Alpha-1-Proteinase Inhibitors (Aralast NP, Glassia, Prolastin-C, Zemaira)

Policy Number: MC/PC 003
Effective Date: April 1, 2026

Table of Contents **Page**

Coverage Rationale 1
Applicable Codes 2
Background 2
Clinical Evidence 2
U.S. Food and Drug Administration 4
References 5
Policy History/Revision Information 5
Instructions for Use 5

Related Policies

- N/A

Coverage Rationale

Alpha-1 proteinase inhibitor deficiency

For initial coverage of Aralast NP, Glassia, Prolastin-C, or Zemaira for Alpha-1 proteinase inhibitor deficiency (also known as alpha-1 antitrypsin (AAT) deficiency), the following will be required:

- Diagnosis of congenital alpha-1 antitrypsin (AAT) deficiency **and**
- Diagnosis of emphysema **and**
- One of the following:
  - Pi*ZZ, Pi*Z(null) or Pi*(null)(null) protein genotypes (homozygous) **or**
  - Other rare AAT disease genotypes associated with pre-treatment serum alpha-1-antitrypsin (AAT) level less than 11 micromole per liter [e.g., Pi(Malton, Malton), Pi(SZ)] **and**
- One of the following:
  - Circulating pre-treatment serum alpha-1-antitrypsin (AAT) level less than 11 micromole per liter (which corresponds to less than 80 mg/dL if measured by radial immunodiffusion or less than 57 mg/dL if measured by nephelometry) **or**
  - Patient has a concomitant diagnosis of necrotizing panniculitis **and**
- Continued optimal conventional treatment for emphysema (e.g., bronchodilators) **and**
- One of the following:
  - The FEV1 level is less than or equal to 65% of predicted **or**
  - Patient has experienced a rapid decline in lung function (i.e., reduction of FEV1 more than 120 mL/year) that warrants treatment **or**
  - Patient has a concomitant diagnosis of necrotizing panniculitis **and**
- Patient is NOT a current smoker

For reauthorization coverage of Aralast NP, Glassia, Prolastin-C, or Zemaira for Alpha-1 proteinase inhibitor deficiency, the following will be required:

- Patient demonstrates positive clinical response to therapy **and**
- Continued optimal conventional treatment for emphysema (e.g., bronchodilators)

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0256	Injection, alpha 1-proteinase inhibitor, human, 10 mg, not otherwise specified
J0257	Injection, alpha 1-proteinase inhibitor (human), (Glassia), 10 mg

ICD-10 Code	Description
E88.01	Alpha-1-antitrypsin deficiency

Background

Alpha-1 antitrypsin (AAT) deficiency is an autosomal, co-dominant, hereditary disorder that affects the lungs, liver, and skin. This deficiency leads to increased levels of neutrophil and neutrophil elastase levels in lung epithelial lining fluid, which causes lung damage leading to chronic obstructive pulmonary disease. The current approach to treatment is alpha 1-proteinase inhibitors, which augments the level of the deficient protein and corrects the imbalance between neutrophil elastase and protease inhibitors (Stoller et al 2026).

Clinical Evidence

A total of 23 subjects with the PiZZ variant and documented emphysema were studied in a single-arm, open-label clinical trial with PROLASTIN (Prolastin Product Information 2022). Nineteen of the subjects received PROLASTIN, 60 mg/kg, once weekly for up to 26 weeks (average 24 weeks). Blood levels of $Alpha_1$ -PI were maintained above 11 µM. Bronchoalveolar lavage studies demonstrated statistically significant increased levels of $Alpha_1$ -PI and functional anti-NE capacity (ANEC) in the epithelial lining fluid of the lower respiratory tract of the lung, as compared to levels prior to dosing.

A clinical trial (Aralast Product Information 2025) (ARALAST versus PROLASTIN trial) was conducted to compare ARALAST to a commercially available preparation of Alpha -PI (PROLASTIN) in 28 subjects with congenital $Alpha_1$ -PI deficiency and emphysema, who had not received $Alpha_1$ -PI augmentation therapy within the preceding six months. Subjects were randomized to receive either ARALAST or PROLASTIN, 60 mg/kg intravenously per week for 10 consecutive weeks. Following their first 10 weekly infusions, the subjects who were receiving PROLASTIN were switched to ARALAST while those who already were receiving ARALAST continued to receive it. Following weekly augmentation therapy with ARALAST or PROLASTIN, a gradual increase in peak and trough serum $Alpha_1$ -PI levels was noted, with stabilization after several weeks. The metabolic half-life of ARALAST was 5.9 days. Serum ANEC trough levels rose substantially in all subjects by Week 2, and by Week 3, serum ANEC trough levels exceeded 11 microM in the majority of subjects. With few exceptions, levels in both treatment groups remained above this level in individual subjects for the duration of the period Weeks 3 through 24. Although only five of fourteen subjects (35.7%) receiving ARALAST had bronchoalveolar lavages (BALs) meeting acceptance criteria for analysis at both baseline and Week 7, a statistically significant increase in the antigenic level of $Alpha_1$ -PI in epithelial lining fluid (ELF) was observed. No statistically significant increase in the ANEC in the ELF was detected. It was concluded that at a dose of 60 mg/kg administered intravenously once weekly,

ARALAST and PROLASTIN had similar effects in maintaining target serum Alpha$_1$ -PI trough levels and increasing antigenic levels of Alpha$_1$ -PI in the ELF with maintenance augmentation therapy.

Clinical trials were conducted pre-licensure with ZEMAIRA in 89 subjects (59 males and 30 females) (ZEMAIRA Product Information 2024). The subjects ranged in age from 29 to 68 years (median age 49 years). Ninety-seven percent of the treated subjects had the PiZZ phenotype of A_1 -PI deficiency, and 3% had the M phenotype. At screening, serum A_1 -PI levels were between 3.2 and 10.1 µM (mean of 5.6 µM). The objectives of the clinical trials were to demonstrate that ZEMAIRA augments and maintains serum levels of A_1 -PI above 11 µM (80 mg/dL) and increases A_1 -PI levels in ELF of the lower lung. In a double-blind, controlled clinical trial to evaluate the safety and efficacy of ZEMAIRA, 44 subjects were randomized to receive 60 mg/kg of either ZEMAIRA or Prolastin once weekly for 10 weeks. After 10 weeks, subjects in both groups received ZEMAIRA for an additional 14 weeks. Subjects were followed for a total of 24 weeks to complete the safety evaluation. The mean trough serum A_1 -PI levels at steady state (Weeks 7-11) in the ZEMAIRA-treated subjects were statistically equivalent to those in the Prolastin-treated subjects within a range of ±3 µM. Both groups were maintained above 11 µM. The mean (range and standard deviation [SD]) of the steady state trough serum antigenic A_1 -PI level for ZEMAIRA-treated subjects was 17.7 µM (range 13.9 to 23.2, SD 2.5) and for Prolastin-treated subjects was 19.1 µM (range 14.7 to 23.1, SD 2.2). The difference between the ZEMAIRA and the Prolastin groups was not considered clinically significant and may be related to the higher specific activity of ZEMAIRA.

A randomized, double-blind trial (Glassia Product Information 2025) with a partial cross-over was conducted to compare GLASSIA to a commercially available preparation of Alpha$_1$ -PI (Prolastin) in 50 Alpha$_1$ -PI deficient subjects. The trial objectives were to demonstrate that the pharmacokinetics of antigenic and/or functional Alpha$_1$ -PI in GLASSIA were not inferior to those of the control product, to determine whether GLASSIA maintained antigenic and/or functional plasma levels of at least 11 microM (57 mg/dL) and to compare Alpha$_1$ -PI trough levels (antigenic and functional) over 6 infusions. For inclusion in the trial, subjects were required to have lung disease related to Alpha -PI deficiency and 'at-risk' alleles associated with Alpha$_1$ -PI plasma levels < 11 microM. Subjects already receiving Alpha$_1$ -PI therapy were required to undergo a 5-week wash-out period of exogenous Alpha$_1$ -PI prior to dosing. Fifty subjects received either GLASSIA (33 subjects) or the comparator product (17 subjects) at a dose of 60 mg/kg intravenously per week for 12 consecutive weeks. From Week 13 to Week 24 all subjects received open-label weekly infusions of GLASSIA at a dose of 60 mg/kg. Trough levels of functional and antigenic Alpha$_1$ -PI were measured prior to treatment, at baseline and throughout the trial until Week 24. The median trough Alpha$_1$ -PI values for Weeks 7-12 for subjects receiving GLASSIA were 14.5 microM (range: 11.6 to 18.5 microM) for antigenic and 11.8 microM (range: 8.2 to 16.9 microM) for functional Alpha$_1$ -PI. Eleven of 33 subjects (33.3%) receiving GLASSIA had mean steady-state functional Alpha$_1$ -PI levels below 11 microM. GLASSIA was shown to be non-inferior to the comparator product. Serum Alpha$_1$ -PI trough levels rose substantially in all subjects by Week 2 and were comparatively stable during Weeks 7 to 12. All subjects receiving GLASSIA had mean serum trough antigenic Alpha$_1$ -PI levels greater than 11 microM during Weeks 7-12. A subset of subjects in both treatment groups (n = 7 for subjects receiving GLASSIA) underwent bronchoalveolar lavage (BAL) and were shown to have increased levels of antigenic Alpha$_1$ -PI and Alpha$_1$ -PI - neutrophil elastase complexes in the epithelial lining fluid at Week 10-12 over levels found at baseline, demonstrating the ability of the product to reach the lung.

Clinical Guidelines

The 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report on the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease gives recommendations on the management of Alpha-1 antitrypsin deficiency (AATD). (GOLD 2025)

- All patients with a diagnosis of COPD should be screened once for AATD, especially in areas with high AATD prevalence.
- The logical approach to minimize the development and progression of lung disease in AATD patients is alpha-1 antitrypsin augmentation. IV augmentation therapy may slow down the progression of emphysema (Evidence B).

- Observational studies suggest a reduction in spirometric progression in treated versus non-treated patients and that this reduction is most effective for patients with FEV1 35-49% predicted. Never or ex-smokers with an FEV1 of 35-60% predicted have been suggested as those most suitable for AATD augmentation therapy (Evidence B).
- The indication for AAT augmentation is emphysema although there are no fixed criteria for diagnosis or confirmation. The evidence for augmentation therapy efficacy varies according to the outcome studied. Intravenous augmentation therapy has been recommended for individuals with AATD and an FEV1 ≤ 65% predicted based on previous observational studies.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

ARALAST NP is an Alpha -Proteinase Inhibitor (Human) (Alpha$_1$ -PI) indicated for chronic augmentation therapy in adults with clinically evident emphysema due to severe congenital deficiency of Alpha$_1$ -PI (alpha -antitrypsin deficiency). ARALAST NP increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid levels of Alpha -PI.

- The effect of augmentation therapy with any Alpha$_1$ -PI, including ARALAST NP, on pulmonary exacerbations and on the progression of emphysema in Alpha$_1$ -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 of individuals with ARALAST NP or ARALAST are not available.
- ARALAST NP is not indicated as therapy for lung disease in patients in whom severe Alpha$_1$ -PI deficiency has not been established.

GLASSIA is an Alpha$_1$ -Proteinase Inhibitor (Human) (Alpha$_1$ -PI) indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe hereditary deficiency of Alpha$_1$ -PI (alpha -antitrypsin deficiency).

- The effect of augmentation therapy with any Alpha$_1$ -PI, including GLASSIA, on pulmonary exacerbations and on the progression of emphysema in Alpha$_1$ -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 of individuals with GLASSIA are not available.
- GLASSIA is not indicated as therapy for lung disease in patients in whom severe Alpha -PI deficiency has not been established.

PROLASTIN-C is an Alpha$_1$ -Proteinase Inhibitor (Human) (Alpha$_1$ -PI) indicated for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe hereditary deficiency of Alpha$_1$ -PI (alpha$_1$ -antitrypsin deficiency). PROLASTIN-C increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid levels of Alpha$_1$ -PI.

- The effect of augmentation therapy with any Alpha$_1$ -PI, including PROLASTIN-C, 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 or maintenance therapy with PROLASTIN-C are not available.
- PROLASTIN-C is not indicated as therapy for lung disease in patients in whom severe Alpha$_1$ -PI deficiency has not been established.

ZEMAIRA is an alpha$_1$ -proteinase inhibitor (Alpha$_1$ -PI) indicated for chronic augmentation and maintenance therapy in adults with A$_1$ -PI deficiency and clinical evidence of emphysema.

- The effect of augmentation therapy with ZEMAIRA or any A_1 -PI product on pulmonary exacerbations and on the progression of emphysema in A_1 -PI deficiency has not been demonstrated in randomized, controlled clinical studies.
- ZEMAIRA is not indicated as therapy for lung disease patients in whom severe A_1 -PI deficiency has not been established.

References

1. Aralast NP Prescribing Information. Takeda Pharmaceuticals USA Inc. Cambridge, MA. May 2025.
2. Glassia Prescribing Information. Baxalta US Inc. Lexington, MA. February 2025.
3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2025 report. https://goldcopd.org/2025-gold-report/ Accessed January 20, 2026.
4. Prolastin-C Prescribing Information. Grifols Therapeutics, Inc. Research Triangle Park, NC. January 2022
5. Stoller JK et al. Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency. UpToDate. Last updated: February 2, 2026. Accessed February 23, 2026.
6. Zemaira Prescribing Information. CSL Behring LLC. Kankakee, IL. January 2024.

Policy History/Revision Information

Date	Summary of Changes
12/13/2023	Approved by OptumRx P&T Committee
3/20/2024	Annual Review. Updated references only.
3/19/2025	Annual Review. Updated references.
3/18/2026	Annual Review. Updated background section and references.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).

70021 07-24 ©2024 Aspirus Health Plan, Inc. All rights reserved.