Clinical Policy: Alpha$_1$-Proteinase Inhibitors (Aralast NP, Glassia, Prolastin-C, Zemaira)

Reference Number: ERX.SPA.87
Effective Date: 03.01.14
Last Review Date: 02.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description
The following are alpha$_1$-proteinase inhibitors requiring prior authorization: alpha$_1$-proteinase inhibitor, human (Aralast™ NP, Glassia®, Prolastin®-C, Zemaira®).

FDA Approved Indication(s)
Aralast NP, Glassia, Prolastin-C, and Zemaira are indicated for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe congenital deficiency of alpha$_1$-PI (alpha$_1$-antitrypsin [AAT] deficiency). Alpha$_1$-PI products increase antigenic and functional (anti-neutrophil elastase capacity) serum levels and antigenic lung epithelial lining fluid levels of alpha$_1$-PI.

Limitation(s) of use:
- The effect of augmentation therapy with alpha$_1$-PI products on pulmonary exacerbations and on the progression of emphysema in alpha$_1$-PI deficiency has not been conclusively demonstrated in randomized, controlled clinical trials.
- Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with alpha$_1$-PI products are not available.
- Alpha$_1$-PI products are not indicated as therapy for lung disease in patients in whom severe alpha$_1$-PI deficiency has not been established.

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Aralast NP, Glassia, Prolastin-C, and Zemaira are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Alpha$_1$-Antitrypsin Deficiency (must meet all)**:**

1. Diagnosis of severe congenital AAT deficiency;
2. Prescribed by or in consultation with a pulmonologist;
3. Age ≥ 18 years;
4. Member meets one of the following (a or b):
   a. Documentation of plasma AAT level < 11 micromol/L (approximately 50 mg/dL using nephelometry or 80 mg/dL by radial immunodiffusion);
   b. If member has an AAT level > 11 micromol/L, then the member has one of the high-risk phenotypes (i.e., PiZZ, PiZnull, Pi(null, null), or one of a few rare phenotypes [e.g. Pi(Malton, Malton)]);
5. Member demonstrates clinical evidence of emphysema (a or b):
   a. Forced expiratory volume in one second (FEV$_1$) from ≥ 30% to ≤ 65% of predicted, post-bronchodilator;

b. FEV_1 from > 65% to < 80% of predicted, post-bronchodilator, and a rapid decline in lung function showing a change in FEV_1 > 100 mL/year;

6. Member is not an active smoker as evidenced by recent (within the last 30 days) negative nicotine metabolite (i.e., cotinine) test;
7. Dose does not exceed 60 mg/kg per week.

Approval duration: 6 months

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Alpha$_1$-Antitrypsin Deficiency (must meet all)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy;
3. If request is for a dose increase, new dose does not exceed 60 mg/kg per week.

Approval duration: 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;

B. Immunoglobulin A (IgA) deficiency (IgA level less than 15 mg/dL) with known antibody against IgA.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

AAT: alpha$_1$-antitrypsin
Alpha$_1$-PI: alpha$_1$-proteinase inhibitors
COPD: chronic obstructive pulmonary disease
FDA: Food and Drug Administration
FEV_1: forced expiratory volume in one second

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): use in IgA deficient patients with known antibodies against IgA and/or a history of anaphylaxis or other severe systemic reaction to alpha$_1$-PI, due to the risk of severe hypersensitivity, including anaphylaxis
- Boxed warning(s): none reported

Appendix D: General Information

- The American Thoracic Society (ATS) and the European Respiratory Society (ERS) state that alpha$_1$-proteinase inhibitor therapy does not confer benefit in, and is not recommended for, patients who have alpha$_1$-proteinase-associated liver disease.
- The 2016 COPD Foundation's clinical practice guidelines for AAT deficiency in the adult recommend intravenous augmentation therapy for individuals with FEV_1 less than 30% predicted with a weak recommendation with a low quality of evidence, and low value placed on the cost of

this therapy. The 2003 ATS-ERS guidelines mirror the COPD Foundation in that evidence of benefit from augmentation therapy is weak in those with severe airflow obstruction.
- Aralast NP, Glassia, Prolastin-C, Zemaira: Safety and effectiveness in the pediatric population have not been established.
- Smoking is an important risk factor for the development of emphysema in patients with AAT deficiency. Both the 2003 ATS and 2016 COPD Foundation AAT guidelines state that smoking cessation is important in this patient population.
- The goal of AAT augmentation is to slow the progression of emphysema/lung function decline. Lung function can be measured with FEV_1, which is most important predictor of survival of patients with emphysema due to AAT deficiency per the 2003 ATS AAT guidelines. Improvement, maintenance, or stabilization in FEV_1 rate of decline is therefore an acceptable example of positive response to therapy.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Emphysema due to AAT deficiency	60 mg/kg IV once weekly	60 mg/kg/week

VI. Product Availability

Drug Name	Availability
Alpha$_1$-proteinase inhibitor, human (Aralast NP)	Single-use vial: 500 mg, 1,000 mg
Alpha$_1$-proteinase inhibitor, human (Glassia)	Single-use vial: 1,000 mg/50 mL
Alpha$_1$-proteinase inhibitor, human (Prolastin-C)	Single-use vial: 1,000 mg (powder) Single-use vial: 1,000 mg/20 mL (liquid)
Alpha$_1$-proteinase inhibitor, human (Zemaira)	Single-use vial: 1,000 mg, 4,000 mg, 5,000 mg

VII. References

1. Aralast NP Prescribing Information. Westlake Village, CA: Baxter Healthcare Corporation; December 2018. Available at: http://www.shirecontent.com/PI/PDFs/ARALASTNP_USA_ENG.pdf. Accessed October 20, 2020.
2. Glassia Prescribing Information. Negev, Israel: Kamada, Ltd.; June 2017. Available at: http://www.liquidglassia.com. Accessed October 20, 2020.
3. Prolastin-C Powder Prescribing Information. Research Triangle Park, NC: Grifols Therapeutics, Inc.; June 2018. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=91edab72-c889-470e-8315-1798b5548dca. Accessed October 20, 2020.
4. Prolastin-C Liquid Prescribing Information. Research Triangle Park, NC: Grifols Therapeutics, Inc.; August 2018. Available at: http://www.prolastin.com. Accessed October 20, 2020.
5. Zemaira Prescribing Information. Kankakee, IL: CSL Behring LLC; April 2019. Available at: http://www.zemaira.com. Accessed October 20, 2020.
6. American Thoracic Society/European Respiratory Society 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.
7. Sandhaus RA, Turino G, and Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Journal of COPD Foundation*. 2016;3(3):668-682.
8. Cazzola M, MacNee W, Martinez FJ, et al.; American Thoracic Society; European Respiratory Society Task Force on outcomes of COPD. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J.* 2008;31:416–469.
9. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2019 Report). Available at: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template. Clarified criteria surrounding supportive measures into 2 different subbullets.	06.17	08.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: Removed requirement for supportive measures (avoidance of cigarette smoking and vaccinations) due to lack of actionability and objectivity; Protective threshold value per nephelometry changed from 57 mg/dL to 50 mg/dL per American Thoracic Society 2003 guidelines; Added "If the member has an AAT level >11 umol/L, then the member has one of the high-risk phenotypes (i.e. PiZZ, PiZnull, Pi(null, null), or one of a few rare phenotypes [e.g. Pi(Malton, Malton)]" to allow treatment before clinical deterioration due to definite diagnosis; Added prescriber requirement due to the complexity of disease diagnosis and management; Changed minimally significant change in FEV from 120 mL to 100 mL per ATC guidelines and specialist feedback	12.05.17	02.18
No significant changes: new Prolastin-C liquid formulation added.	07.16.18	
1Q 2019 annual review: per 2018 GOLD and 2003 ATS guidelines, corrected FEV_1 range to include 65% without requiring demonstration of rapid decline in lung function in FEV_1 of > 100 mL/year; references reviewed and updated.	10.30.18	02.19
No significant changes: new 4g and 5g formulations for Zemaira added.	04.30.19	
1Q 2020 annual review: no significant changes; references reviewed and updated.	11.26.19	02.20
Added requirement that member is not an active smoker as supported by both ATS and COPD Foundation AAT guidelines.	04.14.20	05.20
1Q 2021 annual review: no significant changes; references reviewed and updated.	10.20.20	02.21

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.