Washington State Health Care Authority

Respiratory Agents – MISC :
Alpha-Proteinase Inhibitor (Human)

Medical policy no. 45.10.00.00 Effective Date: July 1, 2019

Background:

Deficiency of alpha1-proteinase inhibitor (A1-PI), also known as alpha1-antitrypsin deficiency, is characterized by reduced levels of A1-PI in the blood and lungs. A1-PI deficiency is an autosomal, co-dominant, hereditary disorder. Patients with severe A1-PI deficiency have increased levels of neutrophil and neutrophil elastase levels in lung epithelial lining fluid that results in destruction of the connective tissue framework of the lung parenchyma. A1-PI (human) therapy augments the level of the deficient protein and theoretically corrects the imbalance between neutrophil elastase and protease inhibitors, which may protect the lower respiratory tract.

Medical necessity:

Drug	Medical Necessity
Zemaira Aralast Glassia Prolastin-C	Treatment of an FDA approved indication for augmentation and maintenance therapy of patients 18 years of age or older with severe hereditary deficiency of alpha1-antitrypsin (AAT) with clinical evidence of emphysema

Clinical policy:

Clinical Criteria (Initial Approval)

Alpha-1-proteinase inhibitors (human) may be considered medically necessary when **ALL** of the following are met:

1. An FDA approved indication for augmentation and maintenance therapy of patients 18 years of age or older with severe hereditary deficiency of alpha1-antitrypsin (AAT) with clinical evidence of emphysema;
2. Diagnosis confirmed by ALL of the following:
    a. Genetic confirmation of PiZZ, PiZ(null), or Pi(null, null) phenotype alpha1-antitrypsin deficiency (AATD) or other alleles determined to increase risk of AATD;
    b. **ONE** of the following lab values testing for ATT:
        i. test levels of AAT: less than 11 µmol/L;
        ii. immunoturbidimetry: less than or equal to 57 mg/dL
        iii. nephelometry: less than or equal to 57 mg/dL;
        iv. radial immunodiffusion: less than or equal to 80 mg/dL;
    c. Documented emphysema with airflow obstruction;
3. Prescriber must document that member's forced expiratory volume in one second (FEV1) is less than or equal to 65% predicted;
4. The prescriber must verify that patient is a non-smoker or initiating smoking cessation;
5. The prescriber must verify the patient does not have antibodies to IgA;
6. The diagnosis was established by, or in consultation with, a specialist in pulmonology;
7. The patient's recent weight must be provided in order to authorize the appropriate amount of drug required according to package labeling;

a. Dose limit: 60 mg/kg every week

If ALL criteria are met, the request will be approved for 6 months

Criteria (Reauthorization)

Alpha-1-proteinase inhibitors (human) may be considered for reauthorization when **ALL** of the following are met:

1. Documentation of a positive clinical response from pretreatment baseline to alpha1-proteinase inhibitor treatment;
2. The prescriber must verify that patient is a non-smoker or initiating smoking cessation;
3. The patient's recent weight must be provided in order to authorize the appropriate amount of drug required according to package labeling;
    a. Dose limit: 60 mg/kg every week

If ALL criteria are met, the request will be approved for 12 months

Preferred therapies:

Drug Name	Preferred For:
Zemaira **Aralast** **Glassia** **Prolastin-C**	Treatment of an FDA approved indication for augmentation and maintenance therapy of patients 18 years of age or older with severe hereditary deficiency of alpha1-antitrypsin (AAT) with clinical evidence of emphysema

Dosage and quantity limits:

Drug Name	Dose and Quantity Limits
Zemaira **Aralast** **Glassia** **Prolastin-C**	60 mg/kg weekly

Coding:

HCPCS Code	Description
J0257	Injection, alpha 1 proteinase inhibitor – (human), 10 mg [Glassia]
J0256	Injection, alpha 1 - proteinase inhibitor - (human), not otherwise specified, 10 mg [Aralast NP, Prolastin-C, Zemaira]
ICD-10 codes	**Description**
E88.01	Alpha-1-antitrypsin deficiency

Table:

Product	Aralast NP	Glassia	Prolastin-C	Zemaira
Dosage form	powder for solution	premixed solution	powder for solution	powder for solution
Concentration	1 gm/50 mL	1 gm/50 mL	1 gm/20 mL	1 gm/20 mL
Rate of infusion (mL/kg/minute)	0.08	0.04	0.08	0.08
Usual infusion time	30-40 minutes	60-80 minutes	15 minutes	15 minutes
Stability after mixing	3 hours	Premixed	3 hours	3 hours

Evidence review:

Several randomized, controlled trials have established the safety and efficacy of AAT augmentation to treat certain patients with AATD. Chapman et al. published a meta-analysis in 2009 which demonstrated slower FEV1 decline rate in patients treated with AAT therapy in 5 trials (13.4 mL/year absolute difference; CI 1.5-25.3 mL/year). Patients with moderate lung obstruction, defined as baseline FEV1 value between 30 and 65% of predicted, were observed to have a significantly greater benefit in FEV1 rate decline compared to the overall group (17.9 mL/year absolute difference; CI 9.6-26.1 mL/year). The meta-analysis showed similar trends in patient groups with mild and severe obstruction, however these results were not statistically significant.

Patients with severe ATTD that were treated with alpha 1 proteinase inhibitor demonstrated slower emphysema progression compared to patients treated with placebo in the initial RAPID-RCT trial published by McElvaney et al. in 2015. This trial was extended with an open-label extension period (RAPID-OLE) in 2017 to test the long-term treatment effects. Patients were divided into the early-start group (treatment group during RAPID-RCT) and the delayed-start group (placebo group during RAPID-RCT). The rate of lung density loss was lower in the early-start group (-1.51 g/L per year at total lung capacity; SE 0.25) than the delayed-start group (-2.26 g/L per year at total lung capacity; SE 0.26) between day one and month 24. The rate of lung density loss was lower in the delayed-start patients (-2.26 g/L per year to -1.26 g/L per year) from month 24 to month 48. During this time period, there was no significant difference in the rate in the early-start group. Overall, these results demonstrate the importance of starting treatment early as the lung density lost is never recovered. The sustainability of the treatment effect was also shown in the early-start group that continued to have a low lung density loss rate after 4 years of treatment.

References:

1. Sandhaus RA. Alpha 1-antitrypsin augmentation therapy. Agents Actions Suppl. 1993;42:97-102.
2. Miravitlles M, Vidal R, Torrella M, et al. Evaluation of replacement therapy in emphysema caused by alpha 1-antitrypsin deficiency. Arch Bronconeumol. 1994;30(10):479-484.
3. MacDonald JL, Johnson CE. Pathophysiology and treatment of alpha 1-antitrypsin deficiency. Am J Health Syst Pharm. 1995;52(5):481-489.
4. Schwaiblmair M, Vogelmeier C, Fruhmann G. Long-term augmentation therapy in twenty patients with severe alpha-1-antitrypsin deficiency -- three-year follow-up. Respiration. 1997;64(1):10-15.
5. Canadian Thoracic Society. Current status of alpha-1-antitrypsin replacement therapy: Recommendation for the management of patients with severe hereditary deficiency. Ad Hoc Committee on alpha-1-antitrypsin replacement therapy of the Standards Committee, Canadian Thoracic Society. CMAJ. 1992;146(6):841-844.
6. Stoller JK. Augmentation therapy for severe alpha 1-antitrypsin deficiency: Is the jury still out on a trial? Thorax. 1998;53(12):1007-1009.
7. Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. Am J Respir Crit Care Med. 1998;158(1):49-59.
8. Schwaiblmair M, Vogelmeier C. Alpha 1-antitrypsin. Hope on the horizon for emphysema sufferers? Drugs Aging. 1998;12(6):429-440.
9. World Health Organization (WHO). Alpha-1-antitrypsin deficiency: Memorandum from a WHO meeting. Bull World Health Organ. 1997;75(5):397-415.
10. Seersholm N, Wencker M, Banik N, et al. Does alpha1-antitrypsin augmentation therapy slow the annual decline in FEV1 in patients with severe hereditary alpha1-antitrypsin deficiency? Wissenschaftliche Arbeitsgemeinschaft zur Therapie von Lungenerkrankungen (WATL) alpha1-AT study group. Eur Respir J. 1997;10(10):2260-2263.
11. Hutchison DC, Hughes MD. Alpha-1-antitrypsin replacement therapy: Will its efficacy ever be proved? Eur Respir J. 1997;10(10):2191-2193.
12. Pierce JA. Alpha1-antitrypsin augmentation therapy. Chest. 1997;112(4):872-874.

13. Coakley RJ, Taggart C, O'Neill S, et al. Alpha1-antitrypsin deficiency: Biological answers to clinical questions. Am J Med Sci. 2001;321(1):33-41.
14. Alpha Therapeutic Corporation. Alpha1-Proteinase Inhibitor (Human). Aralast. Product Information. 08-8127-01. Westlake Village, CA: Baxter Healthcare Corporation; revised January 2003.
15. Aventis Behring LLC. Zemaira. Alpha1-Proteinase Inhibitor (Human). Prescribing Information. 19131-01. Kankakee, IL: Aventis; July 2003.
16. Bayer Corporation Pharmaceutical Division. Prolastin. Alpha1-Proteinase Inhibitor (Human). Package Insert. 14-7601-001. Elkhart, IN: Bayer; revised January 2002.
17. U.S. Pharmacopeial Convention. USP DI Volume I: Drug Information for the Healthcare Professional. Greenwood Village, CO: Micromedex, Inc.; 2003.
18. Parfrey H, Mahadeva R, Lomas DA. Alpha(1)-antitrypsin deficiency, liver disease and emphysema. Int J Biochem Cell Biol. 2003;35(7):1009-1014.
19. Shah P, Ohlsson A. Alpha-1 proteinase inhibitor (a1PI) for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev. 2001;(3):CD002775.
20. Juvelekian GS, Stoller JK. Augmentation therapy for alpha(1)-antitrypsin deficiency. Drugs. 2004;64(16):1743-1756.
21. Abboud RT, Ford GT, Chapman KR. Emphysema in alpha1-antitrypsin deficiency: Does replacement therapy affect outcome? Treat Respir Med. 2005;4(1):1-8.
22. No authors listed. What is the pathophysiology, epidemiology and treatment of alpha-1 antitrypsin deficiency? What tests are required to make the diagnosis? ATTRACT Database. Gwent, Wales, UK: National Health Service; December 18, 2002. Available at:http://www.attract.wales.nhs.uk/question_answers.cfm?question_id=1066. Accessed February 15, 2006.
23. Kerstiens H, Postma D, ten Hacken N. Chronic obstructive pulmonary disease. In: Clincial Evidence. London, UK: BMJ Publishing Group; March 2005.
24. Stocks JM, Brantly M, Pollock D, et al. Multi-center study: The biochemical efficacy, safety and tolerability of a new alpha1-proteinase inhibitor, Zemaira. COPD. 2006;3(1):17-23.
25. Chen S, Farahati F, Marciniuk D, et al. Human a1-proteinase inhibitor for patients with a1-antitrypsin deficiency. Technology Report No. 74. Ottawa, ON: Canadian Agency for Drugs and Technologies in Health (CADTH); 2007.
26. Mordwinkin NM, Louie SG. Aralast: An alpha 1-protease inhibitor for the treatment of alpha-antitrypsin deficiency. Expert Opin Pharmacother. 2007;8(15):2609-2614.
27. Köhnlein T, Welte T. Alpha-1 antitrypsin deficiency: Pathogenesis, clinical presentation, diagnosis, and treatment. Am J Med. 2008;121(1):3-9.
28. Kalsheker NA. alpha1-Antitrypsin deficiency: Best clinical practice. J Clin Pathol. 2009;62(10):865-869.
29. Chapman KR, Stockley RA, Dawkins C, et al. Augmentation therapy for alpha1 antitrypsin deficiency: A meta-analysis. J Chronic Obstruct Pulm Dis. 2009;6(3):177-184.
30. U.S. Food and Drug Administration (FDA). Glassia -- Approval letter. Silver Spring, MD; FDA; July 1, 2010. Available at: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ ApprovedProducts/LicensedProductsBLAs/FractionatedPlasma Products/ucm217888.htm. Accessed July 19, 2010.
31. Kamada, Ltd. Glassia (alpha1-proteinase inhibitor [human]) injection for subcutaneous use. Prescribing Information. Beit Kama, Israel; Kamada; 2010.
32. National Collaborating Centre for Chronic Conditions. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004;59 Suppl 1:1-232 (Reviewed March 2008).
33. Work Loss Data Institute. COPD - Chronic obstructive pulmonary disease. In: Pulmonary (acute & chronic). San Diego, CA: Work Loss Data Institute; 2009.

34. University of Michigan Health System. Chronic obstructive pulmonary disease. Ann Arbor, MI: University of Michigan Health System; May 2010.
35. Gotzsche PC, Johansen HK. Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease. Cochrane Database Syst Rev. 2010;(7):CD007851.
36. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Vancouver, WA: Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2011.
37. Guo S, Booten SL, Watt A, et al. Using antisense technology to develop a novel therapy for α-1 antitrypsin deficient (AATD) liver disease and to model AATD lung disease. Rare Dis. 2014;2:e28511.
38. Wozniak J, Wandtke T, Kopinski P, Chorostowska-Wynimko J. Challenges and prospects for alpha-1 antitrypsin deficiency gene therapy. Hum Gene Ther. 2015;26(11):709-718.
39. Franciosi AN, McCarthy C, McElvaney NG. The efficacy and safety of inhaled human α-1 antitrypsin in people with α-1 antitrypsin deficiency-related emphysema. Expert Rev Respir Med. 2015;9(2):143-151.
40. Gaggar A, Chen J, Chmiel JF, et al. Inhaled alpha1-proteinase inhibitor therapy in patients with cystic fibrosis. J Cyst Fibros. 2016;15(2):227-233.
41. Griese M, Scheuch G. Delivery of alpha-1 antitrypsin to airways. Ann Am Thorac Soc. 2016;13 Suppl 4:S346-S351.
42. Chiuchiolo MJ, Crystal RG. Gene therapy for alpha-1 antitrypsin deficiency lung disease. Ann Am Thorac Soc. 2016;13 Suppl 4:S352-S369.
43. McElvaney NG, Burdon J, Holmes M, et al; RAPID Extension Trial Group. Long-term efficacy and safety of α1 proteinase inhibitor treatment for emphysema caused by severe α1 antitrypsin deficiency: An open-label extension trial (RAPID-OLE). Lancet Respir Med. 2017;5(1):51-60.

History

Date	Action and Summary of Changes
05.03.2019	New Policy