered to members with congenital alpha-1 antitrypsin deficiency (AATD) and **ALL** of the following criteria are met:

   1. Member is a non-smoker
   2. Member has a severe deficiency of AAT as indicated by **either** of the following – documentation must be submitted:

a. Measured serum alpha-1 antitrypsin concentration less than 50 mg/dL if measured by nephelometry

b. Measured serum alpha-1 antitrypsin concentration less than 80 mg/dL (11 micromoles/L) if measured by radial immunodiffusion

3. Member has panacinar emphysema and **either** of the following – documentation must be submitted:

    a. Forced expiratory volume in 1 second (FEV1) of 30 – 65% of predicted

    b. Rapid decline in lung function defined as a change FEV1 of more than 120 mL/year

4. Dose does not exceed 60 mg/kg once weekly

NOTE: Quest Diagnostics® can perform the serum alpha-1 antitrypsin concentration test.

Glassia **meets the definition of medical necessity** when used for the following designated Orphan Drug Indications (http://www.fda.gov/orphan/designat/list.htm) when the dose does not exceed the maximum FDA-approved dose:

1. Treatment of individuals with recent onset (i.e., less than 15 years) type 1A diabetes mellitus with residual beta-cell function.
2. Treatment or prevention of graft versus host disease

Prolastin-C **meets the definition of medical necessity** when used for the following designated Orphan Drug Indications (http://www.fda.gov/orphan/designat/list.htm) when the dose does not exceed the maximum FDA-approved dose:

1. Treatment of individuals with Type 1 diabetes mellitus with residual beta-cell function.

Approval duration: 1 year (all indications)

II. Continuation of alpha-1 proteinase inhibitors (Human) (e.g., Aralast-NP, Prolastin-C, Prolastin-C Liquid, Glassia, Zemaira) **meets the definition of medical necessity** for the treatment of congenital alpha-1 antitrypsin deficiency (AATD) and orphan indications when **ALL** of the following criteria are met:

1. Member has demonstrated a beneficial response to therapy
2. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 2 years before the authorization request must be submitted), **OR** the member currently meets all indication-specific initiation criteria
3. Dose does not exceed 60 mg/kg once weekly

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL

PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

Alpha-1 proteinase inhibitors (A1PI) are indicated for chronic augmentation and maintenance therapy in adults with emphysema due to alpha-1 antitrypsin deficiency (AATD). The effect of augmentation therapy with any A1PI on pulmonary exacerbations and on the progression of emphysema in AATD has not been demonstrated in randomized, controlled clinical trials. Additionally, A1PIs are not indicated as therapy for lung disease in individuals in whom severe AATD has not been established. There are five commercially available products: Aralast-NP, Glassia, Prolastin-C, Prolastin-C Liquid and Zemaira. The recommended dose for all products is 60 mg/kg administered as intravenous (IV) infusion once weekly. Information regarding infusion rates, approximate infusion times, and how each product is supplied can be found in Table 2. The rate of administration should be closely followed until the provider has had sufficient experience with a member; vital signs should be monitored continuously and the member closely observed throughout the infusion. If anaphylactic or severe anaphylactoid reactions occur, the infusion should be discontinued immediately. Epinephrine and other appropriate supportive therapy should be available for the treatment of any acute anaphylactic or anaphylactoid reaction.

Table 2

Product	Infusion rate	How Supplied
Aralast-NP	0.2 ml/kg/min	1 g/50 mL, 0.5 g/25 mL
Glassia	0.2 ml/kg/min	1 g/50 mL
Prolastin-C	0.08 ml/kg/min	1 g/20 mL
Prolastin-C Liquid	0.08 ml/kg/min	0.5 g/10 mL, 1 g/20 mL, 4 g/80 mL
Zemaira	0.08 ml/kg/min	1 g/20 mL, 4 g/76 mL, 5 g/95 mL

PRECAUTIONS:

CONTRAINDICATIONS

A1PI products are contraindicated in IgA deficient members with antibodies against IgA. These members are at greater risk of developing severe hypersensitivity and anaphylactic reactions. Additionally, A1P1 products should not be administered to members with a history of severe immediate hypersensitivity reactions, including anaphylaxis, to any A1P1 product.

WARNINGS

Infectious transmission: Because alpha1-PI is derived from pooled human plasma, it may carry a risk of transmitting infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent).

Severe hypersensitivity: severe hypersensitivity and anaphylactic reactions may occur in IgA deficient members with antibodies against IgA.

Children: Safety and efficacy in children have not been established.

Pregnancy and Lactation: The ability of A1PI products to cause fetal harm or to affect reproductive capacity is unknown. Additionally, caution is advised if A1PI is administered to a woman who is breast-feeding excretion into human milk is unknown.

BILLING/CODING INFORMATION:

The following codes may be used to report Alpha1-Proteinase Inhibitors (Human) (Prolastin®-C, Prolastin®-C Liquid, Glassia™, Zemaira®, Aralast-NP®).

HCPCS Coding:

J0256	Injection, alpha 1-proteinase inhibitor – human, 10 mg
J0257	Injection, alpha 1-proteinase inhibitor (human), (Glassia™), 10mg
S9346	Home infusion therapy, alpha-hyphen1-hyphenproteinase inhibitor (e.g., Prolastin); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

ICD-10 Diagnosis Codes That Support Medical Necessity

D89.810 – D89.813	Graft-versus-host disease
E10.65	Type 1 diabetes mellitus with hyperglycemia
E10.9	Type 1 diabetes mellitus without complications
E88.01	Alpha-1 antitrypsin deficiency
J43.0 – J43.9	Emphysema

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Alpha1-antitrypsin deficiency (AATD): is a chronic, hereditary, usually fatal, autosomal recessive disorder in which a low concentration of Alpha1-PI (alpha1-antitrypsin) is associated with slowly progressive, severe panacinar emphysema that most often manifests itself in the third to fourth decades of life.

Panacinar Emphysema: panlobular emphysema, one of the types of pulmonary emphysema, characterized by relatively uniform enlargement of air spaces throughout the acini.

Panniculitis: A disease that causes inflammation of subcutaneous adipose tissue presenting with symptoms such as tender skin nodules with or without associated vasculitis.

Vasculitis: A group of disorders that are characterized by inflammatory destruction of blood vessels.

RELATED GUIDELINES:

None applicable.

OTHER:

None applicable.

REFERENCES:

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2. Alpha-1 Proteinase Inhibitor Human (Aralast NP) [package insert]. Baxalta Inc. Lexington (MA): October 2024.
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4. Alpha-1 Proteinase Inhibitor Human (Prolastin-C) [package insert]. Grifols Therapeutics, Inc. Research Triangle Park (NC): June 2018.
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6. Alpha-1 Proteinase Inhibitor Human (Zemaira) [package insert]. CSL Behring LLC. Kankakee (IL): January 2024.
7. American Thoracic Society/European Respiratory Society Statement: Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency. 2003. Accessed 12/29/22.
8. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.;2024. URL www.clinicalpharmacilogy-ip.com Accessed 12/26/24.
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/08/25.

GUIDELINE UPDATE INFORMATION:

01/01/05	New Medical Coverage Guideline.
08/15/05	Revised and Updated: added to description, dosage/administration, deleted precautions, updated when services are not covered, definitions, references, and to the related internet links.
09/15/06	Biennial review and updated references.

01/01/07	MCG revised to include Medicare Part D as a program exception.
07/15/07	Reviewed guideline: maintain current coverage and limitations. Reformatted guideline, updated internet links and references.
07/15/08	Review of guideline with no changes made in coverage. Added CPT-4 code for administration and updated references and links.
01/01/09	Annual HCPCS coding update: deleted code 90765; added code 96365.
07/15/09	Review and revision to guideline; consisting of position statement review. Additional background information added in Description, added definition of panniculitis and vasculitis, title revision, and updating references.
02/15/10	Review and revision to guideline; consisting of addition of Aralast-NP®, updating references, revision of applicable ICD-9 codes.
01/15/11	Revision to guideline; consisting of adding ICD-10 codes.
08/17/11	Revision; ICD-10 codes updated.
09/15/11	Revision to guideline; consisting of adding 2 additional agents.
01/01/12	Revision to guideline; consisting of adding codes.
02/15/13	Review and revision to guideline; consisting of revising/reformatting position statement; revising dosage/administration and precautions section; updating references.
11/15/13	Revision to guideline; consisting of updating Program Exceptions section and adding approval duration.
02/15/14	Review and revision to guideline; consisting of reformatting position statement and updating references.
02/15/15	Review and revision to guideline; consisting of reformatting position statement, updating references.
09/15/15	Revision to guideline; consisting of revising codes.
02/15/16	Review and revision to guideline; consisting of reformatting position statement, updating dosing/administration, coding and references.
02/15/17	Review and revision to guideline; consisting of updating references.
02/15/18	Review and revision to guideline; consisting of updating position statement, description, dosing, and references.
04/15/19	Review and revision to guideline; consisting of updating position statement and references.
02/15/23	Review and revision to guideline consisting of updating the position statement to require documentation from other health plans for continuation and inclusion of the prevention of graft versus host disease for Glassia as an Orphan Drug Indication, updating the product availability table, and revising codes and references.
02/15/24	Review and revision to guideline; consisting of updating references.
02/15/25	Review and revision to guideline; consisting of updating billing codes and references.