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Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

**Effective Date: 04/11/2024**

**Alpha – 1 Proteinase Inhibitors**

**Aralast NP<sup>®</sup>** (alpha-1 proteinase inhibitor)

**Glassia<sup>™</sup>** (alpha-1 proteinase inhibitor)

**Prolastin<sup>®</sup>-C** (alpha-1 proteinase inhibitor)

**Prolastin<sup>®</sup>-C Liquid** (alpha-1 proteinase inhibitor)

**Zemaira<sup>®</sup>** (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<sub>1</sub> (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

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\*\*\*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<sub>1</sub>), 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<sub>1</sub> 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<sub>1</sub> values, and evidence that augmentation therapy confers benefit (e.g., slowed rate of FEV<sub>1</sub> decline and decreased mortality) is stronger for individuals with moderate airflow obstruction (e.g., FEV<sub>1</sub> 35–60% predicted) than for those with severe (e.g., FEV<sub>1</sub> ≤ 35% predicted) or mild (e.g., FEV<sub>1</sub> ≥ 50–60% predicted) airflow obstruction. For those with lung disease related to AATD and an FEV<sub>1</sub> > 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<sub>1</sub> 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.

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- 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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Policy History												
#	Date	Change Description										
2.5	Effective Date: 04/11/2024	Annual review of criteria was performed, no changes were made										
2.4	Effective Date: 04/06/2023	Annual review of criteria was performed, no changes were made										
2.3	Effective Date: 04/14/2022	Annual review of criteria was performed, no changes were made.										
2.2	Effective Date: 04/08/2021	Criteria updates as follows: <ol style="list-style-type: none"> <li>1. Clarified serum AAT levels to account for different methods of measurement</li> <li>2. Removed criteria stating Glassia can be self-administered and added to background information</li> <li>3. Updated trial and failure of preferred language to standard verbiage</li> <li>4. Updated quantity limit language</li> <li>5. Changed authorization period from 6 months initial/1 year renewal to 1 year</li> <li>6. Changed renewal criteria to standard verbiage</li> </ol>										
2.1	Effective Date: 4/16/2020	Annual Review										
2.0	Effective Date: 05/09/2019	Added documentation of PFT, reduction in exacerbations, or reduction of daily symptoms to renewal criteria										
1.9	Effective Date: 05/03/2018	New dosage form for Prolastin-C Liquid added										
1.8	Effective Date: 02/08/2018	Annual review of Medical Policy										
1.7	Effective Date: 07/05/2017	UM medical management system update for BCNA and MAPPO for Aralast, Glassia, and Prolastin-C <table border="1" data-bbox="483 1094 1365 1304" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <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> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	Yes	BCNA	Yes
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1.6	Effective Date: 02/09/2017	Criteria Update for Glassia Self-Administration										
1.5	Effective Date: 11/05/2015	Criteria Update										

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1.4	Effective Date: 04/01/2015	UM medical management system update for Aralast, Glassia, Prolastin-C, and Zemaira  <table border="1"> <thead> <tr> <th>Line of Business</th> <th>PA Required in Medical Management System (Yes/No)</th> </tr> </thead> <tbody> <tr> <td>BCBS</td> <td>Yes</td> </tr> <tr> <td>BCN</td> <td>Yes</td> </tr> <tr> <td>MAPPO</td> <td>No</td> </tr> <tr> <td>BCNA</td> <td>No</td> </tr> </tbody> </table>	Line of Business	PA Required in Medical Management System (Yes/No)	BCBS	Yes	BCN	Yes	MAPPO	No	BCNA	No
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1.2	Effective Date: 05/08/2014	Criteria Update										
1.1	Effective Date: 08/09/2012	Criteria Update										
1.0	Effective Date: 10/2010	New Policy										

\* 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>.

**Blue Cross Blue Shield/Blue Care Network of Michigan  
Medication Authorization Request Form  
ARALAST NP, PROLASTIN-C®, ZEMAIRA® J0256, GLASSIA J0257**



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This form is to be used by participating physicians to obtain coverage for ARALAST NP, PROLASTIN-C®, ZEMAIRA® or GLASSIA. For commercial members only, please complete this form and submit via fax to 1-877-325-5979. If you have any questions regarding this process, please contact BCBSM Provider Relations and Servicing or the Medical Drug Helpdesk at 1-800-437-3803 for assistance.

PATIENT INFORMATION	PHYSICIAN INFORMATION
Name	Name
ID Number	Specialty
D.O.B. <span style="float:right"><input type="checkbox"/> Male <input type="checkbox"/> Female</span>	Address
Pt weight (in kg) <span style="float:right">Date recorded: _____</span>	City /State/Zip
Diagnosis	Phone/Fax: P: (     ) -     F: (     ) -
Drug Name	NPI
Dose and Quantity	Contact Person
Directions	Contact Person Phone / Ext.
Date of Service(s)	

**STEP 1: DISEASE STATE INFORMATION**

- Is this an initial request or continuation of therapy?  Initial request  Continuation *Date patient started therapy: \_\_\_\_\_*
- Site of administration?  Provider office/Home infusion  Other: \_\_\_\_\_  
 Hospital outpatient facility (**go to #3**) *Reason for Hospital Outpatient administration: \_\_\_\_\_*
- Please specify location of administration if hospital outpatient infusion:** \_\_\_\_\_
- How is this medication being administered?  Self-administered (**Please fax this completed form to BCBSM at (866) 601-4425**)  
 Health Care Professional administered
- Please provide the NPI number for the place of administration:** \_\_\_\_\_
- Initiation AND Continuation of therapy:**
  - What is the patient's diagnosis (select all that apply)?  
 Alpha-1 antitrypsin deficiency/inhibitors  Emphysema  Asthma  Bronchitis  Other: \_\_\_\_\_
  - Which of the following alpha-1 antitrypsin phenotypes does the patient have?  
 PiZZ phenotype  PiZ (null) phenotype  Pi (null, null) phenotype  Other: \_\_\_\_\_
  - What is the patient's alpha-1 antitrypsin serum level prior to start of therapy? \_\_\_\_\_ mg/dl *Date measured: \_\_\_\_\_*
  - What is the patient's FEV1? (% predictive value): \_\_\_\_\_
  - Which of the following pertain to the patient's diagnosis?  
 Smoker; Please provide the date patient quit smoking: \_\_\_\_\_  
 Declining pulmonary function  
 Symptomatic emphysema  
 None of the above
- Continuation request:**
  - How has the patient responded to therapy?  
 Elevated alpha-1 antitrypsin level above 80mg/dl  
 FEV1 testing showing:  
 Stable lung function  
 Improvement in lung function  
 Reduction in exacerbations  
 Reduction in daily symptoms  
 Patient has progressively worsened while on therapy  
 Other: \_\_\_\_\_

**Please add any other supporting medical information necessary for our review**

**Coverage will not be provided if the prescribing physician's signature and date are not reflected on this document.**

Request for expedited review: I certify that applying the standard review time frame may seriously jeopardize the life or health of the member or the member's ability to regain maximum function

Physician's Name	Physician Signature	Date
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<b>Step 2:</b> Checklist	<input type="checkbox"/> Form Completely Filled Out <input type="checkbox"/> Attached Chart Notes	
<b>Step 3:</b> Submit	<b>By Fax: BCBSM Specialty Pharmacy Mailbox 1-877-325-5979</b>	<b>By Mail: BCBSM Specialty Pharmacy Program P.O. Box 312320, Detroit, MI 48231-2320</b>

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