National PBM Drug Monograph
Alpha$_1$-Proteinase Inhibitor Human (Zemaira®)
VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

INTRODUCTION
Zemaira was approved in July 2003 and is the third alpha$_1$-proteinase inhibitor (A_1-PI) to enter the market. Prolastin has been available since 1989 and Aralast was approved in December 2002.

A_1-PI is indicated for chronic augmentation and maintenance therapy in individuals with alpha$_1$-proteinase inhibitor deficiency (also referred to as alpha$_1$-antitrypsin deficiency) and clinical evidence of emphysema. Alpha$_1$-proteinase inhibitor deficiency is an autosomal, co-dominant, hereditary disorder characterized by low serum and lung levels of A_1-PI. There are many genetic variants of A_1-PI deficiency, only some of which result in very low levels of A_1-PI. The more severe types are the PiZZ, PiZ(null) and Pi(null)(null) phenotypes.

Alpha-1 proteinase inhibitor is needed to inhibit neutrophil elastase (NE), which degrades protein components of the alveolar wall. Serum A_1-PI levels less than 11μM (80mg/dL) are associated with the risk of prematurely developing emphysema. It is hoped that increasing A1-PI, via augmentation therapy, will ameliorate the progression of emphysema. Unfortunately, there are no randomized controlled trials definitively showing the clinical efficacy of augmentation therapy with A1-PIs. Currently, outcome data comes from patients enrolled in alpha 1- antitrypsin deficiency registries.

Certain phenotypes are uncommonly associated with development of liver disease or cirrhosis. Replacement with A1-PI is not thought to ameliorate the development of liver disease.

UTILIZATION
Currently, none are listed on the VANF or on the VISN formularies. Table 1 shows VA use of A_1-PI over a 1-year period.

Table 1. A_1-PI use (Q1fy03-q4fy03)

	Total Rxs	Total quantity	30-day Rxs
A_1-PI 1000mg	238	903,745	242
A_1-PI 500mg	50	250	50

PURIFICATION
A_1-PI is derived from pooled human plasma. The product undergoes a viral reduction process, via pasteurization and 2 sequential ultrafiltration steps, to remove and/or inactivate enveloped and non-enveloped viruses. This viral reduction process has been validated using *in vitro* studies with the following viral agents: HIV, HAV, Bovine Viral Diarrhea Virus (BVDV) as model virus for HCV, Canine Parvovirus (CPV) as a model for Parvovirus B19, and Pseudorabies Virus (PRV) as a non-specific model virus.

CLINICAL TRIALS
There are no published clinical trials using Zemaira. The following information was obtained from the product package insert. The FDA transcripts have not been posted to the FDA website. The manufacturer, Aventis Behring was contacted and asked to provide more in depth details of the study. They replied that they were unable to do so.

The following study demonstrates comparability of Zemaira to Prolastin using trough serum alpha-1 proteinase inhibitor levels as the primary outcome of interest. In a randomized, double-blind study, 44 patients with A_1-PI deficiency received Zemaira or Prolastin 60mg/kg once weekly for 10 weeks. After the 10-week period, all patients received Zemaira for 14 weeks. Ninety-seven of patients had the PiZZ phenotype.

Table 2. Trough Serum A_1-PI levels

	Steady state trough serum antigenic A1-PI level at weeks 7-11
Zemaira (n=30)	17.7 ± 2.5μM (13.9 – 23.2)
Prolastin (n=14)	19.1 ± 2.2μM (14.7 – 23.1)

Mean ± SD (range)

A subgroup of 15 patients underwent bronchoalveolar lavage at baseline and week 11. Measurements in epithelial lining fluid (ELF) included antigenic A1-PI, free neutrophil elastase (NE), A1-PI: NE complexes, and functional A1-PI (anti-neutrophil elastase capacity, ANEC). Free neutrophil elastase was immeasurably low in all samples.

Table 3. Epithelial Lining Fluid Analytes

	Zemaira (n=10)	Prolastin (n=5)
Δ A1-PI (nM)	1358.3 [822.6, 1894]	949.9 [460, 1439.7]
Δ A1-PI: NE complexes (nM)	118 [39.9, 196.1]	287.1 [49.8, 524.5]
Δ ANEC (nM)	-588.1 [-2032.3, 856.1]	497.5 [–392.3, 1387.2]
Post-tx ANEC (nM)	1725	1418

Mean [95% CI]

SAFETY

The following adverse events were observed in 1% of patients: asthenia, injection site pain, dizziness, headache, paresthesia, and pruritus.

A retrospective analysis of COPD exacerbation was performed in the clinical trial previously described. There was a 44% difference in exacerbation rate between the 2 products with a wide confidence interval of [95%CI 8%, 70%]. Over the entire 24-week study, which includes the open-label phase (n=30), 7 patients had a total of 11 exacerbations of COPD.

Table 4. COPD exacerbation during 10-week blinded portion of study

	Zemaira	Prolastin
COPD exacerbation (n/%)	6 (20%)	9 (64%)
Total # of COPD exacerbations	7	11

CONTRAINDICATIONS/WARNINGS

A_1-PI is contraindicated in individuals with selective IgA deficiencies who have antibodies against IgA. These patients may experience severe reactions such as anaphylaxis.

Zemaira is contraindicated in individuals with a history of anaphylaxis or severe systemic response to A_1-PI products.

Several measures have been taken to reduce the risk of viral transmission. Despite these measures, the product may still carry the risk of transmitting infectious agents.

DOSAGE AND ADMINISTRATION

The recommended dose is 60mg/kg administered once weekly. At this dose, serum A_1-PI levels are maintained above the target threshold of 11μM. The IV rate of administration is 0.08mL/kg/min as determined by patient comfort. In general, the infusion should take approximately 15 minutes.

Each vial contains approximately 1000mg of functionally active A_1-PI that must be reconstituted with 20ml of sterile water for injection. Several vials may be needed to provide the required dose. Allow product to reach room temperature prior to reconstitution. Once reconstituted, transfer the solution from the vials into an empty IV bag or glass IV bottle. Use within 3 hours of reconstitution.

PRODUCT COMPARISON

All 3 products are available as single-use vials.

	Zemaira	Aralast	Prolastin
Volume of sterile water for injection needed to reconstitute 1000mg	20ml	50ml	40ml
Time needed to infuse product at a rate of 0.08ml/kg/hr	~ 15 minutes	~ 37.5 minutes	~ 30 minutes
Product storage	May be stored up to 77°F and is stable for the period indicated by the expiration date on the label. Avoid freezing	Store at 35-46°F or at temperatures not to exceed 77°F. Once removed from refrigeration, must be used within 1 month. Do not freeze.	Store at 36-46°F or at temperatures not to exceed 77°F. Avoid freezing.
Cost	1000mg- $300/vial	Has not yet been offered 500mg 1000mg	1000mg - $150/vial 500mg - $80/vial

RECOMMENDATION

The recommendation is to not add to the National or the VISN formularies.