**Prior Authorization Policy**

**Subject:**

alpha₁-proteinase inhibitors infusions (Prolastin® – Talecris Biotherapeutics, Prolastin®-C – Talecris Biotherapeutics, Aralast NP™ - Baxter, and Zemaira™ - Aventis Behring, Glassia® - Baxter)

**Date Revised:**

10/19/2011; selected revision 6/13/2012

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**Overview**

Alpha₁-proteinase inhibitor (also known as alpha₁-antitrypsin [AAT]), is approved by the Food and Drug Administration (FDA) for use as a chronic replacement or augmentation therapy for individuals with a congenital deficiency of AAT with clinically demonstrable emphysema.¹⁻³ In the scientific literature, the disorder is referred to as AAT deficiency whereas the deficiency or replacement protein is referred to as alpha₁-proteinase inhibitor. Five products are available commercially in the United States: Prolastin, Prolastin-C, Aralast NP, Zemaira, and Glassia.¹⁻³,³⁶⁻³⁷,⁴⁰ The products vary in their availability and in some of their purification and viral inactivation processes.¹⁻³,³⁶⁻³⁷ Prolastin was approved by the FDA in 1987 and is prepared from pooled human plasma and undergoes pasteurization (60°C for 10 hours) to reduce transmission of viral agents.¹ Aralast NP was modified from Aralast, which was approved by the FDA in 2002. Aralast-NP contains significantly less truncated C-terminal lysine (removal of LYS394) compared with Aralast (2% vs. 67%).²,⁴⁰ Studies have shown Aralast to have bioequivalence to Prolastin.²,⁶ In a study involving 28 patients with congenital alpha₁-antitrypsin deficiency who were given both agents at a dose of 60 mg/kg intravenously (IV) once per week, similar effects in maintaining target serum AAT levels and increasing antigenic levels of AAT were achieved. Aralast NP is also derived from pooled human plasma and to reduce the risk of viral transmission, the manufacturing process utilizes treatment with a solvent detergent and nanofiltration. Zemaira was approved by the FDA in 2003 and is also prepared from pooled human plasma. Viral reduction steps used in the manufacturing process for Zemaira include pasteurization (60°C for 10 hours) and ultrafiltration.³ A study of 44 patients with congenital AAT deficiency compared 60 mg/kg IV of Zemaira to the same dose of Prolastin once per week.³⁷ No clinically significant differences were seen in serum AAT levels or antigenic AAT levels between the two treatments. Prolastin-C was approved in 2009.³⁶ Prolastin-C has improved product purity and has higher concentrations of alpha₁-proteinase inhibitor when reconstituted compared with Prolastin. Studies have shown Prolastin-C to be pharmacokinetically equivalent to Prolastin.³⁶ Glassia, approved in 2010, is the only product available as a solution; it does not require reconstitution.³⁷ Studies have shown Glassia to be similar to Prolastin.

Clinical and biochemical studies have established that with use of these products, target serum alpha₁-proteinase inhibitor trough levels are maintained and increased levels of alpha₁-proteinase inhibitor are noted in the epithelial lining fluid. The product labeling for Prolastin cites more specific recommendations such as only patients with evidence of disease should be considered for chronic replacement therapy. The product labeling for all preparations notes that the safety and effectiveness in pediatric patients have not been established and that the therapy is not indicated for lung disease patients in whom congenital alpha₁-antitrypsin inhibitor deficiency has not been established.¹⁻³ AAT deficiency is a rare, chronic, hereditary, autosomal, co-dominant disorder marked by low concentrations of AAT which leads to progressive, severe emphysema that often does not manifest until the third to fourth decades of life.¹ AAT deficiency is more common in populations of European ancestry and the estimated prevalence is one case per 3,000 to 5,000 persons in the US.⁸ Liver disease is also

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associated with AAT deficiency and occurs in approximately 10%, predominantly children.9 The natural history of AAT deficiency in adulthood is not fully understood. The diagnosis of AAT deficiency generally occurs after a diagnosis of chronic obstructive pulmonary disease (COPD) or liver disease, or after deficiency has been diagnosed in a family member. Many patients may not have substantial impairment. Cigarette smoking greatly increases and accelerates the risk of COPD in patients, especially those with the Z protein phenotype. A large number of phenotypic variants exist, which have different clinical consequences.1,10,38 This disease is most severe in those with null phenotypes (with no detectable circulating AAT in the plasma) or the PiZZ variant (AAT levels typically < 35% of normal).1,10 The S phenotypes have plasma levels about 60% of normal whereas the M phenotypes are generally characterized by normal plasma AAT levels.10 The goal of treatment is to increase lung AAT levels to provide adequate anti-elastase activity to protect the lung. Epidemiological studies have demonstrated that individuals with endogenous serum levels of AAT ≤ 50 mg/dL have approximately a much greater risk for developing emphysema over a typical lifespan.9 Individuals who maintain endogenous serum AAT levels > 80 mg/dL do not appear to have an increased risk for developing emphysema compared with the general population. From these observations, AAT levels < 80 mg/dL (< 11 µM) was determined to be the serum concentration necessary to provide adequate anti-elastase activity.9,10 The ranges of serum levels of AAT according to phenotype are shown in Table 1.10

Table 1. Range of Serum Levels* of AAT According to Phenotype.10

<table>
<thead>
<tr>
<th>Units</th>
<th>PiMM</th>
<th>PiMZ</th>
<th>PiSS</th>
<th>PiSZ</th>
<th>PiZZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum levels in mg/dL</td>
<td>150-350 mg/dL</td>
<td>90-210 mg/dL</td>
<td>100-200 mg/dL</td>
<td>75-120 mg/dL</td>
<td>20-45 mg/dL</td>
</tr>
<tr>
<td>Serum levels in µM</td>
<td>20-48 µM</td>
<td>17-33 µM</td>
<td>15-33 µM</td>
<td>8-16µM</td>
<td>2.5-7 µM</td>
</tr>
</tbody>
</table>

* Serum levels are measured using a typical commercial standard (mg/dL) and the purified standard (µM) used in the U.S Registry. A level of less than 11 µM is associated with an increased emphysema risk. AAT = alpha1-antitrypsin.

Alpha1-proteinase inhibitor is the only treatment approved to correct AAT deficiency. The FDA-approved dosage regimen to achieve adequate concentrations in the lung is 60 mg/kg of body weight administered IV once weekly. However, other dosage regimens with prolonged intervals, including once-monthly administration, have been utilized in an attempt to enhance patient convenience.1,2,11,14,40 Due to the limitations of performing randomized, double-blind clinical trials (e.g., expense of the study drug, limited patient population, slow progression of the disease), the majority of the published literature evaluating this agent’s efficacy consists of observational cohort studies.10,15-17,41-43 Subjects (n = 1,129) with AAT levels ≤ 11 µM (80 mg/dL) or a PiZZ phenotype were followed longitudinally for 3.5 to 7 years.10,11 Those who received alpha1-proteinase inhibitor therapy had decreased mortality (risk ratio = 0.64; 95% CI: 0.43, 0.94; P = 0.02) compared with matched controls not receiving therapy. Patients with a mean forced expiratory volume in 1 second (FEV1) of 35% to 49% of predicted experienced a slower decline in lung function (P = 0.03). Another analysis revealed that for patients with the phenotype PiZZ or AAT deficiency, alpha1-proteinase inhibitor administered once weekly slowed the annual decline in FEV1 for those with moderately reduced lung function.18 An uncontrolled prospective study (n = 20) involving primarily patients of the PiZZ phenotype found that treatment with alpha1-proteinase inhibitor once weekly for up to 36 months resulted in a reduced annual loss of FEV1 compared with historically untreated similar patients.16 Data also suggests that AAT replacement therapy might reduce emphysema progression in some subsets of patients with AAT deficiency, although further study is needed.19 A 2009 meta-analysis of five randomized and non-randomized studies (n = 1,509) support that augmentation with alpha1-proteinase inhibitor can slow lung function decline in those with AAT deficiency and moderate pulmonary impairment.43 However, a 2010 meta-analysis that only included the two randomized controlled trials (total n = 140) failed to show the beneficial effects of AAT augmentation therapy compared with placebo.44 A third on-going randomized controlled trial plans to address the question of mortality as a secondary endpoint.45
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Although not FDA-approved, alpha_1-proteinase inhibitor therapy has been utilized for AAT-associated panniculitis, a rare complication characterized by erythematous nodules and plaques located on subcutaneous (skin) tissue in wide areas of the lower extremities, arms, trunk, and/or face.\textsuperscript{20-28,39} The literature mainly documents case reports.\textsuperscript{20-28} In the American Thoracic Society (ATS) and the European Respiratory Society (ERS) standards for the diagnosis and management of individuals with AAT deficiency (updated in 2003), it is stated that AAT replacement therapy is a reasonable option for AAT deficiency-associated panniculitis.\textsuperscript{10}

**POLICY STATEMENT**

Prior authorization is recommended for prescription benefit coverage of alpha_1-proteinase inhibitor.

**RECOMMENDED AUTHORIZATION CRITERIA**

Coverage of alpha_1-proteinase inhibitor (Prolastin, Prolastin-C, Aralast NP, Zemaira, Glassia) is recommended for those who meet the following criteria.

**FDA-Approved Indications**

1. **Alpha_1-antitrypsin deficiency with emphysema (or COPD).** Approve in patients with baseline (pretreatment) AAT serum concentration < 80 mg/dL or 11 \(\mu\)M (11 \(\mu\)mol/L). These products are FDA-approved for chronic augmentation and maintenance therapy of individuals having congenital deficiency of alpha_1-proteinase inhibitor (AAT deficiency) with clinically demonstrable panacinar emphysema.\textsuperscript{1-3} Patients with endogenous levels < 80 mg/dL (or 11 \(\mu\)M) have been noted to have an increased risk for the development of emphysema.\textsuperscript{1} Maintenance of AAT levels > 80 mg/dL (> 11 \(\mu\)M) was determined to be the serum concentration necessary to provide adequate anti-elastase activity per epidemiologic studies for most patients with AAT deficiency.\textsuperscript{1,8-10}

2. **AAT deficiency-associated panniculitis.** Approve.

Many case reports are available for the treatment of this rare complication.\textsuperscript{20-28} The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency state the panniculitis is an uncommon but well-recognized complication of AAT deficiency.\textsuperscript{10} Although no controlled trials provide a clear treatment recommendation, augmentation therapy with purified human AAT or fresh frozen plasma to restore plasma and local tissue levels of AAT appears rational, safe, and effective.

**EXCLUSIONS**

Coverage of alpha_1-proteinase inhibitor is not recommended in the following circumstances.

1. **Cystic fibrosis.** The use of alpha_1-proteinase inhibitor is considered investigational due to the lack of literature available regarding use of the agent for this disease state and many studies utilized an investigational aerosolized AAT delivery mechanism.\textsuperscript{29-33}
2. **Chronic obstructive pulmonary disease (COPD) without alpha₁-antitrypsin deficiency.** The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines\(^{34}\) for the diagnosis management and prevention of COPD, updated in 2010, state that young patients with severe hereditary AAT deficiency and established emphysema may be candidates for AAT augmentation therapy. However, this therapy is very expensive, is not available in most countries, and is not recommended for COPD that is unrelated to AAT deficiency.\(^{34}\)

3. **Alpha₁-antitrypsin deficiency without lung disease, even if deficiency-induced hepatic disease is present.** The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency (2003) states that the pathophysiology of liver disease in AAT deficiency is different from that of lung disease and the use of alpha₁-proteinase inhibitor for these patients is not discussed.\(^{10}\) There is an absence of information that suggests that alpha₁-proteinase inhibitor is useful in patients with AAT deficiency-related liver disease.

4. **Bronchiectasis (without alpha₁-antitrypsin deficiency).** Studies have not demonstrated alpha₁ proteinase inhibitor to be effective for this condition. The ATS/ERS standards for the diagnosis and management of individuals with AAT deficiency (2003) states that despite the well recognized association between AAT deficiency and the early development of emphysema, only a limited number of studies have assessed the association between AAT deficiency and bronchiectasis.\(^{10}\) Studies suggest that bronchiectasis is more a result of emphysematous changes in the parenchyma than of AAT deficiency.

5. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

**REFERENCES**

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OTHER REFERENCES UTILIZED


HISTORY

Evaluation completed by Express Scripts, Inc. on March 10, 1995.
Updated by Express Scripts, Inc./Value Rx, Inc. on May 4, 1999.
Reviewed and approved by Express Scripts, Inc. Clinical Criteria Committee on April 24, 2000; May 1, 2001.
Reviewed by Express Scripts Therapeutic Assessment Committee (TAC): April 3, 2002.
Selected revision to add Aralast to the policy on June 12, 2003.
Selected revision to remove case-by-case exceptions on 06/13/2012.