Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 04/11/2024

Alpha – 1 Proteinase Inhibitors

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

HCPCS: Aralast NP: J0256; Glassia: J0257; Prolastin-C: J0256; Prolastin-C Liquid: J0256; Zemaira: J0256

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved age
   b. Must be a nonsmoker
   c. Member must have pre-treatment serum levels of alpha-1 antitrypsin (AAT) that are less than 11 micromol/L measured by ELISA (less than 80 mg/dL measured by radial immunodiffusion or less than 57 mg/dL measured by nephelometry) consistent with phenotypes PiZZ, PiZ (null), or Pi (null, null) of AAT
      i. Phenotype/genotype testing may be requested for additional support of alpha-1 antitrypsin deficiency diagnosis
   d. Member must have symptomatic emphysema
   e. Member must have deteriorating pulmonary function, as demonstrated by a decline in the FEV_1 (35-60% of predictive value)
   f. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list and/or BCBSM/BCN's prior authorization and step therapy documents

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: One year at a time
   c. Renewal Criteria: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Alpha-1 antitrypsin deficiency (AATD) is a rare autosomal recessive genetic disorder that results in decreased production of alpha-1 antitrypsin (AAT) protein (also referred to as alpha-1 proteinase inhibitor), or production of abnormal types of the protein that are functionally deficient. AAT inhibits the neutrophil elastase enzyme from degrading elastin tissues in the lung. Deficiency leads to early onset of severe pulmonary emphysema in adults, which leads to a decline in lung function (FEV_1), exacerbation of symptoms, decline in ability to function, and even death. Replacement therapies have not been shown to prevent or reverse emphysema in AATD; however, data has shown that treatment of symptomatic patients with low serum levels of AAT due to congenital deficiencies of this enzyme will slow the progression of disease.

- Intravenous augmentation therapy with AAT is the most direct and efficient means of elevating serum AAT levels, with the goal of slowing progression of emphysema. Guidelines from the Global Initiative for Chronic Obstructive Lung Disease (GOLD; 2023) and the Medical and Scientific Advisory Committee of the Alpha-1 Foundation (2016) recommend augmentation therapy for non-smokers with emphysema and an FEV_1 of 35-60% predicted. Patients must have an AAT genetic variant consistent with severe AAT deficiency (Pi*ZZ, Pi*Z null, Pi* (null) (null)) and a low serum level of AAT below the protective threshold (ie <11 µmol/L via ELISA or <57 mg/dL via nephelometry or < 80 mg/dL via radial immunodiffusion).

- Clinically evident emphysema may not be evident in AAT deficient patients with higher FEV_1 values, and evidence that augmentation therapy confers benefit (e.g., slowed rate of FEV_1 decline and decreased mortality) is stronger for individuals with moderate airflow obstruction (e.g., FEV_1 35–60% predicted) than for those with severe (e.g., $FEV_1 \leq$ 35% predicted) or mild (e.g., $FEV_1 \geq$ 50–60% predicted) airflow obstruction. For those with lung disease related to AATD and an $FEV_1 >$ 65% predicted, discussion with each individual regarding potential benefits of reducing lung function decline is recommended, with consideration of the cost of therapy and lack of evidence for such a benefit.

- The FDA has approved the use of four AAT products derived from human plasma: Glassia, Prolastin, Zemaira, and Aralast; available guidelines do not differentiate between products. These agents are administered intravenously at an FDA approved dose of 60 mg/kg once weekly. All products require administration by a healthcare professional; however, Glassia may be self-administered by the patient/caregiver after appropriate training. Studies support that weekly infusions at this dose maintain AAT levels in the serum and epithelial lining fluid above protective thresholds (i.e. >11 µmol/L via ELISA or >57 mg/dL via nephelometry or >80 mg/dL via radial immunodiffusion) throughout the week and over long-term. Minimal data is available describing improved clinical outcomes; therefore, outside of restoration of serum AAT levels, therapeutic response and efficacy can be evaluated via surrogate outcome measures including stability or improvement in FEV_1 and other pulmonary function testing, reductions in exacerbations, and reductions in daily symptoms.

- All AAT products appear to be similar in biologic activity for slowing emphysema progression in AATD. No evidence is available suggesting clinically meaningful differences in safety and/or efficacy between the available products. One trial is available comparing Prolastin and Aralast which showed equivalent results. No published trials comparing Zemaira to another alpha-1 proteinase inhibitor product are available. However, data within FDA product labeling describes a comparison of Zemaira and Prolastin which showed equivalent results. In one unpublished, randomized, controlled study comparing Glassia to Prolastin in fifty patients with congenital AATD and clinical signs and symptoms of emphysema, Glassia met pre-specified criteria for non-inferiority; however, no clinical endpoints were assessed.

- The administration of alpha-1 proteinase inhibitors (human) increases plasma levels of alpha-1 proteinase inhibitors, and levels of functionally active alpha-1 proteinase inhibitors in the lung are increased proportionately. However, long-term controlled clinical trials that evaluate the effect of chronic replacement therapy with alpha-1 proteinase inhibitor on the development or progression of emphysema in patients with congenital AATD have not yet been performed. The slow and progressive nature of the disease, as well as estimates of the sample size required of this rare disorder render the ability to conduct such trials very challenging. Nonetheless, studies to monitor the long-term effects are continuing as part of the post-approval process. FDA-required Phase IV clinical trials are currently being conducted

References:

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14. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2023 Report. www.goldcopd.org (Accessed on January 24,, 2023).
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<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>2.5</td><td>Effective Date: 04/11/2024</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>2.4</td><td>Effective Date: 04/06/2023</td><td>Annual review of criteria was performed, no changes were made</td></tr>
<tr><td>2.3</td><td>Effective Date: 04/14/2022</td><td>Annual review of criteria was performed, no changes were made.</td></tr>
<tr><td>2.2</td><td>Effective Date: 04/08/2021</td><td>Criteria updates as follows:
1. Clarified serum AAT levels to account for different methods of measurement
2. Removed criteria stating Glassia can be self-administered and added to background information
3. Updated trial and failure of preferred language to standard verbiage
4. Updated quantity limit language
5. Changed authorization period from 6 months initial/1 year renewal to 1 year
6. Changed renewal criteria to standard verbiage</td></tr>
<tr><td>2.1</td><td>Effective Date: 4/16/2020</td><td>Annual Review</td></tr>
<tr><td>2.0</td><td>Effective Date: 05/09/2019</td><td>Added documentation of PFT, reduction in exacerbations, or reduction of daily symptoms to renewal criteria</td></tr>
<tr><td>1.9</td><td>Effective Date: 05/03/2018</td><td>New dosage form for Prolastin-C Liquid added</td></tr>
<tr><td>1.8</td><td>Effective Date: 02/08/2018</td><td>Annual review of Medical Policy</td></tr>
<tr><td>1.7</td><td>Effective Date: 07/05/2017</td><td>UM medical management system update for BCNA and MAPPO for Aralast, Glassia, and Prolastin-C
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.6</td><td>Effective Date: 02/09/2017</td><td>Criteria Update for Glassia Self-Administration</td></tr>
<tr><td>1.5</td><td>Effective Date: 11/05/2015</td><td>Criteria Update</td></tr>
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<tr><td>1.4</td><td>Effective Date: 04/01/2015</td><td>UM medical management system update for Aralast, Glassia, Prolastin-C, and Zemaira

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<tr><td>1.3</td><td>Effective Date: 02/01/2015</td><td>UM medical management system update for Aralast, Glassia, Prolastin-C, and Zemaira

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<tr><td>1.2</td><td>Effective Date: 05/08/2014</td><td>Criteria Update</td></tr>
<tr><td>1.1</td><td>Effective Date: 08/09/2012</td><td>Criteria Update</td></tr>
<tr><td>1.0</td><td>Effective Date: 10/2010</td><td>New Policy</td></tr>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*