



PRODUCT PROFILER

Zemaira[®]

Alpha₁-proteinase inhibitor (Human)

For chronic augmentation and maintenance therapy in individuals with alpha₁-proteinase inhibitor deficiency and clinical evidence of emphysema

Contents

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THE PRODUCT PROFILER

The Product Profiler provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about pharmacology, clinical studies and FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package. Articles are written by experts in the field.

ABOUT THE AUTHORS

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DISCLOSURES

Maxine Losseff and Alan Caspi, PhD, PharmD, MBA, both report that they have no financial arrangements or affiliations that might constitute a conflict of interest with respect to this publication. CSL Behring provided funding for this publication.



PRODUCT PROFILER

Zemaira[®]

Alpha₁-Proteinase Inhibitor (Human)

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Zemaira®

Alpha₁-Proteinase Inhibitor (Human)

INTRODUCTION

This Product Profiler introduces health care professionals to Alpha₁-Proteinase Inhibitor (Human), Zemaira®, a U.S. Food and Drug Administration-approved treatment indicated for chronic augmentation and maintenance therapy in individuals with alpha₁-proteinase inhibitor (alpha₁-PI) deficiency and clinical evidence of emphysema.

Zemaira® is a sterile, stable, lyophilized preparation of highly purified human alpha₁-PI, also known as alpha₁-antitrypsin (AAT), derived from human plasma. Clinical studies have shown Zemaira® to be a safe and effective treatment for alpha₁-PI deficiency when administered once weekly at the recommended dose of 60 mg/kg body weight (CSL Behring 2007).

The following text presents a brief overview of alpha₁-PI deficiency and current treatment options, followed by a review of the evidence-based literature supporting the FDA-approved indication for the administration of alpha₁-proteinase inhibitor (Human).

DISEASE OVERVIEW

Alpha₁ antitrypsin deficiency (AATD) is a relatively common but under-recognized genetic disorder in which the protease inhibitor, AAT, is appropriately produced in the liver but is not secreted into the serum, instead collecting in the endoplasmic reticulum of hepatocytes (ATS 2003, Perlmutter 1996). The main function of AAT circulating in the bloodstream is to protect normal body tissue from damage by nonspecific, neutrophil proteolytic enzymes, particularly neutrophil elastase, an enzyme that can attack lung elastin and compromise bronchial and alveolar wall integrity (ATS 2003, Mahadeva 2005, Ranes 2005). Interference with the protective activity of AAT predisposes patients to the development of lung damage and emphysema and, by its collecting in hepatic cells, liver damage (ATS 2003).

AATD was first described by Dr. Carl-Bertil Laurell and medical student Sten Eriksson at the University of Lund in Sweden when they observed the absence of the AAT protein band in serum electrophoresis gels from a series of samples (Eriksson 1964). Eriksson subsequently noted that three of the five affected patients developed emphysema in their 30s or 40s, including one individual with a family history of chronic obstructive pulmonary disease (COPD) (Eriksson 1964). Since the discovery of neutrophil elastase by Janoff and Schaefer in 1967 and its association with AAT — AAT serves as a protective inhibitor against host tissue degradation by neutrophil proteases — much has been learned about the biologic

role of AAT in healthy lung function, and the genetics and clinical manifestations of AAT deficiency (Janoff 1967, Ranes 2005, Stoller 2005).

AATD has been estimated to affect approximately 80,000 to 100,000 individuals in the United States (Ranes 2005). Although AATD predominantly affects individuals of white European descent, there are reports of cases in nearly all countries and regions of the world, including sub-Saharan Africa, Asia, Australasia, and the Middle East as well as Europe and North America, and it has been observed in all racial and ethnic groups (Rachelefsky 2008, de Serres 2002). About 1% to 4.5% of all cases of emphysema are believed to be related to underlying AATD, and it has been suggested that if all 19.3 million patients with COPD in a hypothetical population were tested, as many as 1.8 million cases of AATD might be identified (ATS 2003, Rachelefsky 2008, de Serres 2006).

Yet even though organizations like the World Health Organization, the American Thoracic Society (ATS), and the European Respiratory Society have tried to increase awareness and promote early detection of AATD, the fact remains that AATD is largely misdiagnosed (ATS 2003, WHO 1997). In 2005, the diagnostic history over nearly four decades of patients enrolled in a not-for-profit health management company that functions to provide disease management services to patients with AATD was evaluated (Campos 2005). The investigators found that nearly two thirds of subjects visited one or two physicians to achieve a correct diagnosis, there was a substantial delay in correct diagnosis among a large portion of subjects, a high mean age at diagnosis, and a long symptomatic interval prior to diagnosis. Furthermore, the proportion of subjects diagnosed by the first or second physician has significantly decreased in recent years while the proportion who needed to see three to four physicians to obtain a diagnosis has increased (Figure 1).

Despite evidence of improved diagnosis of symptomatic AATD in elderly individuals between 1990 and 2003, there either was no change or a small increase in the number of physicians visited and number of symptomatic years among younger patients aged 35 to 54 years (Campos 2005). Thus, the authors concluded that to better manage AATD and reduce the risk for associated lung disease and its complications, health care providers need to increase the use of genetic testing, screen all individuals with obstructive lung diseases, and increase awareness of AATD among patients and clinicians alike.

Still, fewer than 10% of individuals with AATD are diagnosed (Alpha-1 Association 2009). This may be due to the

fact that despite being a disorder determined at birth, AATD symptoms often are absent or do not appear until at least young adulthood or middle age, even among individuals with severe deficiency. In addition, due to the variable phenotypic expression, clinicians may not think of AATD in the patient with respiratory and/or liver disease (Ranes 2005). A large number of individuals with AATD are likely misclassified as having bronchial asthma or smoking-related pulmonary disease (Kohnlein 2008). In fact, a correct diagnosis of AATD has been found to take a mean of seven years from first presentation, and 43% of patients see at least three physicians before diagnosis is made (Stoller 1994). In the same survey, 12% of subjects visited 6 to 10 physicians before reaching the AATD diagnosis.

This failure to improve early and accurate diagnosis is troubling because AATD can be a lethal disease. The yearly mortality from AATD is estimated at 3.5%, predominantly due to emphysema (72%) and cirrhosis of the liver (10%) (AATD Registry Study Group 1998, Larsson 1978). The accumulation of abnormal AAT in hepatocytes can cause cellular congestion, potentially leading to severe liver damage and organ failure (ATS 2003). The absence of AAT in blood and alveoli can result in progressive, severe, and potentially fatal emphysema (Rachelefsky 2008). Furthermore, mortality from respiratory disease has been shown to increase with advancing age, and among individuals with impaired lung function and smokers (AATD Registry Study Group 1998).

The recent availability of augmentation therapy with a replacement alpha₁-PI has proven to be a safe and effective method to increase alpha₁-PI levels, and thereby improve lung function, diminish progression of pulmonary disease, and extend survival in patients with

AATD (Dirksen 2007, Rachelefsky 2008, Stocks 2006, Wencker 2001). Thus, treatment options are broadening and warrant proactive diagnosis aimed at early and optimal intervention. Future efforts, therefore, should focus on ensuring earlier diagnosis of AATD (Rachelefsky 2008). With early diagnosis, individuals with AATD can initiate preventive measures, such as smoking avoidance or limiting exposure to environmental airway irritants, in an effort to reduce the risk of emphysema. It also prompts entry into the health care system so that clinicians can monitor affected individuals to ensure timely recognition of symptoms and use of advanced therapies to prevent disease progression.

Particularly with the advent of effective augmentation therapy, early detection and proactive treatment is the key to improving the quality of life and survival of patients with AATD.

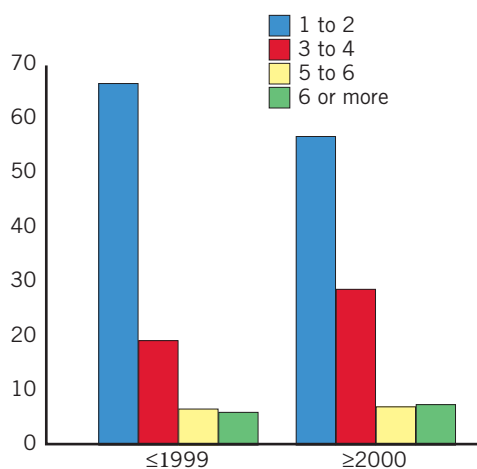
Genetics

AATD is an autosomal codominant disorder affecting the SERPINA1 gene, located on the long arm of chromosome 14 (Stoller 2005). SERPINA1 is highly pleomorphic, and there have been at least 30 genetic variants described that can lead to reduced serum levels of AAT (ATS 2003, Kohnlein 2008). The risk for lung and liver manifestations is determined by the extent of reduced AAT secretion or impaired function associated with the particular genetic defect.

The SERPINA1 alleles are identified by a letter code from A to Z, assigned according to the speed of migration of the molecule on an isoelectric pH gradient: the codes advance from A, which designates a highly anodal variant, to Z, defining variants of slower migration (ATS 2003, DeMeo 2004). The genetic variant is named according to the protein phenotype reflecting the codominant status. The most common allelic form associated with AATD involves the M alleles, and thus the homozygous form is termed PI*MM. PI*MM is considered a “normal variant” because it does not alter serum AAT levels or function (DeMeo 2004).

Disease expression is associated with null variants or deficiency genotypes that, in homozygous or heterozygous mutation combinations, impair AAT secretion and result in serum levels below a theoretical “protective threshold” of 11 μmol/L (ATS 2003). The most frequent mutation causing symptoms of severe AAT deficiency, responsible for an estimated 95% of symptomatic AATD, involves the Z allele (Stoller 2005). The homozygote PI*ZZ, highly prevalent in individuals of northern European heritage, generally is associated with serum concentrations of AAT about 15% of normal and carries significant risk for the development of pulmonary disease (ATS 2003). In comparison, the S variant, frequently associated with individuals of Mediterranean background, yields average serum concentrations 60% of normal among homozygous individuals resulting in a potentially

FIGURE 1
Number of Physicians Seen Before an Accurate Diagnosis of AATD is Made (By Year)



*P<0.05
Source: Campos 2005

less aggressive form of disease (ATS 2003). The null alleles, designated PI QOQO, induce the greatest AAT deficiency, generally producing concentrations <1% of normal (ATS 2003). Other frequent AAT allelic mutant genotypes include PI*SZ, PI*MS, and PI*MZ and all impair AAT secretion to some degree and confer increased risk for AATD-associated respiratory disease (ATS 2003).

In addition, AATD-associated mutant alleles can be classified into four groups defined by the level of serum AAT or functional defect (Stoller 2005). *Normal alleles* yield serum concentrations of approximately 20 to 53 µmol/L (Stoller 2005). *Deficient alleles* are associated with concentrations less than 20 µmol/L, although in some variants like Z, there also may be functional impairment of AAT (Stoller 2005). *Null variants* comprise that group of patients virtually absent of AAT due to transcriptional or translational errors that interfere with synthesis (Stoller 2005). *Dysfunctional alleles* are marked by abnormal function of AAT, leading to reduced binding to target tissue or other impairment of normal AAT activity (Stoller 2005). Table 1 lists the common allelic mutations of the AAT gene and the corresponding disease association.

Pathophysiology

AAT is a member of the *serine* PI (serpin) superfamily of proteins (Lomas 2002). These compounds are key inhibitors of the activity of serine proteases, helping to maintain a desired balance between protease and antipro-

tease activity (Stoller 2005). Kinetic studies have suggested that neutrophil elastase, a 29-kD extracellular endopeptide released from neutrophils during inflammation that destroys antigen and host tissue alike, is the preferential target of AAT (ATS 2003).

AAT is primarily produced in the liver and to a lesser degree in enterocytes and leukocytes, then released into the circulation during infection or inflammation. The function of AAT is to protect against the nonspecific activity of neutrophil elastase — the damage of tissue of the lower respiratory tract that occurs as neutrophil elastase carries out its primary function of fighting infection and inflammation (Stoller 2005). AAT exists in a high-energy, unstable state and, when its docking site, a methionine amino acid side-chain on the reactive center loop of AAT, binds to neutrophil elastase (Figure 2a), it induces a conformational change in the antiprotease (Carrell 2002, Stoller 2005). The cleaved reactive loop with protease in tow snaps back to the alternate pole of the molecule (Figure 2b), which distorts and inactivates the elastase (Huntington 2000, Stoller 2005). Both the protease and antiprotease are destroyed in this process.

The Z mutation of AAT, caused by substitution of lysine for glutamic acid at position 342 of the Z protein, leads to abnormal folding of the molecule that predisposes it to serial linking between reactive loops of nearby AAT molecules, resulting in irreversible polymerization (Stoller 2005). This polymerization of AAT within the hepatocyte impedes its secretion into the circulation, so that in homozygous Z mutant individuals, only about 15% of anti-trypsin reaches the plasma (Lomas 2002, Stoller 2005). As a result of the decrease in AAT in the plasma, the destruction of lung tissue by neutrophil elastase can go unhindered (Janoff 1985, Lomas 2002, Stoller 2005). In the Z mutated phenotype, AAT activity is impaired: it has been shown to be about five times less effective as an inhibitor of neutrophil elastase than is the normal variant, or M form, of the protein (Ogushi 1987, Stoller 2005). Subjects in this state are at risk for accelerated lung breakdown and ultimately emphysema, a risk that can be further heightened in individuals who smoke or experience a lung infection (Stoller 2005).

The S mutation is characterized by substitution of glutamic acid for valine at position 264, a defect that impedes the formation of an integral salt bridge in the AAT molecule, making AAT susceptible to intracellular proteolysis (Ranes 2005). Like polymerized AAT, the degraded AAT is not released into the bloodstream, leading to mild reductions in plasma AAT. In addition, null mutations are due to deletions in the gene portion coding for AAT or to frameshift mutations that block messenger RNA production and impede protein translation (Ranes 2005).

Accumulation of mutated AAT within the endoplasmic reticulum of hepatocytes has been shown on electron microscopy and confirmed with periodic acid-Schiff stain (Stoller 2005). Although accumulation of AAT within the

PI allele	Disease association
Normal alleles M (various subtypes) Xchristchurch	Normal Normal
Deficiency alleles S Z* Mmalton Siyama Mheerlen Mprocida Mmineral springs*	Lung Lung, liver Lung, liver Lung Lung Lung Lung
Null alleles QOgranite falls QOludwigshafen QOhongkong 1 QOisola di procida	Lung Lung, liver Lung Lung
Dysfunctional alleles Pittsburgh Mmineral springs* Z*	Bleeding diathesis Lung Lung, liver
*Note that Mmineral springs and Z have dysfunctional characteristics described based on altered rates of association and inhibition of neutrophil elastase, as well as deficiency characteristics.	
Source: DeMeo 2004	

liver cells can lead to hepatic impairment, there is a wide inter-individual variation in expression of liver disease. Most patients, in fact, will not exhibit hepatic dysfunction, despite clear aggregation of AAT in the liver (Stoller 2005). Those phenotypes associated with uncontrolled intra-hepatic polymerization are responsible for the bulk of AATD-associated liver disease, a condition not driven by the “protective threshold” concept (Ranes 2005). In one clinical trial, the expression of clinical liver damage and cirrhosis was shown specifically to closely correlate with delayed degradation of the ZZ mutated-type protein within the hepatocyte (Stoller 2005, Wu 2002).

Clinical Features

The most frequent clinical outcomes of AATD are lung disease, liver disease, panniculitis, and C-ANCA-positive vasculitis (Ranes 2005).

Lung disease. The most common clinical manifestation of AATD is panacinar emphysema. AATD-associated emphysema often presents with an early onset (fourth or fifth decade of life) and symptoms including dyspnea, cough, phlegm production, asthma-like wheezing with upper respiratory tract infections, and clear evidence of pulmonary obstruction (McElvaney 1997, Ranes 2005). Like patients with AAT-replete COPD, airflow obstruction may be partially reversible, with forced expiratory volume in one second (FEV₁) rising by as much as 12%, or 200 mL, on serial spirometries (Stoller 2005). Unlike AAT-replete disease, radiographic changes are disproportionately confined to the lung bases. In addition, in one series, three or more symptoms of asthma, such as wheezing, bronchodilator responsiveness, atopy, and increased serum IgE, were observed in 22% of patients with AATD, an overlap that can confuse correct diagnosis of AATD (ATS 2003).

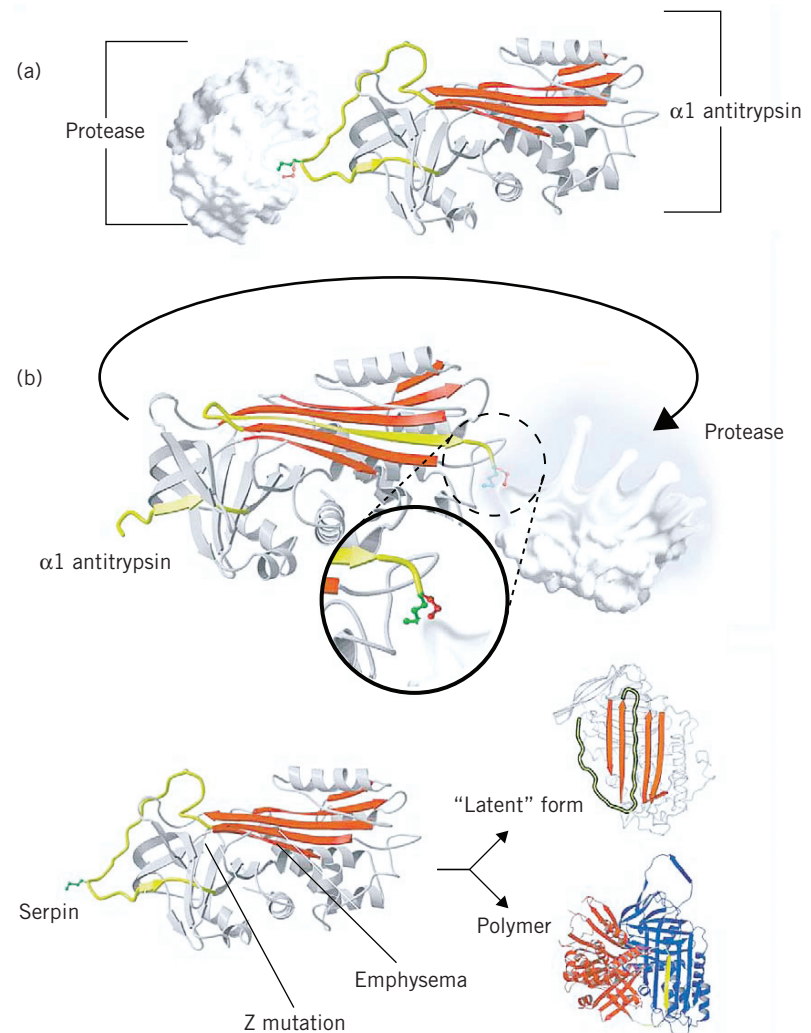
Liver disease. Liver dysfunction affects approximately 10% to 34% of individuals with homozygous Z mutation AATD (Ranes 2005). The expression of clinically significant liver disease is generally confined to phenotypes marked by excessive intra-hepatic polymerization and

rarely occurs in null or dysfunctional allelic forms (Ranes 2005). AATD-related liver disease manifests as hepatitis, cirrhosis, and/or hepatoma (Stoller 2005).

The likelihood of clinically evident liver disease increases with advancing age, and the biochemical and histopathologic findings of AATD, similar to those of alcoholic liver disease, may be confusing (Teckman 2006). The high association of liver disease with the homozygous Z variant of AATD has led to a recommendation by the combined ATS and European Respiratory Society for AATD testing in any case in which active liver disease

FIGURE 2

When neutrophil elastase docks on the reactive center loop of AAT (a), it induces a conformational change in the antiprotease, where the reactive center snaps back to the opposite pole (b). Mutations in AAT can alter this process and lead to biologic impairments consistent with several diseases.



Source: Stoller 2005. Reprinted from: Stoller JK, Aboussouan LS. Alpha1-antitrypsin deficiency. Lancet. 2005;365:2225-2236. Copyright 2005, with permission from Elsevier. With permission from Massachusetts Medical Society.

remains unexplained after thorough evaluation, especially in the elderly (ATS 2003).

Panniculitis. Panniculitis, generally observed as tender, indurated cutaneous nodules on the trunk and proximal extremities, occurs in an estimated 1 in 1,000 individuals with AATD (Stoller 2005). The nodules are believed to result from unopposed proteolysis in the skin, and will drain an oily serosanguinous fluid similar to that seen in cellulitis. This symptom is most common in patients with ZZ, SZ, and SS phenotypes and was additionally reported in one subject with the MS phenotype but normal AAT serum levels (Loche 1999, Stoller 2005). Panniculitis generally responds extremely well to treatment with augmentation therapy, with inflamed skin and pain symptoms resolving rapidly with treatment (Chowdhury 2002, O’Riordan 1997, Stoller 2005).

C-ANCA-positive vasculitis. AATD has reportedly been observed in up to 17% of individuals with Wegener’s granulomatosis, or antiproteinase 3 antibody (C-ANCA)-positive vasculitis (Stoller 2005). Although the exact pathophysiology of this association is unclear the relationship is considered strong and established. Therefore, AATD testing is recommended for all adult patients with C-ANCA-positive vasculitis (ATS 2003).

Diagnosis

Laboratory tests. Evidence of a reduced or absent α 1-globulin band on routine plasma protein electrophoresis should prompt both qualitative and quantitative testing for AATD (ATS 2003). Quantitative measures of AAT can be obtained via rocket immunoelectrophoresis, radial immunodiffusion, or nephelometry, with the threshold protective cut points at 11 μ mol/L, 80 mg/dL, and 50 mg/dL, respectively (ATS 2003). As AAT is an acute phase reactant, it is important to remember that inflammatory conditions may augment AAT levels in Z heterozygotes, warranting reevaluation. Isoelectric focusing — or phenotyping — is the primary method for qualitative testing to identify the variants of AATD disease (e.g., Z or S forms) (ATS 2003). This approach requires specific expertise and therefore in most cases should be outsourced to a reference laboratory (ATS 2003). It also can be supplemented by an immunoblot or immobilized pH gradient IEF gel. Basic molecular diagnosis can be performed with test kits available for S and Z allele mutation identification, but these often overestimate AAT concentration (ATS 2003). More specific genotyping,

however, must be performed in the laboratory. Furthermore, failure to reveal a known mutation on qualitative testing may indicate a new variant rather than a negative test result, and will need to be further evaluated to establish if the subject indeed may have AATD (ATS 2003).

Prenatal genetic testing on samples from amniocentesis or chorionic villus sampling may be called for if there is a history of perinatal liver disease in a previous birth. However, cost often limits use of these techniques (ATS 2003). Postnatal testing when suspicion is high for AATD (e.g., neonatal hepatitis or strong family history) can be rapidly accomplished via DNA amplification using heel blood (ATS 2003).

Lung function tests. Spirometry is the most reliable and reproducible test of pulmonary function and therefore is the principle examination for following subjects with AATD (ATS 2003). Disease-specific indicators to watch for include a reduction in FEV₁ and a normal or reduced forced vital capacity (FVC) (ATS 2003). A reduced FEV₁/FVC ratio indicates impaired pulmonary elasticity secondary to emphysema and airway collapse (ATS 2003). Although the decreased lung volume that results is evident by concavity of the expiratory portion of the flow curve, a concurrent increase in pulmonary compliance leads to air trapping and an increase in residual volume and total lung capacity. This may be associated with elevations on plethysmography compared with traditional measures of indicator gas dilution (ATS 2003).

In addition, single-breath CO-diffusing capacity should be a supplemental measure to determine the overall severity of respiratory impairment, and arterial oxygen tension measures can reveal ventilation-perfusion disturbances (ATS 2003). Additional examinations that might further clarify the extent of physiologic compromise in patients with advanced disease include maximal inspiratory and expiratory mouth pressure (correlating with muscle activity of the thorax and diaphragm) and exercise testing to determine cardiopulmonary status (ATS 2003).

Radiologic evaluations. In advanced disease, X-ray or high-resolution computed tomography (CT) of the chest may be useful to characterize the extent and type of emphysema (ATS 2003). The X-ray can detect suggestive lung lesions or localized bullous disease. CT is a more sensitive diagnostic tool for emphysema than chest x-ray or pulmonary function tests (ATS 2003). In addition, ventilation-perfusion scanning may detect early pulmonary changes consistent with AATD (ATS 2003).

Current Treatment Options

Traditional Interventions

As previously mentioned, traditional treatments for AAT-replete COPD have long been used to manage the symptoms of AATD (Ranes 2005). Established treatments for COPD include bronchodilators, pulmonary rehabilitation, corticosteroids, preventive vaccinations, and oxygen when indicated (Ranes 2005). Patients should be advised that they can exercise to a point that does not challenge their pulmonary capacity (ATS 2003). In addition, all patients with AATD should be advised to avoid cigarette smoke and environmental irritants (ATS 2003).

In patients with signs of liver dysfunction, treatment should be aimed at preventing or delaying serious complications such as bleeding, ascites, pruritus, malnutrition, vitamin deficiencies, infection, and growth inhibition (Teckman 2006). Many patients with AATD liver disease (even some with cirrhosis and/or liver injury) will remain in good health and require conservative management with only periodic monitoring by a liver specialist (Teckman 2006). In the event of worsening liver disease despite aggressive management, liver transplantation has had consistent success (Teckman 2006).

Augmentation Therapy

Pharmacologic options currently are available to correct the deficiency of AAT and thereby minimize the risk of pulmonary sequelae. These augmentation therapies include intravenous (IV) forms of human plasma-derived AAT protein, which is the most direct approach to AAT augmentation (CSL Behring 2007).

There are three purified human alpha₁-proteinase inhibitor products currently approved by the FDA: Zemaira® (CSL Behring), Prolastin® (Talecris BioTherapeutics), and Aralast (Baxter). All of these therapies have been shown in clinical trials to be safe and to increase serum AAT levels above the theoretical threshold value of 11 µmol/L as well as neutralize neutrophil elastase activity, resulting in preservation of lung functional integrity. However, due to high costs and other challenges, randomized controlled data is lacking. The studies completed to date suggest that weekly infusion of human AAT may slow the decline in FEV₁ in patients with moderately reduced lung function and reduce overall mortality (AATD Registry 1998, Dirksen 1999).

Product Information

INDICATIONS AND USAGE

Zemaira® is indicated for chronic augmentation and maintenance therapy in individuals with alpha₁-proteinase inhibitor (A1-PI) deficiency and clinical evidence of emphysema.

Zemaira® increases antigenic and functional (ANEC) serum levels and lung epithelial lining fluid levels of A1-PI.

Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with Zemaira® are not available.

Safety and effectiveness in pediatric patients have not been established.

Zemaira® is not indicated as therapy for lung disease patients in whom severe congenital A1-PI deficiency has not been established.

DESCRIPTION

Zemaira®, Alpha₁-Proteinase Inhibitor (Human), is a sterile, stable, lyophilized preparation of highly purified human alpha₁-proteinase inhibitor (A1-PI), also known as alpha₁-antitrypsin, derived from human plasma. Zemaira® is manufactured from large pools of human plasma by cold ethanol fractionation according to a modified Cohn process followed by additional purification steps. Zemaira® is supplied as a sterile, white, lyophilized powder to be administered by the intravenous route. The specific activity of Zemaira® is ≥0.7 mg of functional A1-PI per milligram of total protein. The purity is ≥90% A1-PI. Following reconstitution with 20 mL of Sterile Water for Injection, USP, each vial contains approximately 1000 mg of functionally active A1-PI, 81 mM sodium, 38 mM chloride, 17 mM phosphate, and 144 mM mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH. Zemaira® contains no preservatives.

Each vial of Zemaira® contains the labeled amount of functionally active A1-PI in milligrams as stated on the vial label as determined by its capacity to neutralize human neutrophil elastase.

All Source Plasma used in the manufacture of this product was tested by FDA-licensed Nucleic Acid Tests (NAT) for HCV and HIV-1 and found to be nonreactive (negative). An investigational NAT for HBV was also performed on all Source Plasma used in the manufacture of this product and found to be nonreactive (negative). The aim of the HBV test is to detect low levels of viral material, how-

ever, the significance of a nonreactive (negative) result has not been established.

Two viral reduction steps are employed in the manufacture of Zemaira®: pasteurization at 60°C for 10 hours in an aqueous solution with stabilizers and two sequential ultrafiltration steps. These viral reduction steps have been validated in a series of *in vitro* experiments for their capacity to inactivate/remove a wide range of viruses of diverse physicochemical characteristics including: Human Immunodeficiency Virus (HIV), Hepatitis A Virus (HAV), and the following model viruses: Bovine Viral Diarrhea Virus (BVDV) as a model virus for HCV, Canine Parvovirus (CPV) as a model virus for Parvovirus B19, and Pseudorabies Virus (PRV) as a nonspecific model virus for large DNA viruses, e.g. herpes. Total mean log₁₀ reductions range from 6.8 to >12.2 log₁₀ as shown in Table 2.

CLINICAL PHARMACOLOGY

Alpha₁-proteinase inhibitor (A₁-PI) deficiency is a chronic, hereditary, autosomal, co-dominant disorder that is usually fatal in its severe form. Low blood levels of A₁-PI are most commonly associated with progressive, severe emphysema that becomes clinically apparent by the third to fourth decade of life. However, an unknown percentage of individuals with severe A₁-PI deficiency apparently never develop clinically evident emphysema during their lifetimes.

A recent registry study showed 54% of A₁-PI deficient subjects had emphysema. Another registry study showed 72% of A₁-PI deficient subjects had pulmonary symptoms.

Smoking is an important risk factor for the development of emphysema in patients with A₁-PI deficiency. Less commonly, low blood levels of A₁-PI are associated with liver disease and liver cirrhosis.

Approximately 100 genetic variants of A₁-PI deficiency can be identified electrophoretically, only some of which are associated with the clinical disease. Ninety-five percent of A₁-PI deficient individuals are of the severe PiZZ phenotype. Up to 39% of A₁-PI deficient patients may have an asthmatic component to their lung disease, as evidenced by symptoms and/or bronchial hyperreactivity. Pulmonary infections, including pneumonia and acute bronchitis, are common in A₁-PI deficient patients and contribute significantly to the morbidity of the disease.

The most direct approach to therapy for A₁-PI deficiency in patients with emphysema has been to partially replace the missing protease inhibitor by IV infusion and, thus, attempt to ameliorate the imbalance in the anti-neutrophil elastase protection of the lower respiratory tract. Individuals with endogenous levels of A1-PI below 11 μM,

TABLE 2
Mean (cumulative) virus reduction factors

	Mean Reduction Factor Pasteurization [\log_{10}]	Mean Reduction Factor Two Ultrafiltration Steps [\log_{10}]	Cumulative Reduction Factor [\log_{10}]
HIV-1	≥ 6.7	≥ 5.5	≥ 12.2
BVDV	≥ 5.9	5.1	≥ 11.0
PRV	4.3	≥ 6.9	≥ 11.2
HAV	≥ 5.4	≥ 6.3	≥ 11.7
CPV	(0.9)	6.8	6.8

in general, manifest a significantly increased risk for development of emphysema above the general population background risk. Therefore, the maintenance of blood serum levels of A₁-PI (antigenically measured) above 11 μ M is historically thought to provide therapeutically relevant antineutrophil elastase protection. However, the hypothesis that maintaining a serum level of antigenic A₁-PI will restore protease-antiprotease balance and prevent further lung damage has never been tested in an adequately-powered controlled clinical trial.

Mechanism of Action

Pulmonary disease, particularly emphysema, is the most frequent manifestation of A₁-PI deficiency. The pathogenesis of emphysema is understood to evolve as described in the “protease-antiprotease imbalance”

model. A₁-PI is now understood to be the primary antiprotease in the lower respiratory tract, where it inhibits neutrophil elastase (NE). Normal healthy individuals produce sufficient A₁-PI to control the NE produced by activated neutrophils and are thus able to prevent inappropriate proteolysis of lung tissue by NE.

Conditions that increase neutrophil accumulation and activation in the lung, such as respiratory infection and smoking, will in turn increase levels of NE.

However, individuals who are severely deficient in endogenous A₁-PI are unable to maintain an appropriate antiprotease defense and are thereby subject to more rapid proteolysis of the alveolar walls leading to chronic lung disease. Zemaira® serves as A₁-PI augmentation therapy in this patient population, acting to increase and maintain serum levels and lung epithelial lining fluid (ELF) levels of A₁-PI.

In 18 subjects treated with a single dose (60 mg/kg) of Zemaira®, the mean area under the curve (AUC) and standard deviation (SD) were 144 μ M \times day (SD 27), maximum serum concentration was 44.1 μ M (SD 10.8), clearance was 603 mL per day (SD 129), and terminal half-life was 5.1 days (SD 2.4). Weekly repeated infusions of A₁-PI at a dose of 60 mg/kg lead to serum A₁-PI levels above the historical target threshold of 11 μ M.

Clinical Trials

A number of trials have established the natural history of AATD and indicated a role for AAT augmentation therapy in mitigating symptoms of the disease. In addition to the registry of the Alpha-1-Antitrypsin Deficiency study group, which followed the natural history of untreated and treated AATD, other trials have established the safety and efficacy of AAT replacement therapy in restoring serum levels of AAT, preserving lung integrity and function, reducing the incidence of lung infections, and prolonging survival in subjects with AATD. Additionally, Zemaira® proved equally effective at increasing serum AAT when compared to another human AAT.

Survival and FEV₁ Decline in Individuals with Severe Deficiency of Alpha₁-Antitrypsin

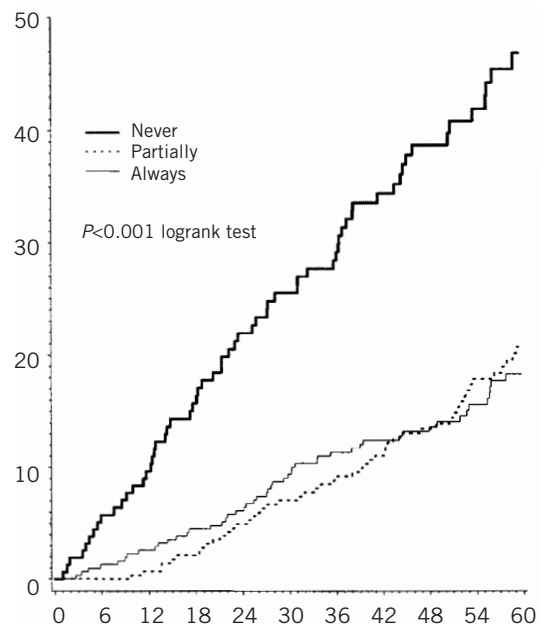
The Registry of Patients with Severe Deficiency of Alpha₁-AT is a compilation of data collected by the National Heart, Lung and Blood Institute. Using registry subjects, this study attempted to establish for the first time that achieving desirable serum AAT protease levels by augmentation therapy correlates with improved lung function and increased survival (AATD Registry 1998). The Registry Study Group followed 1,129 subjects aged 18 or older with AAT levels $\geq 11 \mu\text{M}$ or a PI*ZZ genotype with spirometry measures every 6 to 12 months for a period of 3.5 to 7 years and assessed survival using Kaplan-Meier, log-rank test, and Cox's proportional hazards regression methods. Augmentation therapy was assigned at the discretion of the managing physicians. Subjects were classified as always (continuous), partly (initiated >3 months after enrollment or discontinued for >1 month), or never receiving augmentation therapy. Only subjects contacted ≥ 6 months after enrollment were considered in the survival analysis and those undergoing two or more FEV₁ measures ≥ 1 year apart were included in the lung function analysis.

Results. Overall mortality at 3 and 5 years after enrollment was $10.5 \pm 0.9\%$ and $18.6 \pm 1.3\%$, respectively, and could be clearly correlated to the baseline lung function and the presence of augmentation therapy. For instance, mortality was significantly higher among subjects with initial FEV₁ $<50\%$ predicted who were never treated in comparison to those who were partly or always treated ($P \leq 0.001$; Figure 3); however, there was no difference in mortality rates between treatment groups in patients with baseline FEV₁ $\geq 50\%$ predicted.

Although the overall rate of decline in FEV₁ did not differ between augmentation groups, there was a clear benefit in slowed rate of decline among the subgroup of subjects with a baseline FEV₁ of 35% to 49% predicted who

received augmentation therapy compared with those who did not. The mean difference of 27 mL/year was statistically significant ($P=0.03$). These results suggest a significant benefit for augmentation when delivered to patients with moderately impaired lung function (i.e., FEV₁ values of 35% to 49% predicted). The nonrandomized design of this analysis, however, leaves open the possibility that other uncontrolled factors that contributed to some degree to the study outcome. Thus, the findings of this study should be confirmed in a randomized controlled trial.

FIGURE 3
Kaplan-Meier Plot of Cumulative Mortality From Time of Enrollment for Subjects With FEV₁ $<50\%$ Predicted: Always, Partly, and Never Receiving Augmentation Therapy



Source: AATD Registry 1998. Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. 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. Official Journal of the American Thoracic Society. Diane Gern, Publisher.

A Randomized Clinical Trial of Alpha₁-Antitrypsin Augmentation Therapy

Based on the theory that restoring the balance between neutrophil elastase and its inhibitor AAT could prevent the progression of emphysema, investigators in Denmark and Holland treated 56 ex-smokers (n=26 and n=30, respectively) with documented AATD PI*ZZ type and moderate emphysema with either AAT (250 mg/kg) or placebo (albumin 625 mg/kg) in a randomized, parallel, double-blind, placebo-controlled trial (Dirksen 1999). Patients were stratified by age, baseline FEV₁, and nationality before being randomized to one of the two treatment groups. Infusions continued at 4-week intervals for at least 3 years. Patients underwent pulmonary function testing in a respiratory laboratory every 3 months and self-administered spirometry testing twice daily. Annual CT examinations were performed to yield lung density histograms quantified to the 15th percentile point, the level found to show the strongest time trend.

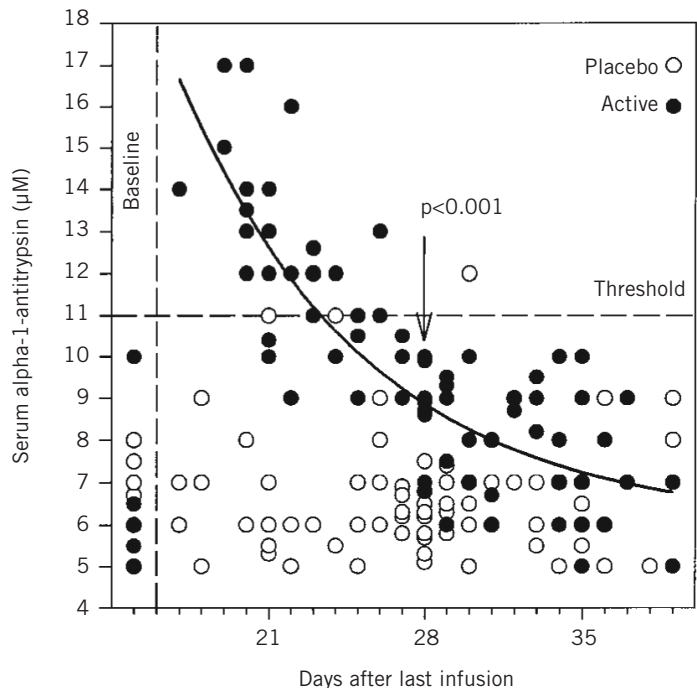
Results. Treatment with AAT augmentation significantly increased serum levels of the antiprotease compared with placebo, raising them above the protective threshold of 11 μM for an average of 23 to 24 days after the infusion as shown in Figure 4.

Although the primary endpoint of change in FEV₁ did not differ between the two treatment groups, the investigators estimated that a population of 550 would be needed to reveal a 50% reduction in annual decline of FEV₁. Additionally, it is important to note that this trial employed an administration regimen with longer than usual periods between infusions — 4 weeks rather than one week as recommended at most institutions. The CT histograms for lung density distributions suggested that, in this setting, the increased anti-neutrophil elastase activity associated with AAT augmentation significantly reduced the annual loss of lung tissue by 1.07 g/L (P=0.07). Lung densities correlated well with microscopically detected emphysema. Thus, these data suggest that CT is more than twice as sensitive as pulmonary function testing for determining progression of emphysema (CT: 6.3 vs. FEV₁: 2.7). This trial revealed a significant protection against the loss of lung tissue associated with raising serum AAT levels above the protective threshold.

Augmentation Therapy Reduces Frequency of Lung Infections in Antitrypsin Deficiency

Previous studies have established the efficacy of augmentation therapy in increasing serum levels of AAT, with

FIGURE 4
Serum Levels of Alpha₁-Antitrypsin Significantly Increased (P<0.001) During Active Treatment With Augmentation Therapy (Closed Circles) Compared With Placebo (Open Circles)



This beneficial change was associated with some protection against loss of lung tissue on CT lung density measurements in the former versus latter group.

Source: Dirksen 1999. Reprinted with permission of the American Thoracic Society. Copyright © American Thoracic Society. Dirksen A, Dijkman JH, Madsen F, et al. A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. *Am J Respir Crit Care Med.* 1999;160(5 Pt 1):1468-1472. Official Journal of the American Thoracic Society. Diane Gern, Publisher.

the goal of protecting the lung from destruction by unchecked neutrophil elastase activity (AATD 1998, Dirksen 1999). Participants in an Internet group for AATD patients subsequently observed that they also experienced fewer and less severe respiratory infections once they had started augmentation therapy. It was thus hypothesized that, based on evidence that AAT has immunosuppressive activity, antiprotease have antibiotic efficacy, and AAT increases during infection or inflammatory states, that alpha₁-PI augmentation might reduce the risk of lung infection during therapy. Using a questionnaire administered to both treated (1 to 10 years) and untreated AATD patients with the PI*ZZ genotype (n=96) recruited through an international Internet support group, the study gathered information on the frequency and number of respiratory infections, as well as patient perception of therapy benefit (Lieberman 2000).

Results. Among 96 subjects on augmentation therapy

with PI*ZZ who filled out and submitted questionnaires, 54 received weekly infusions, 35 received biweekly infusions, and 7 received monthly infusions. Seven patients were excluded from analysis because they were treated for less than 1 year. Eighty-nine treated patients were evaluated, and 74 reported definite benefit associated with AAT augmentation therapy. Twelve did not know if they benefited and 3 reported no benefit. Specifically, 56 of 74 subjects claiming benefit from therapy noted a reduction in the number of lung infections while on therapy. Before starting therapy, the majority of AATD sufferers reported 3 to 5 infections annually, whereas on therapy the number fell to 0 to 1 infection per year ($P<0.001$; Figure 5).

The number of patients with 0 or 1 infection per year rose with therapy from 27 to 73, and the percentage with two or more infections per year fell from 64.6% to 18% ($P<0.001$). In contrast, the number of respiratory infections reported by 47 untreated patients was consistent with the incidence in the treated group prior to initiation of AAT therapy. These findings are compelling because a reduction in the number and severity of lung infections may not only improve patient comfort and quality of life, but also may diminish the release of neutrophil elastase, which in turn might slow progression of emphysema.

Multi-Center Study: The Biochemical Efficacy, Safety and Tolerability of a New Alpha₁-Proteinase Inhibitor, Zemaira®

Zemaira® is a highly purified, lyophilized alpha₁-PI approved for use in the treatment of AATD. For nearly two decades the only available treatment to raise serum levels of AAT was another human-derived AAT product (Prolastin®, Talecris BioTherapeutics, Inc.). Because Zemaira® undergoes a different purification process, the Blood Products Advisory Committee of the FDA recommended a double-blind, randomized, controlled clinical trial comparing the two products to establish whether the different processes altered the purity, isoform composition, and/or non-therapeutic protein content of Zemaira® (Stocks 2006). This study enrolled 44 subjects aged 18 to 70 years with AATD (serum alpha₁-PI level $<11\mu\text{M}$ and PI*ZZ, Z null, or null null genotypes, clinical evidence of emphysema by CT scan, and either x-ray evidence, $\text{FEV}_1 \leq 80\%$ predicted, or evidence of substantial pulmonary function decline). Subjects were randomly assigned in a 2:1 ratio to weekly infusion of either Zemaira® or Prolastin® at a dose of 60 mg/kg for 10 weeks of double-blind therapy, after which all were crossed over to open-label treatment with Zemaira®. Bronchoalveolar lavage was performed at baseline and 7 ± 1 day after final blinded infusion in 15 subjects with $\text{FEV}_1 \geq 50\%$ to determine alpha₁-PI levels in the ELF. The primary study objectives were to demonstrate the bioequivalence of steady-state trough serum AAT levels between the two agents

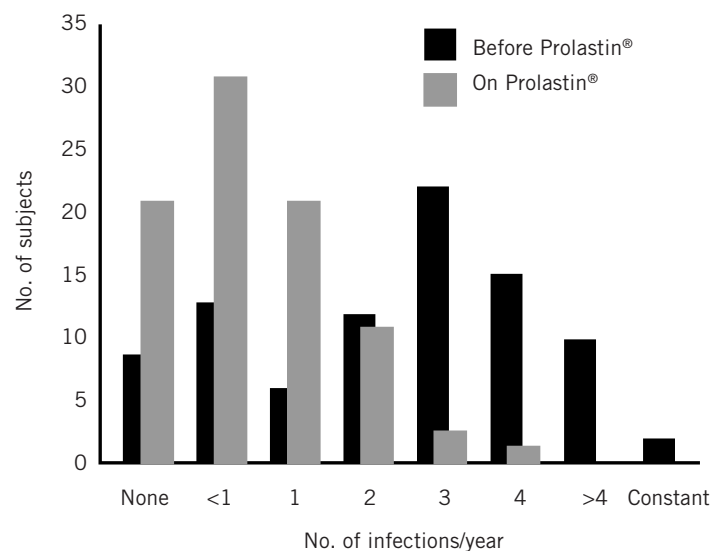
and maintenance of such levels above the protective threshold of 11 μM . Secondary objectives included establishment of the safety and tolerability of both drugs and confirmation of increase in AAT in the ELF of the lower lung.

Results. Bioequivalence in serum trough levels of alpha₁-PI after Zemaira® and Prolastin® administration was established in this trial. The two groups fell within 3 μM , with the lower limit of the 90% confidence interval at $-2.77\mu\text{M}$. Furthermore, the mean serum trough level of Zemaira® remained above the protective threshold at 17.7 μM from weeks 7 to 11 (Figure 6).

In the 15 samples of bronchoalveolar tissue, ELF levels of alpha₁-PI also were equivalent in the two treatment groups, and both achieved a statistically significant increase over baseline values at week 11 (Table 3).

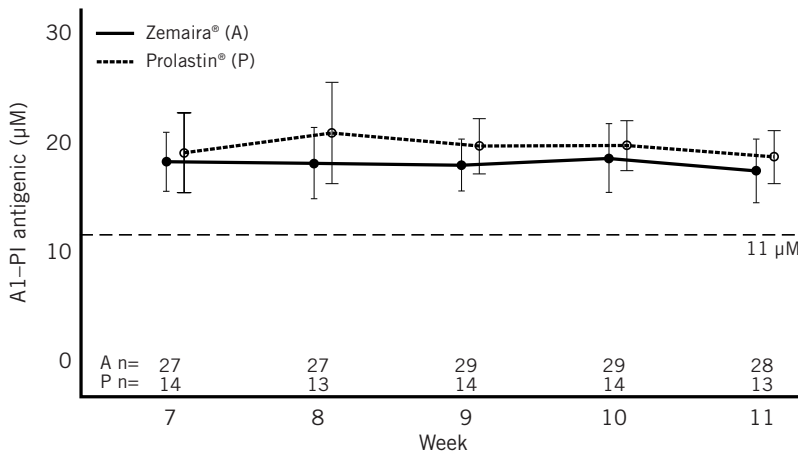
There were no serious or severe adverse events (AEs) related to therapy identified by investigators in either group. The most frequently reported AEs were cough, sore throat, fatigue, fever, bronchitis, bronchospasm, and flushing. There were no significant AE-related differences detected between groups. There was one death during the blinded phase in the

FIGURE 5
Number of Respiratory Infections per Year During Augmentation Therapy With Alpha₁-PI (Prolastin®) Among 89 Patients with PI*ZZ AATD



Source: Adapted from Lieberman 2000

FIGURE 6
Mean ± SD of Trough Serum Antigenic Alpha₁-PI During Weeks 7–11



Source: Stocks 2006. Reprinted by permission of Taylor & Francis Group. Stocks JM, Brantly M, Pollock D, et al. Multi-center study: the biochemical efficacy, safety and tolerability of a new a1-proteinase inhibitor, Zemaira. *COPD*. 2006;3:17–23.

Prolastin® group (a 72-year-old women with COPD and osteoporosis) not considered related to study medication; no other patients discontinued due to AEs. During the open-label period one subject experienced mild fatigue one day after starting Zemaira®, which lasted for 7 days. There was no evidence of viral transmission in either group.

Overall these results indicate that Zemaira® meets the primary and secondary objectives of the study: it is bioequivalent to Prolastin®, yielding increases in serum AAT levels that remain above the protective threshold for lung damage in AATD, and it is effective and well-tolerated. The investigators concluded that, given the goal of increased diagnosis and aggressive treatment of patients with AATD, the availability of Zemaira® will be an important addition to the pharmacologic treatment options of this disease.

TABLE 3
Individual and Between-Group Comparisons of Change in Epithelial Lining Fluid (ELF) Levels of Antigenic Alpha₁-PI From Baseline to Week 11

ELF levels of antigenic alpha ₁ -PI	Zemaira® (N=10)	Prolastin® (N=5)
Baseline mean (nM)	245.8	380.4
Week 11 mean (nM)	1675.3	1362.4
Mean change from baseline (nM)	1429.5	982.0
P-value	0.0025	0.011
Mean change from baseline (nM) [Zemaira®-Prolastin®]	447.5	
P-value	0.4041	

Source: Adapted from Stocks 2006

Safety

CONTRAINDICATIONS

Zemaira® is contraindicated in individuals with a known hypersensitivity to any of its components.

Zemaira® is also contraindicated in individuals with a history of anaphylaxis or severe systemic response to A1-PI products.

Individuals with selective IgA deficiencies who have known antibodies against IgA (anti-IgA antibodies) should not receive Zemaira®, since these patients may experience severe reactions, including anaphylaxis, to IgA that may be present in Zemaira®.

WARNINGS

Zemaira® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Zemaira® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture. (See **DESCRIPTION** section for viral reduction measures.) The manufacturing procedure for Zemaira® includes processing steps designed to reduce further the risk of viral transmission. Stringent procedures utilized at plasma collection centers, plasma testing laboratories, and fractionation facilities are designed to reduce the risk of viral transmission. The primary viral reduction steps of the Zemaira® manufacturing process are pasteurization (60°C for 10 hours) and two sequential ultrafiltration steps. Additional purification procedures used in the manufacture of Zemaira® also potentially provide viral reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents can not be totally eliminated. Any infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 800-504-5434. The physician should discuss the risks and benefits of this product with the patient. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections (see **Information For Patients**).

Source of information in Safety section: Zemaira® [package insert]. CSL Behring LLC; 2007.

During clinical studies, no cases of hepatitis A, B, C, or HIV viral infections were reported with the use of Zemaira®.

PRECAUTIONS

General - Infusion rates and the patient's clinical state should be monitored closely during infusion. The patient should be observed for signs of infusion-related reactions.

As with any colloid solution, there may be an increase in plasma volume following intravenous administration of Zemaira®. Caution should therefore be used in patients at risk for circulatory overload.

Information For Patients - Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.

As with all plasma-derived products, some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect pregnant women and immune-compromised individuals. Symptoms of parvovirus B19 include fever, drowsiness, chills, and runny nose followed two weeks later by a rash and joint pain. Patients should be encouraged to consult their physician if such symptoms occur.

Pregnancy Category C - Animal reproduction studies have not been conducted with Zemaira®, Alpha₁-Proteinase Inhibitor (Human). It is also not known whether Zemaira® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zemaira® should be given to a pregnant woman only if clearly needed.

Nursing Mothers - It is not known whether Zemaira® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zemaira® is administered to a nursing woman.

Pediatric Use - Safety and effectiveness in the pediatric population have not been established.

Geriatric Use - Clinical studies of Zemaira® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

ADVERSE REACTIONS

Intravenous administration of Zemaira®, 60 mg/kg weekly, has been shown to be generally well tolerated.

In clinical studies, the following treatment-related adverse reactions were reported: asthenia, injection site pain, dizziness, headache, paresthesia, and pruritus. Each of these related adverse events was observed in 1 of 89 subjects (1%). The adverse reactions were mild. Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly and appropriate countermeasures and supportive therapy should be administered.

Table 4 summarizes the adverse event data obtained with single and multiple doses during clinical trials with Zemaira® and Prolastin®. No clinically significant differences were detected between the two treatment groups.

The frequencies of adverse events per infusion that were ≥0.4% in Zemaira®-treated subjects, regardless of causality, were: headache (33 events per 1296 infusions, 2.5%), upper respiratory infection (1.6%), sinusitis (1.5%), injection site hemorrhage (0.9%), sore throat (0.9%), bronchitis (0.8%), asthenia (0.6%), fever (0.6%), pain (0.5%), rhinitis (0.5%), bronchospasm (0.5%), chest pain (0.5%), increased cough (0.4%), rash (0.4%), and infection (0.4%).

The following adverse events, regardless of causality, occurred at a rate of 0.2% to <0.4% per infusion: abdominal pain, diarrhea, dizziness, ecchymosis, myalgia, pruritus, vasodilation, accidental injury, back pain, dyspepsia, dyspnea, hemorrhage, injection site reaction, lung disorder, migraine, nausea, and paresthesia. Diffuse interstitial lung disease was noted on a routine chest x-ray of one subject at Week 24. Causality could not be determined.

In a retrospective analysis, during the 10-week blinded portion of the 24-week clinical study, 6 subjects (20%) of the 30 treated with Zemaira® had a total of 7 exacerbations of their chronic obstructive pulmonary disease (COPD). Nine subjects (64%) of the 14 treated with Prolastin® had a total of 11 exacerbations of their COPD. The observed difference between groups was 44% (95% confidence interval from 8% to 70%). Over the entire 24-week treatment period, of the 30 subjects in the Zemaira® treatment group, 7 subjects (23%) had a total of 11 exacerbations of their COPD.

DOSAGE AND ADMINISTRATION

Each vial of Zemaira® contains the labeled amount of functionally active A₁-PI in milligrams as stated on the vial label as determined by capacity to neutralize human neutrophil elastase. The recommended dose of Zemaira® is 60 mg/kg body weight administered once weekly.

When reconstituted as directed, Zemaira® may be

TABLE 4
Summary of Adverse Events

	Zemaira®	Prolastin®
No. of subjects treated	89	32
No. of subjects with adverse event regardless of causality (%)	69 (78%)	20 (63%)
No. of subjects with related adverse events (%)	5 (6%)	4 (13%)
No. of subjects with related serious adverse events (%)	0	0
No. of infusions	1296	160
No. of adverse events regardless of causality (rates per infusion)	298 (0.230)	83 (0.519)
No. of related adverse events (rates per infusion)	6 (0.005)	5 (0.031)

administered intravenously at a rate of approximately 0.08 mL/kg/min as determined by the response and comfort of the patient. The recommended dosage of 60 mg/kg body weight will take approximately 15 minutes to infuse.

Preparation

Each product package contains one Zemaira® single use vial, one 20 mL vial of Sterile Water for Injection, USP (diluent), and one color-coded vented transfer device with air inlet filter. Administer within three hours after reconstitution.

Administration

Parenteral drug preparations should be inspected visually for particulate matter and discoloration prior to administration. Administer at room temperature within three hours after reconstitution.

The reconstituted solution should be filtered during administration. To ensure proper filtration of Zemaira®, use an I.V. administration set with a suitable 5 micron infusion filter (not supplied). Follow the appropriate procedure for I.V. administration.

After administration, any unused solution and administration equipment should be discarded in accordance with biohazard procedures.

HOW SUPPLIED

Zemaira® is supplied in a single use vial containing the labeled amount of functionally active A₁-PI, as stated on the label. Each product package (NDC 0053-7201-02) contains one single use vial of Zemaira®, one 20 mL vial of Sterile Water for Injection, USP (diluent), and one vented transfer device.

STORAGE

When stored up to 25°C (77°F), Zemaira® is stable for the period indicated by the expiration date on its label. Avoid freezing which may damage container for the diluent.

P&T Committee Considerations

In guidelines set forth by the ATS and the European Respiratory Society, it has been acknowledged that correction of AAT deficiency may prevent further destruction of lung tissue and subsequently stabilize the disease (ATS 2003). These guidelines suggest that pulmonary function testing, including spirometry, static lung volumes, arterial blood gas analysis, and gas transfer, be assessed at baseline. The guidelines also recommend that spirometry be assessed both before and after bronchodilator treatment and that it be performed annually as part of routine patient follow-up.

There is a clear need for randomized, controlled studies on AATD, and the scarcity of such studies can be attributed to cost and logistical challenges. However, the data that are currently available are consistent in demonstrating the efficacy and safety of augmentation therapy in the treatment of AATD (AATD Registry Group 1998, Dirksen 1999, Stocks 2006). Such studies have shown that treatment with infusion of human AAT may slow the decline in FEV₁ in patients with moderately reduced lung function as well as reduce overall mortality. Additionally, the slowed progression of lung destruction achieved with IV human alpha₁-PI therapy may lessen the requirement of COPD therapies such as bronchodilators, pul-

monary rehabilitation, and corticosteroids. This, in turn, may reduce the burden of polypharmacy that patients with COPD face. Similarly, the decreased frequency of lung infections associated with augmentation therapy that was seen in observational data may lead to reduced hospitalizations and better quality of life outcomes for patients (Lieberman 2000).

To date, the FDA has approved three purified human alpha₁-proteinase inhibitor products [Zemaira®, CSL Behring; Prolastin®, Talecris BioTherapeutics; Aralast, Baxter]. Considering the wide inter-patient variability that may occur when treating any chronic illness, it is important that P&T decision makers recognize the need for multiple treatment options in this class of medications. Similarly, as the push to identify and treat more patients with this disease grows, there will be a greater need for approved, proven effective and safe products for AAT augmentation. Sufficient supply of such medications is imperative for adequate treatment of patients diagnosed with AATD. Through maintaining an open formulary in which all of such products are accessible to patients, hospitals and managed care organizations can help to ensure the availability of these necessary treatments.

Conclusion

AATD is a common, chronic, genetically inherited disorder that may predispose affected individuals to life-threatening lung and liver disease. Although there is no cure for AATD, the most direct approach to controlling the biochemical factors that contribute to AATD symptoms and to reduce the risk for progressive pulmonary disease is to replace the deficient AAT with virally inactivated plasma-derived human AAT.

Zemaira® is a highly purified, lyophilized IV AAT product obtained from human plasma. It has been proven effective in clinical studies at augmenting serum AAT levels, maintaining AAT levels above the protective threshold of 11 μM , and increasing levels

of AAT in the ELF of the lower lung (CSL Behring 2007). In an equivalency trial against an established human AAT derivative, Zemaira® afforded equivalent serum and ELF levels of AAT to the comparator drug and maintained serum levels above the protective threshold during the 7- to 11-week post-infusion period (Stocks 2006). Thus, Zemaira® is an important addition to the pharmacologic armamentarium for the treatment of AATD, and will be a valuable resource as the screening and diagnosis of AATD gains a footing, leading to more frequent and aggressive treatment of this challenging disease.

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CSL Behring

Zemaira®

Alpha₁-Proteinase Inhibitor (Human)

Key only DESCRIPTION

Zemaira® (Alpha₁-Proteinase Inhibitor (Human)), is a sterile, stable, lyophilized preparation of highly purified human alpha₁-proteinase inhibitor (A₁-PI), also known as alpha₁-antitrypsin, derived from human plasma. Zemaira® is manufactured from large pools of human plasma by cold ethanol fractionation according to a modified Cohn process followed by additional purification steps.

Zemaira® is supplied as a sterile, white, lyophilized powder to be administered by the intravenous route. The specific activity of Zemaira® is ≥ 0.7 mg of functional A₁-PI per milligram of total protein. The purity is $\geq 90\%$ A₁-PI. Following reconstitution with 20 mL of Sterile Water for Injection, USP, each vial contains approximately 1000 mg of functionally active A₁-PI, 81 mM sodium, 38 mM chloride, 17 mM phosphate, and 144 mM mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH. Zemaira® contains no preservatives.

Each vial of Zemaira® contains the labeled amount of functionally active A₁-PI in milligrams as stated on the vial label as determined by its capacity to neutralize human neutrophil elastase.

All Source Plasma used in the manufacture of this product was tested by FDA-licensed Nucleic Acid Tests (NAT) for HCV and HIV-1 and found to be nonreactive (negative).

An investigational NAT for HBV was also performed on all Source Plasma used in the manufacture of this product and found to be nonreactive (negative). The aim of the HBV test is to detect low levels of viral material, however, the significance of a nonreactive (negative) result has not been established.

Two viral reduction steps are employed in the manufacture of Zemaira®: pasteurization at 60°C for 10 hours in an aqueous solution with stabilizers and two sequential ultrafiltration steps. These viral reduction steps have been validated in a series of *in vitro* experiments for their capacity to inactivate/remove a wide range of viruses of diverse physicochemical characteristics including: Human Immunodeficiency Virus (HIV), Hepatitis A Virus (HAV), and the following model viruses: Bovine Viral Diarrhea Virus (BVDV) as a model virus for HCV, Canine Parvovirus (CPV) as a model virus for Parvovirus B19, and Pseudorabies Virus (PRV) as a non-specific model virus for large DNA viruses, e.g. herpes. Total mean log₁₀ reductions range from 6.8 to >12.2 log₁₀ as shown in Table 1.

Table 1: Mean (cumulative) virus reduction factors

	Mean Reduction Factor Pasteurization [log ₁₀]	Mean Reduction Factor Two Ultrafiltration Steps [log ₁₀]	Cumulative Reduction Factor [log ₁₀]
HIV-1	≥ 6.7	≥ 5.5	≥ 12.2
BVDV	≥ 5.9	5.1	≥ 11.0
PRV	4.3	≥ 6.9	≥ 11.2
HAV	≥ 5.4	≥ 6.3	≥ 11.7
CPV	(0.9)	6.8	6.8

CLINICAL PHARMACOLOGY

Alpha₁-proteinase inhibitor (A₁-PI) deficiency is a chronic, hereditary, autosomal, co-dominant disorder that is usually fatal in its severe form. Low blood levels of A₁-PI are most commonly associated with progressive, severe emphysema that becomes clinically apparent by the third to fourth decade of life. However, an unknown percentage of individuals with severe A₁-PI deficiency apparently never develop clinically evident emphysema during their lifetimes. A recent registry study showed 54% of A₁-PI deficient subjects had emphysema.¹ Another registry study showed 72% of A₁-PI deficient subjects had pulmonary symptoms.² Smoking is an important risk factor for the development of emphysema in patients with A₁-PI deficiency. Less commonly, low blood levels of A₁-PI are associated with liver disease and liver cirrhosis.^{3,4,5}

Approximately 100 genetic variants of A₁-PI deficiency can be identified electrophoretically, only some of which are associated with the clinical disease.^{6,7} Ninety-five percent of A₁-PI deficient individuals are of the severe PIZZ phenotype. Up to 39% of A₁-PI deficient patients may have an asthmatic component to their lung disease, as evidenced by symptoms and/or bronchial hyperreactivity.¹ Pulmonary infections, including pneumonia and acute bronchitis, are common in A₁-PI deficient patients and contribute significantly to the morbidity of the disease.

The most direct approach to therapy for A₁-PI deficiency in patients with emphysema has been to partially replace the missing protease inhibitor by intravenous infusion and, thus, attempt to ameliorate the imbalance in the anti-neutrophil elastase protection of the lower respiratory tract. Individuals with endogenous levels of A₁-PI below 11 μ M, in general, manifest a significantly increased risk for development of emphysema above the general population background risk.^{3,4,7,8} Therefore, the maintenance of blood serum levels of A₁-PI (antigenically measured) above 11 μ M is historically thought to provide therapeutically relevant anti-neutrophil elastase protection.⁹ However, the hypothesis that maintaining a serum level of antigenic A₁-PI will restore protease-antiprotease balance and prevent further lung damage has never been tested in an adequately-powered controlled clinical trial.

Mechanism of Action

Pulmonary disease, particularly emphysema, is the most frequent manifestation of A₁-PI deficiency.⁷ The pathogenesis of emphysema is understood to evolve as described in the "protease-antiprotease imbalance" model. A₁-PI is now understood to be the primary antiprotease in the lower respiratory tract, where it inhibits neutrophil elastase (NE).¹⁰ Normal healthy individuals produce sufficient A₁-PI to control the NE produced by activated neutrophils and are thus able to prevent inappropriate proteolysis of lung tissue by NE. Conditions that increase neutrophil accumulation and activation in the lung, such as respiratory infection and smoking, will in turn increase levels of NE. However, individuals who are severely deficient in endogenous A₁-PI are unable to maintain an appropriate antiprotease defense and are thereby subject to more rapid proteolysis of the alveolar walls leading to chronic lung disease. Zemaira® serves as A₁-PI augmentation therapy in this patient population, acting to increase and maintain serum levels and lung epithelial lining fluid (ELF) levels of A₁-PI.

In 18 subjects treated with a single dose (60 mg/kg) of Zemaira®, the mean area under the curve (AUC) and standard deviation (SD) were 144 μ M x day (SD 27), maximum serum concentration was 44.1 μ M (SD 10.8), clearance was 603 mL per day (SD 129), and terminal half-life was 5.1 days (SD 2.4).

Weekly repeated infusions of A₁-PI at a dose of 60 mg/kg lead to serum A₁-PI levels above the historical target threshold of 11 μ M.

CLINICAL STUDIES

Clinical studies were conducted with Zemaira®, Alpha₁-Proteinase Inhibitor (Human), in 89 subjects (59 males and 30 females). 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 A₁-PI deficiency, and 3% had the M₁MALTON phenotype. At screening, serum A₁-PI levels were between 3.2 and 10.1 μ M (mean of 5.6 μ M). The objectives of the clinical studies were to demonstrate that Zemaira® augments and maintains serum levels of A₁-PI above 11 μ M and increases A₁-PI levels in ELF of the lower lung.

In a double-blind, controlled clinical study to evaluate the safety and efficacy of Zemaira®, 44 subjects were randomized to receive 60 mg/kg of either Zemaira® or Prolastin® (a commercially available Alpha₁-Proteinase Inhibitor [Human] product) once weekly for 10 weeks. After 10 weeks, all subjects received Zemaira® for an additional 14 weeks. All subjects were followed for a total of 24 weeks to complete the safety evaluation. The mean trough serum A₁-PI levels at steady state (Weeks 7-11) in the Zemaira®-treated subjects were statistically equivalent to those in the Prolastin®-treated subjects. Both groups were maintained above 11 μ M (80 mg/dL). The mean (range and standard deviation) of the steady state trough serum antigenic A₁-PI level for Zemaira®-treated subjects was 17.7 μ M (range 13.9 to 23.2, SD 2.5) and for Prolastin®-treated subjects was 19.1 μ M (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®.

In a subgroup of subjects enrolled in the study (10 Zemaira®-treated subjects and 5 Prolastin®-treated subjects), bronchoalveolar lavage was performed at baseline and at Week 11. Four A₁-PI related analytes in ELF were measured: antigenic A₁-PI, A₁-PI:NE complexes, free NE, and functional A₁-PI (anti-neutrophil elastase capacity, ANEC). A blinded retrospective analysis, which revised the prospectively established acceptance criteria showed that within each treatment group, ELF levels of antigenic A₁-PI and A₁-PI:NE complexes increased from baseline to Week 11. Free elastase was immeasurably low in all samples. The post-treatment ANEC values in ELF were not significantly different between the Zemaira®-treated and Prolastin®-treated subjects (mean 1725 nM vs. 1418 nM). No conclusions can be drawn about changes of ANEC values in ELF during the study period as baseline values in the Zemaira®-treated subjects were unexpectedly high. No A₁-PI analytes showed any clinically significant differences between the Zemaira® and Prolastin® treatment groups.

Table 2: ELF Analytes - change from baseline

Analyte	Treatment	Mean change from baseline	90% CI
A ₁ -PI (nM)	Zemaira®	1358.3	822.6 to 1894.0
	Prolastin®	949.9	460.0 to 1439.7
ANEC (nM)	Zemaira®	-588.1	-2032.3 to 856.1
	Prolastin®	497.5	-392.3 to 1387.2
A ₁ -PI:NE Complexes (nM)	Zemaira®	118.0	39.9 to 196.1
	Prolastin®	287.1	49.8 to 524.5

Subjects were also monitored for the presence of antibodies to HIV and markers for viral hepatitis (HAV, HBV, and HCV). Subjects who were negative for Hepatitis B surface antigen (HBsAg) at screening were vaccinated against Hepatitis B. Zemaira®-treated subjects were tested six months after the end of treatment for HAV, HBV, HCV, HIV, and Parvovirus B19, and no evidence of viral transmission was observed. No subjects developed detectable antibodies to Zemaira®.

INDICATIONS AND USAGE

Zemaira® is indicated for chronic augmentation and maintenance therapy in individuals with alpha₁-proteinase inhibitor (A₁-PI) deficiency and clinical evidence of emphysema.

Zemaira® increases antigenic and functional (ANEC) serum levels and lung epithelial lining fluid levels of A₁-PI. Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with Zemaira® are not available.

Safety and effectiveness in pediatric patients have not been established.

Zemaira® is not indicated as therapy for lung disease patients in whom severe congenital A₁-PI deficiency has not been established.

CONTRAINDICATIONS

Zemaira® is contraindicated in individuals with a known hypersensitivity to any of its components. Zemaira® is also contraindicated in individuals with a history of anaphylaxis or severe systemic response to A₁-PI products.

Individuals with selective IgA deficiencies who have known antibodies against IgA (anti-IgA antibodies) should not receive Zemaira®, since these patients may experience severe reactions, including anaphylaxis, to IgA that may be present in Zemaira®.

WARNINGS

Zemaira® is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. Because Zemaira® is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically the Creutzfeldt-Jakob disease (CJD) agent. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses during manufacture. (See DESCRIPTION section for viral reduction measures.) The manufacturing procedure for Zemaira® includes processing steps designed to reduce further the risk of viral transmission. Stringent procedures utilized at plasma collection centers, plasma testing laboratories, and fractionation facilities are designed to reduce the risk of viral transmission. The primary viral reduction steps of the Zemaira® manufacturing process are pasteurization (60°C for 10 hours) and two sequential ultrafiltration steps. Additional purification procedures used in the manufacture of Zemaira® also potentially provide viral reduction. Despite these measures, such products may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents can not be totally eliminated. Any infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to CSL Behring at 800-504-5434. The physician should discuss the risks and benefits of this product with the patient. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections (see Information For Patients).

During clinical studies, no cases of hepatitis A, B, C, or HIV viral infections were reported with the use of Zemaira®.

PRECAUTIONS

General - Infusion rates and the patient's clinical state should be monitored closely during infusion. The patient should be observed for signs of infusion-related reactions.

As with any colloid solution, there may be an increase in plasma volume following intravenous administration of Zemaira®. Caution should therefore be used in patients at risk for circulatory overload.

Information For Patients - Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Patients should be advised to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.

As with all plasma-derived products, some viruses, such as parvovirus B19, are particularly difficult to remove or inactivate at this time. Parvovirus B19 may most seriously affect pregnant women and immune-compromised individuals. Symptoms of parvovirus B19 include fever, drowsiness, chills, and runny nose followed two weeks later by a rash and joint pain. Patients should be encouraged to consult their physician if such symptoms occur.

Pregnancy Category C - Animal reproduction studies have not been conducted with Zemaira®, Alpha₁-Proteinase Inhibitor (Human). It is also not known whether Zemaira® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Zemaira® should be given to a pregnant woman only if clearly needed.

Nursing Mothers - It is not known whether Zemaira® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Zemaira® is administered to a nursing woman.

Pediatric Use - Safety and effectiveness in the pediatric population have not been established.

Geriatric Use - Clinical studies of Zemaira® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation.

ADVERSE REACTIONS

Intravenous administration of Zemaira®, 60 mg/kg weekly, has been shown to be generally well tolerated. In clinical studies, the following treatment-related adverse reactions were reported: asthenia, injection site pain, dizziness, headache, paresthesia, and pruritus. Each of these related adverse events was observed in 1 of 89 subjects (1%). The adverse reactions were mild.

Should evidence of an acute hypersensitivity reaction be observed, the infusion should be stopped promptly and appropriate countermeasures and supportive therapy should be administered.

Table 3 summarizes the adverse event data obtained with single and multiple doses during clinical trials with Zemaira® and Prostasin®. No clinically significant differences were detected between the two treatment groups.

Table 3: Summary of Adverse Events

	Zemaira®	Prostasin®
No. of subjects treated	89	32
No. of subjects with adverse events regardless of causality (%)	69 (78%)	20 (63%)
No. of subjects with related adverse events (%)	5 (6%)	4 (13%)
No. of subjects with related serious adverse events	0	0
No. of infusions	1296	160
No. of adverse events regardless of causality (rates per infusion)	298 (0.230)	83 (0.519)
No. of related adverse events (rates per infusion)	6 (0.005)	5 (0.031)

The frequencies of adverse events per infusion that were ≥0.4% in Zemaira®-treated subjects, regardless of causality, were: headache (33 events per 1296 infusions, 2.5%), upper respiratory infection (1.6%), sinusitis (1.5%), injection site hemorrhage (0.9%), sore throat (0.9%), bronchitis (0.8%), asthenia (0.6%), fever (0.6%), pain (0.5%), rhinitis (0.5%), bronchospasm (0.5%), chest pain (0.5%), increased cough (0.4%), rash (0.4%), and infection (0.4%).

The following adverse events, regardless of causality, occurred at a rate of 0.2% to <0.4% per infusion: abdominal pain, diarrhea, dizziness, ecchymosis, myalgia, pruritus, vasodilation, accidental injury, back pain, dyspepsia, dyspnea, hemorrhage, injection site reaction, lung disorder, migraine, nausea, and paresthesia. Diffuse interstitial lung disease was noted on a routine chest x-ray of one subject at Week 24. Causality could not be determined.

In a retrospective analysis, during the 10-week blinded portion of the 24-week clinical study, 6 subjects (20%) of the 30 treated with Zemaira® had a total of 7 exacerbations of their chronic obstructive pulmonary disease (COPD). Nine subjects (64%) of the 14 treated with Prostasin® had a total of 11 exacerbations of their COPD. The observed difference between groups was 44% (95% confidence interval from 8% to 70%). Over the entire 24-week treatment period, of the 30 subjects in the Zemaira® treatment group, 7 subjects (23%) had a total of 11 exacerbations of their COPD.

DOSE AND ADMINISTRATION

Each vial of Zemaira® contains the labeled amount of functionally active A₁-PI in milligrams as stated on the vial label as determined by capacity to neutralize human neutrophil elastase. The recommended dose of Zemaira® is 60 mg/kg body weight administered once weekly.

When reconstituted as directed, Zemaira® may be administered intravenously at a rate of approximately 0.08 mL/kg/min as determined by the response and comfort of the patient. The recommended dosage of 60 mg/kg body weight will take approximately 15 minutes to infuse.

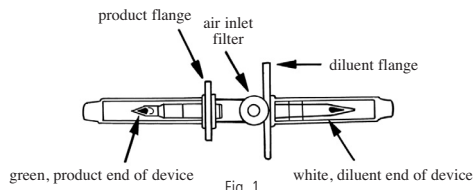
Preparation

Each product package contains one Zemaira® single use vial, one 20 mL vial of Sterile Water for Injection, USP (diluent), and one color-coded vented transfer device with air inlet filter. Administer within three hours after reconstitution.

Reconstitution

1. Bring both product (green cap) vial and diluent (white cap) vial to room temperature prior to reconstitution.
2. Remove the plastic flip-top caps from the vials. Aseptically cleanse the rubber stoppers with antiseptic solution and allow them to dry.

NOTE: The transfer device (Fig. 1) provided in the package is comprised of a white (diluent) end, which has a double orifice, and a green (product) end, which has a single orifice. Incorrect use of the transfer device will result in loss of vacuum and prevent transfer of the diluent, thereby preventing reconstitution of the product.



The transfer device is sterile. Do not touch the exposed ends of the spike after removing the protective covers.

3. Remove the protective cover from the white (diluent) end of the transfer device. Insert the white end of the transfer device into the center of the stopper of the upright diluent vial first. (Fig. 2)
4. Remove the protective cover from the green (product) end of the transfer device. Invert the diluent vial with the attached transfer device and, using minimum force, insert the green end of the transfer device into the center of the rubber stopper of the upright Zemaira® vial (green top). (Fig. 3) The flange of the transfer device should rest on the surface of the stopper so that the diluent flows into the Zemaira® vial.
5. Allow the vacuum in the Zemaira® vial to pull the diluent into the Zemaira® vial.

6. During diluent transfer, wet the lyophilized cake completely by gently tilting the Zemaira®, Alpha₁-Proteinase Inhibitor (Human), vial. (Fig. 4) Do not allow the air inlet filter to face downward. Care should be taken not to lose the vacuum, as this will prolong reconstitution of the product.
7. After diluent transfer is complete, the transfer device will allow filtered air into the Zemaira® vial through the air filter. Additional venting of the product vial after diluent transfer is complete is not required. When diluent transfer is complete, withdraw the transfer device and diluent vial and properly discard in accordance with biohazard procedures.
8. Gently swirl the Zemaira® vial until the powder is completely dissolved. (Fig. 5) **DO NOT SHAKE.**
9. Parenteral drug preparations should be inspected visually for particulate matter and discoloration prior to administration. Administer at room temperature within three hours after reconstitution.

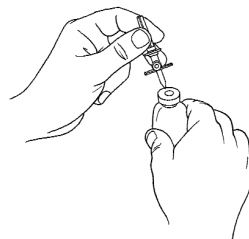


Fig. 2

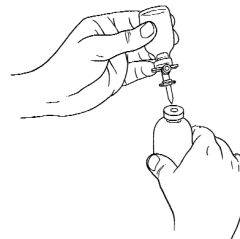


Fig. 3

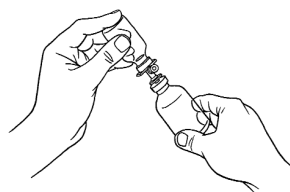


Fig. 4



Fig. 5

Pooling Reconstituted Vials

If more than one vial of Zemaira® is needed to achieve the required dose, use an aseptic technique to transfer the reconstituted solution from the vials into the administration container (e.g., empty I.V. bag or glass bottle).

Administration

Parenteral drug preparations should be inspected visually for particulate matter and discoloration prior to administration. Administer at room temperature within three hours after reconstitution.

The reconstituted solution should be filtered during administration. To ensure proper filtration of Zemaira®, use an I.V. administration set with a suitable 5 micron infusion filter (not supplied). Follow the appropriate procedure for I.V. administration.

After administration, any unused solution and administration equipment should be discarded in accordance with biohazard procedures.

HOW SUPPLIED

Zemaira® is supplied in a single use vial containing the labeled amount of functionally active A₁-PI, as stated on the label. Each product package (NDC 0053-7201-02) contains one single use vial of Zemaira®, one 20 mL vial of Sterile Water for Injection, USP (diluent), and one vented transfer device.

STORAGE

When stored up to 25°C (77°F), Zemaira® is stable for the period indicated by the expiration date on its label. Avoid freezing which may damage container for the diluent.

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