Alpha-1 Proteinase Inhibitors Medical Drug Criteria Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
06-30-2025

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Aralast® NP (alpha1-proteinase inhibitor [human]) Intravenous injection	Chronic augmentation therapy in adults with clinically evident emphysema due to severe congenital deficiency of alpha1-proteinase inhibitor (Alpha1-PI)		1
Glassia® (alpha1-proteinase inhibitor [human]) Intravenous injection	Chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe hereditary deficiency of alpha1-proteinase inhibitor (Alpha1-PI), also known as alpha1-antritrypsin deficiency		2
Prolastin-C® (alpha1-proteinase inhibitor [human]) Intravenous injection	Chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe deficiency of alpha1-proteinase inhibitor (Alpha1-PI)		3
Zemaira® (alpha1-proteinase inhibitor [human]) Intravenous injection	Chronic augmentation and maintenance therapy in adults with alpha1-proteinase inhibitor (Alpha1-PI) deficiency and clinical evidence of emphysema		4

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Alpha1-Antitrypsin Deficiency	Alpha1-antitrypsin (AAT) is a protein produced mainly in the liver which protects the lungs from proteolytic damage by neutrophil elastase. AAT is highly expressed by hepatocytes and the protein is excreted into the blood. By inhibiting neutrophil elastase and other proteases, the host tissue is protected from injury associated with episodes of inflammation. Deficiency of this enzyme leads to a genetic disorder called alpha1-antitrypsin deficiency (AATD) and can confer risk of early onset emphysema and liver disease.(5,10,11) Literature suggests this genetic disorder is under-recognized and affects approximately 1 in 2,000 to 1 in 5,000 people.(5,10) There are numerous genetic variants. Patients homozygous for the Z allele (ZZ or PIZZ) are most commonly associated with AATD.(5,6) Symptomatic disease varies by patient; some may show symptoms in childhood whereas others may remain asymptomatic until late adulthood. Signs and symptoms of liver dysfunction may be seen in as many as 50% of ZZ children; however, cirrhosis and life-threatening disease only occur in about 5% before age 18. Emphysema associated with AATD takes years to develop and is therefore not seen in children. Adults with AATD may have normal liver enzymes with no symptoms of liver disease or may present with advanced cirrhosis or hepatocellular carcinoma.(6,7) Testing is recommended in patients with liver disease of unknown etiology as well as those diagnosed with chronic obstructive pulmonary disease (COPD) who are less than 65 years of age or with a smoking history of less than 20 pack years, or those who are adherent and do not respond to maximal medical COPD therapy.(6,7,8,9,10,11) Diagnosis is confirmed by demonstrating a serum AAT level less than 11 micromol/L (approximately 57 mg/dL using nephelometry, and 80 mg/dL by radial immunodiffusion), which is considered a "protective threshold" above which the risk of emphysema is believed to decrease.(5,7,10) Genotyping of the protease inhibitor (Pi) locus can detect the normal M allele and the most common known pathogenic variants (e.g., F, I, S, Z).(10) Literature recommends patients with COPD due to AATD be treated with the same therapy as other COPD patients, including smoking cessation, preventive vaccinations, bronchodilators, supplemental oxygen, and pulmonary rehabilitation.(5,8,10,11) Augmentation therapy is recommended in nonsmoking or ex-smoking patients with COPD attributable to emphysema and documented AAT deficiency, who are receiving optimal pharmacological and nonpharmacological therapies.(7,10) Since the purpose of augmentation therapy is to preserve lung function and structure, it seems logical to reserve such expensive therapy for those with evidence of continued and rapid progression following smoking cessation.(8,9) Evidence of conferred benefit is stronger for patients with moderate airflow obstruction (e.g., FEV1 35-60% predicted) than for those with severe airflow obstruction.(8,10) Augmentation therapy is not recommended for patients without emphysema, and benefits in patients with severe (e.g., FEV1 less than or equal to 35% predicted) or mild (e.g., FEV1 greater than or equal to 50-60% predicted) airflow obstruction are less clear.(10) Patients with normal or nearly normal pulmonary function can be treated if they experience a rapid decline in lung function (e.g., decrease in FEV1 greater than 120 mL/year).(8,10,11) Intravenous augmentation therapy is not recommended for individuals with MZ genotype of AATD, individuals with AATD who continue to smoke, individuals with AATD and emphysema or bronchiectasis who do not have airflow obstruction, the treatment of liver disease due to AATD, or individuals who have undergone liver transplantation.(11)
Efficacy	In the National Heart, Lung, and Blood Institute (NHLBI) Registry of Individuals with Severe Deficiency of AAT, 1,129 subjects with severe deficiency of AAT (serum levels less than 11 micromol) were registered. They were monitored for 3.5 to 7 years. The 5-year mortality rate was 19%. In a multivariate analysis, the mortality rate was lower in those receiving augmentation therapy as compared with those not receiving therapy (OR, 0.79; p=0.02). The mean FEV1 decline was 54 ml/year and there was no overall

	difference between those receiving augmentation therapy and nonrecipients. However, among those in the subgroup with moderate emphysema (i.e., American Thoracic Society Stage II emphysema with FEV1 35–49% predicted), the rate of FEV1 decline was significantly slower in subjects receiving augmentation therapy (p=0.03). These two observational studies suggest that progression of emphysema may be slowed in patients with moderate emphysema (FEV1 31–65% predicted). Moreover, mortality may be decreased in patients with a lower FEV1.(10) In the RAPID randomized trial, the rates of change of CT lung density were compared between 93 patients receiving weekly AAT augmentation (also called A1PI) therapy and 87 placebo recipients. The rate of loss of lung density among A1PI recipients tended to be lower on the coprimary endpoint of CT density assessed at functional residual capacity (FRC) and at total lung capacity (TLC) and achieved significance on the density measured at TLC. No differences were observed between the compared groups regarding change in FEV1 or diffusing capacity for carbon monoxide (DLCO), scores on the St George's Respiratory Questionnaire, or exacerbation frequency.(9)
Safety	Alpha 1-proteinase inhibitor agents are all contraindicated in IgA deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity.(1,2,3,4) The effect of augmentation therapy, with any alpha 1-proteinase inhibitor agent, on pulmonary exacerbations and on the progression of emphysema in alpha1-antitrypsin deficiency has not been conclusively demonstrated in randomized, controlled clinical trials. Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy are not available. Alpha 1-proteinase inhibitor augmentation therapy is not indicated as therapy for lung disease in patients in whom severe congenital AAT deficiency has not been established.(1,2,3,4)

REFERENCES

Number	Reference
1	Aralast NP prescribing information. Baxalta Inc. March 2023.
2	Glassia prescribing information. Takeda Pharmaceuticals USA, Inc. September 2023.
3	Prolastin-C prescribing information. Grifols Therapeutics LLC. May 2020.
4	Zemaira prescribing information. CSL Behring LLC. January 2024.
5	Stoller NK, Aboussouan LS. A review of alpha1-antitrypsin deficiency. Am J Respir Crit Care Med. 2012;185(3):246-259.
6	Nelson D, Teckman J, Di Bisceglie A, Brenner DA. Diagnosis and management of patients with alpha1-antitrypsin (A1AT) deficiency. Clin Gastroenterol Hepatol. 2012 Jun;10(6):575-580.
7	Marciniuk DD, Hernandez P, Balter M, et al. Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: A Canadian Thoracic Society clinical practice guideline. Can Respir J. 2012;19(2):109-116.
8	Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2024. Available at: http://www.goldcopd.org.
9	Miravitlles M, Dirksen A, Ferrarotti I, et al. European Respiratory Society statement: Diagnosis and treatment of pulmonary disease in alpha-1 antitrypsin deficiency. Eur Respir J. 2017;50:1-24.
10	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;168:818-900.
11	Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. Chronic Obstr Pulm Dis. 2016;3(3):668-682.

POLICY AGENT SUMMARY – MEDICAL PRIOR AUTHORIZATION

HCPC Codes	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
		alpha-1-proteinase inhibitor (human)	1000 MG	M ; N ; O ; Y	N		
J0256	Aralast np	alpha-1-proteinase inhibitor (human)	500 MG	M ; N ; O ; Y	N		
J0256	Aralast np	alpha-1-proteinase inhibitor (human)	1000 MG	M ; N ; O ; Y	N		
J0257	Glassia	alpha	4 GM/200ML	M ; N ; O ; Y	N		
J0257	Glassia	alpha	5 GM/250ML	M ; N ; O ; Y	N		
J0257	Glassia	alpha-1-proteinase inhibitor (human)	1000 MG/50ML	M ; N ; O ; Y	N		
J0256	Prolastin-c	alpha-1-proteinase inhibitor (human)	1000 MG/20ML	M ; N ; O ; Y	N		
J0256	Zemaira	alpha-1-proteinase inhibitor (human)	1000 MG	M ; N ; O ; Y	N		
J0256	Zemaira	alpha-1-proteinase inhibitor (human)	4000 MG	M ; N ; O ; Y	N		
J0256	Zemaira	alpha-1-proteinase inhibitor (human)	5000 MG	M ; N ; O ; Y	N		

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
	alpha-1-proteinase inhibitor (human)	1000 MG	Commercial ; HIM ; ResultsRx
Aralast np	alpha-1-proteinase inhibitor (human)	1000 MG	Commercial ; HIM ; ResultsRx
Aralast np	alpha-1-proteinase inhibitor (human)	500 MG	Commercial ; HIM ; ResultsRx
Glassia	alpha	4 GM/200ML	Commercial ; HIM ; ResultsRx
Glassia	alpha	5 GM/250ML	Commercial ; HIM ; ResultsRx
Glassia	alpha-1-proteinase inhibitor (human)	1000 MG/50ML	Commercial ; HIM ; ResultsRx
Prolastin-c	alpha-1-proteinase inhibitor (human)	1000 MG/20ML	Commercial ; HIM ; ResultsRx
Zemaira	alpha-1-proteinase inhibitor (human)	5000 MG	Commercial ; HIM ; ResultsRx
Zemaira	alpha-1-proteinase inhibitor (human)	4000 MG	Commercial ; HIM ; ResultsRx
Zemaira	alpha-1-proteinase inhibitor (human)	1000 MG	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of alpha-1 antitrypsin deficiency (AATD) with clinically evident emphysema **AND** 2. If the patient has an FDA labeled indication, then ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient has a pre-treatment serum alpha-1 antitrypsin (AAT) level less than 11 micromol/L (80 mg/dL by radial immunodiffusion or 57 mg/dL using nephelometry) (medical records required) **AND** 4. The patient does NOT have PI*MZ genotype **AND** 5. The patient is currently on and will continue optimal conventional treatment for COPD (e.g., bronchodilators, preventive vaccinations, supplemental oxygen when indicated, pulmonary rehabilitation) **AND** 6. ONE of the following: A. The patient has a baseline (prior to therapy for the requested indication) FEV1 of 65% or less of predicted (medical records required) **OR** B. The patient has experienced a rapid decline in lung function (e.g., change in FEV1 greater than 120 mL/year) (medical records required) **AND** 7. ONE of the following: A. The patient is a non-smoker **OR** B. The patient is participating in a smoking cessation program **AND** 8. The prescriber is a specialist in the area of the patient's diagnosis (e.g., pulmonologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 9. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 10. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Medical Drug Review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. ONE of the following: A. The patient is a non-smoker **OR** B. The patient is participating in a smoking cessation program **AND** 4. The patient is currently on and will continue optimal conventional treatment for COPD (e.g., bronchodilators, preventive vaccinations, supplemental oxygen when indicated, pulmonary rehabilitation) **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., pulmonologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

