ZEMAIRA- alpha-1-proteinase inhibitor human
CSL Behring LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Zemaira safely and effectively. See full prescribing information for Zemaira.

Zemaira®, Alpha$_1$-Proteinase Inhibitor (Human)
For Intravenous Use. Lyophilized Powder for Reconstitution.
Initial U.S. Approval: 2003

INDICATIONS AND USAGE

- Zemaira is an alpha$_1$-proteinase inhibitor (A_1-PI) indicated for chronic augmentation and maintenance therapy in adults with A_1-PI deficiency and clinical evidence of emphysema (1).
- The effect of augmentation therapy with Zemaira or any A_1-PI product on pulmonary exacerbations and on the progression of emphysema in A_1-PI deficiency has not been demonstrated in randomized, controlled clinical studies (1).
- Zemaira is not indicated as therapy for lung disease patients in whom severe A_1-PI deficiency has not been established (1).

DOSAGE AND ADMINISTRATION

- **For intravenous use after reconstitution only** (2).
- The recommended weekly dose of Zemaira is 60 mg/kg body weight. Dose ranging studies using efficacy endpoints have not been performed with Zemaira or any A_1-PI product (2).
- Administer at room temperature within 3 hours after reconstitution (2.1).
- Do not mix with other medicinal products. Administer through a separate dedicated infusion line (2.2).
- Administer through a suitable 5 micron infusion filter (not supplied) at a rate of approximately 0.08 mL/kg/min as determined by the response and comfort of the patient (2.2).
- Monitor closely the infusion rate and the patient's clinical state, including vital signs, throughout the infusion. Slow or stop the infusion if adverse reactions occur. If symptoms subside promptly, the infusion may be resumed at a lower rate that is comfortable for the patient (2.2).

DOSAGE FORMS AND STRENGTHS

Zemaira is supplied in a single-use vial containing approximately 1000 mg of functionally active A_1-PI (the measured amount per vial is printed on the vial label and carton) as a lyophilized powder for reconstitution with 20 mL of Sterile Water for Injection, USP (3).

CONTRAINDICATIONS

- History of anaphylaxis or severe systemic reactions to Zemaira or A_1-PI protein (4).
- Immunoglobulin A (IgA)-deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity (4).

WARNINGS AND PRECAUTIONS

- Use caution when administering Zemaira to individuals who have experienced anaphylaxis or severe systemic reactions to another A_1-PI product (5.1).
- Patients with selective or severe IgA deficiency can develop antibodies to IgA and, therefore, have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. If anaphylactic or severe anaphylactoid reactions occur, discontinue the infusion immediately (5.2).
- Because Zemaira is made from human plasma, it may carry a risk of transmitting infectious agents (e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease [CJD] agent) (5.3).

ADVERSE REACTIONS

The most common adverse reactions occurring in at least 5% of subjects receiving Zemaira in all clinical trials were headache, sinusitis, upper respiratory infection, bronchitis, asthenia, cough increased, fever, injection site hemorrhage, rhinitis, sore throat, and vasodilation (6).

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed (8.1).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Zemaira is an alpha$_1$-proteinase inhibitor (A_1-PI) indicated for chronic augmentation and maintenance therapy in adults with A_1-PI deficiency and clinical evidence of emphysema.

Zemaira increases antigenic and functional (anti-neutrophil elastase capacity [ANEC]) serum levels and lung epithelial lining fluid (ELF) levels of A_1-PI.

Clinical data demonstrating the long-term effects of chronic augmentation therapy of individuals with

Zemaira are not available.

The effect of augmentation therapy with Zemaira or any A_1-PI product on pulmonary exacerbations and on the progression of emphysema in A_1-PI deficiency has not been demonstrated in randomized, controlled clinical studies.

Zemaira is not indicated as therapy for lung disease patients in whom severe A_1-PI deficiency has not been established.

2 DOSAGE AND ADMINISTRATION

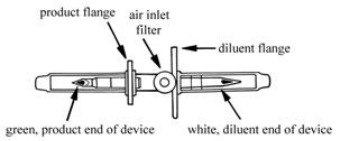
For Intravenous Use After Reconstitution Only.

The recommended dose of Zemaira is 60 mg/kg body weight administered once weekly. Dose ranging studies using efficacy endpoints have not been performed with Zemaira or any A_1-PI product.

2.1 Preparation and Reconstitution

- Check the expiration date on the vial label and carton. Do not use Zemaira after the expiration date.
- Reconstitute prior to use.
- Reconstitute Zemaira using aseptic technique to maintain product sterility.
- Inspect the reconstituted solution prior to administration. The solution should be clear, colorless to slightly yellow, and free from visible particles.
- Administer Zemaira at room temperature within 3 hours after reconstitution. Reconstituted Zemaira may be stored at room temperature. Do not freeze the reconstituted solution.

Follow the steps below to reconstitute Zemaira:

1. Ensure that the Zemaira (green cap) vial and diluent (white cap) vial are at room temperature.	
2. Remove the plastic flip-top caps from the vials. Aseptically cleanse the rubber stoppers with antiseptic solution and allow them to dry.	
Notes on Using the Transfer Device (Steps 3 through 7): • The transfer device (Figure 1) provided in the Zemaira carton has a white (diluent) end with a double orifice and a green (Zemaira) end with a single orifice. • Incorrect use of the transfer device will result in loss of vacuum and prevent transfer of the diluent, thereby prolonging or preventing reconstitution of Zemaira. • The transfer device is sterile. Once the protective covers have been removed (Steps 3 and 4), do not touch the exposed ends of the spikes.	 Figure 1
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 (Figure 2).	 Figure 2

4. Remove the protective cover from the green (Zemaira) 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) (Figure 3). The flange of the transfer device should rest on the surface of the stopper so that the diluent flows into the Zemaira vial.	 Figure 3
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 vial (Figure 4). Do not allow the air inlet filter to face downward. Care should be taken not to lose the vacuum, as this will prolong or prevent reconstitution.	 Figure 4
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 Zemaira vial is not required. When diluent transfer is complete, withdraw the transfer device from the diluent vial and discard the diluent vial and transfer device.	
8. Gently swirl the Zemaira vial until the powder is completely dissolved (Figure 5). **DO NOT SHAKE**.	 Figure 5

If more than 1 vial of Zemaira is needed to achieve the required dose, use aseptic technique to transfer the reconstituted solution from the vials into the administration container (e.g., empty intravenous bag or glass bottle).

2.2 Administration

- For intravenous use only.
- Do not mix Zemaira with other medicinal products. Administer Zemaira through a separate dedicated infusion line.
- Perform a visual inspection of the reconstituted solution. The solution should be clear, colorless to slightly yellow, and free from visible particles.
- Administer at room temperature within 3 hours after reconstitution.
- Filter the reconstituted solution during administration. To ensure proper filtration of Zemaira, use an intravenous administration set with a suitable 5 micron infusion filter (not supplied).
- Administer Zemaira 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.
- Monitor closely the infusion rate and the patient's clinical state, including vital signs, throughout the infusion. Slow or stop the infusion if adverse reactions occur. If symptoms subside promptly, the

infusion may be resumed at a lower rate that is comfortable for the patient.
- Zemaira is for single use only. Following administration, discard any unused solution and all administration equipment in an appropriate manner as per local requirements.

3 DOSAGE FORMS AND STRENGTHS

Zemaira is supplied in a single-use vial containing approximately 1000 mg of functionally active A_1-PI as a lyophilized powder for reconstitution with 20 mL of Sterile Water for Injection, USP. The amount of functional A_1-PI is printed on the vial label and carton.

4 CONTRAINDICATIONS

- Zemaira is contraindicated in patients with a history of anaphylaxis or severe systemic reactions to Zemaira or A_1-PI protein.
- **Zemaira is contraindicated in immunoglobulin A (IgA)-deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity** *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity to Other A_1-PI Products

Caution should be used when administering Zemaira to individuals who have experienced anaphylaxis or severe systemic reaction to another A_1-PI product. **IF ANAPHYLACTIC OR SEVERE ANAPHYLACTOID REACTIONS OCCUR, DISCONTINUE THE INFUSION IMMEDIATELY**. Have epinephrine and other appropriate supportive therapy available for the treatment of any acute anaphylactic or anaphylactoid reaction. Zemaira is contraindicated in patients with a history of anaphylaxis or severe systemic reactions to Zemaira or A_1-PI protein.

5.2 Hypersensitivity to IgA

Zemaira may contain trace amounts of IgA. Patients with selective or severe IgA deficiency can develop antibodies to IgA and, therefore, have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions. **IF ANAPHYLACTIC OR SEVERE ANAPHYLACTOID REACTIONS OCCUR, DISCONTINUE THE INFUSION IMMEDIATELY**. Have epinephrine and other appropriate supportive therapy available for the treatment of any acute anaphylactic or anaphylactoid reaction. Zemaira is contraindicated in IgA-deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity.

5.3 Transmissible Infectious Agents

Because Zemaira is made from human plasma, it may carry a risk of transmitting infectious agents (e.g., viruses, and theoretically the Creutzfeldt-Jakob disease [CJD] agent). The risk of infectious agent transmission has been reduced by screening plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal steps in the manufacturing process for Zemaira *[see Description (11)]*. Despite these measures, Zemaira, like other products made from human plasma, may still potentially contain human pathogenic agents, including those not yet known or identified. Thus, the risk of transmission of infectious agents cannot be totally eliminated.

All infections thought by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

6 ADVERSE REACTIONS

Serious adverse reactions identified during postmarketing use were hypersensitivity reactions *[see Warnings and Precautions (5.1, 5.2)]*.

The serious adverse reactions reported following administration of Zemaira in clinical trials included one event each in separate subjects of bronchitis and dyspnea, and one event each in a single subject of chest pain, cerebral ischemia and convulsion. The most common adverse reactions (ARs) occurring in at least 5% of subjects receiving Zemaira in all clinical trials were headache, sinusitis, upper respiratory infection, bronchitis, asthenia, cough increased, fever, injection site hemorrhage, rhinitis, sore throat, and vasodilation.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Four clinical trials were conducted with Zemaira: 1) a controlled, double-blind trial in 44 subjects, who received a 60 mg/kg dose of either Zemaira (30 subjects) or Prolastin® (a commercially available $Alpha_1$-Proteinase Inhibitor [Human] product) (14 subjects) weekly for 10 weeks, followed by an open-label phase in which 43 subjects received Zemaira weekly for 14 weeks; 2) an open-label trial in 9 subjects who received a 60 mg/kg dose of Zemaira weekly for 26 weeks, followed by a 7-week to 22-week extension; 3) a crossover, double-blind trial in 18 subjects who received a single 60 mg/kg dose of Zemaira and a single 60 mg/kg dose of Prolastin; and 4) an open-label trial of 19 subjects who received a single 15 mg/kg (2 subjects), 30 mg/kg (5 subjects), 60 mg/kg (6 subjects), or 120 mg/kg (6 subjects) dose of Zemaira. A total of 89 subjects were administered Zemaira in clinical trials, 23 of whom participated in more than 1 trial *[see Clinical Studies (14)]*.

Table 1 summarizes the ARs, expressed as events per subject-year, and the corresponding number of ARs per infusion, expressed as % of all infusions, for each treatment in all clinical trials of Zemaira.

Table 1: Overall Adverse Reactions (ARs) and Serious ARs

	Number of Subjects* **(Events per Subject-Year†)**		**Number of Infusions‡ (% of all Infusions)**	
	Zemaira (n=66, SY§=28.72)	**Prolastin (n=32), SY§=3.83)**	**Zemaira (n=1296)**	**Prolastin (n=160)**
ARs (AEs assessed by investigator as at least possibly related or occurring during or within 72 hours after the end of the infusion or for which causality assessment was missing or indeterminate).	54 (5.6)	16 (3.8)	160 (12.3)	31 (19.4)
Serious ARs (Serious AEs assessed by investigator as at least possibly related or occurring during or within 72 hours after the end of the infusion	4 (0.2)	1 (1.0)	6 (0.5)	1 (0.6)

or for which causality assessment was missing or indeterminate).				

* Based on unique subjects. If a subject experienced more than one AR, the subject was only counted once.

† The exposure adjusted event rate was based on total exposure time presented in subject-years and the total number of adverse reactions in the database.

‡ If there were multiple occurrences of ARs following a single infusion, only one occurrence was counted.

§ SY=subject-year.

Table 2 summarizes the ARs occurring in 5% or more (>3) subjects, expressed as events per subject-year, and the corresponding number of ARs per infusion, expressed as % of all infusions, for each treatment in all clinical trials of Zemaira.

Table 2: Adverse Reactions Occurring in ≥5% of Subjects

ARs (AEs assessed by investigator as at least possibly related or occurring during or within 72 hours after the end of the infusion or for which causality assessment was missing or indeterminate).	**Number of Subjects* (Events per Subject-Year†)**		**Number of Infusions‡ (% of all Infusions)**	
	Zemaira (n=66, SY§=28.72)	**Prolastin (n=32, SY§=3.83)**	**Zemaira (n=1296)**	**Prolastin (n=160)**
Headache	13 (0.7)	5 (1.3)	19 (1.5)	5 (3.1)
Sinusitis	10 (0.5)	1 (0.3)	13 (1.0)	1 (0.6)
Upper Respiratory Infection	10 (0.4)	1 (0.3)	10 (0.8)	1 (0.6)
Bronchitis	5 (0.2)	0 (0.0)	6 (0.5)	0 (0.0)
Asthenia	5 (0.2)	2 (0.5)	5 (0.4)	2 (1.3)
Cough Increased	5 (0.2)	1 (0.5)	5 (0.4)	2 (1.3)
Fever	4 (0.1)	0 (0.0)	4 (0.3)	0 (0.0)
Injection Site Hemorrhage	4 (0.1)	0 (0.0)	4 (0.3)	0 (0.0)
Rhinitis	4 (0.1)	0 (0.0)	4 (0.3)	0 (0.0)
Sore Throat	4 (0.1)	0 (0.0)	4 (0.3)	0 (0.0)
Vasodilation	4 (0.1)	1 (0.3)	4 (0.3)	1 (0.6)

* Based on unique subjects. If a subject experienced more than one AR of the same type, the subject was only counted once.

† The exposure adjusted event rate was based on total exposure time presented in subject-years and the total number of adverse reactions in the database.

‡ If more than one of the same type of an event occurred after an infusion, only one event was counted.

§ SY=subject-year.

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 trial, 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 [CI] 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.

In the 24-week double-blind trial, Zemaira-treated subjects were tested for HAV, HBV, HCV, HIV, and parvovirus B19 (B19V), and no evidence of virus transmission was observed.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. No anti-A_1PI antibodies have been detected in clinical trials of Zemaira. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Zemaira with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Table 3 lists the ARs that have been identified during postmarketing use of Zemaira. This list does not include reactions already reported in clinical trials with Zemaira *[see Adverse Reactions (6.1)]*.

Table 3: ARs Reported During the Postmarketing Use of Zemaira

System Organ Class	Preferred Term/Symptoms
Blood and lymphatic system disorders	Lymph node pain
Gastrointestinal disorders	Nausea
General disorders and administration site conditions	Chills, infusion site reactions, facial, periorbital, lip and extremity swelling
Immune system disorders	Hypersensitivity, anaphylactic reactions, tachycardia, hypotension, confusion, syncope, oxygen consumption decreased, pharyngeal edema
Nervous system disorders	Hypoesthesia, paresthesia
Skin disorders	Hyperhidrosis, pruritus, rash including exfoliative and generalized, urticaria
Vascular disorders	Flushing

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Zemaira. Safety and effectiveness in pregnancy have not been established. Zemaira should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether Zemaira is excreted in human milk. Use Zemaira only if clearly needed when treating nursing women.

8.4 Pediatric Use

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

8.5 Geriatric Use

The safety and efficacy of Zemaira in the geriatric population have not been established due to an insufficient number of subjects.

11 DESCRIPTION

Zemaira is a sterile, white, lyophilized preparation of purified Alpha$_1$-Proteinase Inhibitor (Human) (A_1-PI), also known as alpha$_1$-antitrypsin, to be reconstituted and administered by the intravenous route. The specific activity of Zemaira is ≥0.7 mg of functional A_1-PI per milligram of total protein. The purity (total A_1-PI/total protein) is ≥90% A_1-PI. Each vial contains approximately 1000 mg of functionally active A_1-PI. The measured amount per vial of functionally active A_1-PI as determined by its capacity to neutralize human neutrophil elastase (NE) is printed on the vial label and carton. Following reconstitution with 20 mL of Sterile Water for Injection, USP, the Zemaira solution contains 73 to 89 mM sodium, 33 to 42 mM chloride, 15 to 20 mM phosphate, and 121 to 168 mM mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH. Zemaira contains no preservative.

All plasma used in the manufacture of Zemaira is obtained from US donors and is tested using serological assays for HBsAg and antibodies to HIV-1/2 and HCV. The plasma is tested with Nucleic Acid Testing (NAT) for HBV, HCV, HIV-1, and HAV, and found to be nonreactive (negative). The plasma is also tested by NAT for B19V. Only plasma that passed the virus screening is used for production. The limit for B19V in the fractionation pool is $\leq 10^4$ International Units of B19V per mL.

Zemaira is manufactured from large pools of human plasma by cold ethanol fractionation according to a modified Cohn process followed by additional purification steps. The manufacturing process includes two virus clearance steps: heat treatment at 60°C for 10 hours in an aqueous solution with stabilizers; and nanofiltration. These virus clearance steps have been validated in a series of *in vitro* experiments for their capacity to inactivate/remove both enveloped and non-enveloped viruses. Table 4 shows the virus clearance capacity of the Zemaira manufacturing process, expressed as mean $\log_{10}$ reduction factor.

Table 4: Cumulative (Log_{10}) Virus Inactivation/Removal in Zemaira

Manufacturing Step	Virus Reduction Factor (Log_{10})					
	Enveloped Viruses				Non-Enveloped Viruses	
	HIV-1	BVDV	WNV	PRV	HAV	CPV
Heat treatment*†	≥6.8	≥5.2	≥8.3	4.4	≥5.4	na
Nanofiltration	≥5.5	≥5.4	≥8.4	≥6.3	≥5.3	≥6.4
Cumulative Virus Reduction ($\log_{10}$)	**≥12.3**	**≥10.6**	**≥16.7**	**≥10.7**	**≥10.7**	**≥6.4**

HIV, human immunodeficiency virus type 1, a model for HIV-1 and HIV-2.

BVDV, bovine viral diarrhea virus, a model for HCV.

WNV, West Nile virus.

PRV, pseudorabies virus, a non-specific model for large DNA viruses, eg. herpes.

HAV, hepatitis A virus.

CPV, canine parvovirus, model for B19V.

na, not applicable.

* Studies using B19V, which are considered experimental in nature, have demonstrated a virus reduction factor of 1.9 $\log_{10}$.

† At 60°C for 10 hours.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

A_1-PI deficiency is a chronic, hereditary, autosomal, co-dominant disorder that is usually fatal in its severe form. Low blood levels of A_1-PI (i.e., below 11 µM) are most commonly associated with progressive, severe emphysema that becomes clinically apparent by the third to fourth decade of life. In addition, PiSZ individuals, whose serum A_1-PI levels range from approximately 9 to 23 µM, are considered to have a moderately increased risk for developing emphysema, regardless of whether their serum A_1-PI levels are above or below 11 µM.[1] Not all individuals with severe genetic variants of A_1-PI deficiency have emphysema. **Augmentation therapy with Alpha$_1$-Proteinase Inhibitor (Human) is indicated only in patients with severe congenital A_1-PI deficiency who have clinically evident emphysema**. A registry study showed 54% of A_1-PI deficient subjects had emphysema.[2] Another registry study showed 72% of A_1-PI deficient subjects had pulmonary symptoms.[3] Smoking is an important risk factor for the development of emphysema in patients with A_1-PI deficiency.

Approximately 100 genetic variants of A_1-PI deficiency can be identified electrophoretically, only some of which are associated with the clinical disease.[4,5] Ninety-five percent of clinically symptomatic A_1-PI deficient individuals are of the severe PiZZ phenotype. Up to 39% of A_1-PI deficient patients may have an asthmatic component to their lung disease, as evidenced by symptoms and/or bronchial hyperreactivity.[2] Pulmonary infections, including pneumonia and acute bronchitis, are common in A_1-PI deficient patients and contribute significantly to the morbidity of the disease.

Augmenting the levels of functional protease inhibitor by intravenous infusion is an approach to therapy for patients with A_1-PI deficiency. However, the efficacy of augmentation therapy in affecting the progression of emphysema has not been demonstrated in randomized, controlled clinical studies. The intended theoretical goal is to provide protection to the lower respiratory tract by correcting the imbalance between NE and protease inhibitors. Whether augmentation therapy with Zemaira or any A_1-PI product actually protects the lower respiratory tract from progressive emphysematous changes has not been evaluated. Individuals with endogenous levels of A_1-PI below 11 µM, in general, manifest a significantly increased risk for development of emphysema above the general population background risk.[5,6,7,8] Although the maintenance of blood serum levels of A_1-PI (antigenically measured) above 11 µM has been historically postulated to provide therapeutically relevant anti-neutrophil elastase protection[9], this has not been proven. Individuals with severe A_1-PI deficiency have been shown to have increased neutrophil and NE concentrations in lung epithelial lining fluid compared to normal PiMM individuals, and some PiSZ individuals with A_1-PI above 11 µM have emphysema attributed to A_1-PI deficiency.[1] These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of A_1-PI during augmentation therapy.

Pulmonary disease, particularly emphysema, is the most frequent manifestation of A_1-PI deficiency.[5] The pathogenesis of emphysema is understood to evolve as described in the "protease-antiprotease imbalance" model. A_1-PI is now understood to be the primary antiprotease in the lower respiratory tract, where it inhibits NE.[10] Normal healthy individuals produce sufficient A_1-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 A_1-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 A_1-PI augmentation therapy in this patient population, acting to increase and maintain serum levels and (ELF)

levels of A_1-PI.

12.2 Pharmacodynamics

Weekly repeated infusions of A_1-PI at a dose of 60 mg/kg lead to serum A_1-PI levels above the historical target threshold of 11 µM.

The clinical benefit of the increased blood levels of A_1-PI at the recommended dose has not been established for any A_1-PI product.

12.3 Pharmacokinetics

A double-blind, randomized, active-controlled, crossover pharmacokinetic study was conducted in 13 males and 5 females with A_1-PI deficiency, ranging in age from 36 to 66 years. Nine subjects received a single 60 mg/kg dose of Zemaira followed by Prolastin, and 9 subjects received Prolastin followed by a single 60 mg/kg dose of Zemaira, with a wash-out period of 35 days between doses. A total of 13 post-infusion serum samples were taken at various time points up to Day 21. Table 5 shows the mean results for the Zemaira pharmacokinetic parameters.

Table 5: Pharmacokinetic Parameters for Antigenic A_1-PI in 18 Subjects Following a Single 60 mg/kg Dose of Zemaira

Pharmacokinetic Parameter	Mean (SD)*
Area under the curve ($AUC_{0-\infty}$)	144 (±27) µM × day
Maximum concentration (C_{max})	44.1 (±10.8) µM
Terminal half-life ($t_{1/2ß}$)	5.1 (±2.4) days
Total clearance	603 (±129) mL/day
Volume of distribution at steady state	3.8 (±1.3) L

* n=18 subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenesis, mutagenesis, or impairment of fertility have not been conducted.

13.2 Animal Toxicology and/or Pharmacology

In a safety pharmacology study, dogs were administered a 60 or 240 mg/kg intravenous dose of Zemaira. At the clinical dose of 60 mg/kg, no changes in cardiovascular and respiratory parameters or measured hematology, blood chemistry, or electrolyte parameters were attributed to the administration of Zemaira. A minor transient decrease in femoral resistance and increase in blood flow were observed after administration of the 240 mg/kg dose.

In single-dose studies, mice and rats were administered a 0, 60, 240, or 600 mg/kg intravenous dose of Zemaira and observed twice daily for 15 days. No signs of toxicity were observed up to 240 mg/kg. Transient signs of distress were observed in male mice and in male and female rats after administration of the highest dose (600 mg/kg).

In repeat-dose toxicity studies, rats and rabbits received 0, 60, or 240 mg/kg intravenous doses of Zemaira once daily for 5 consecutive days. No treatment-related effects on clinical signs, body weight, hematology, coagulation, or urinalysis were observed in rats administered up to 240 mg/kg. No signs of toxicity were observed in rabbits administered 60 mg/kg. Changes in organ weights and minimal epidermal ulceration were observed in rabbits administered 240 mg/kg, but had no clinical effects.

The local tolerance of Zemaira was evaluated in rabbits following intravenous, perivenous, and

intraarterial administration. No treatment-related local adverse reactions were observed.

14 CLINICAL STUDIES

Clinical trials were conducted with Zemaira 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 A_1-PI deficiency, and 3% had the M_{MALTON} phenotype. At screening, serum A_1-PI levels were between 3.2 and 10.1 µM (mean of 5.6 µM). The objectives of the clinical trials were to demonstrate that Zemaira augments and maintains serum levels of A_1-PI above 11 µM (80 mg/dL) and increases A_1-PI levels in ELF of the lower lung.

In a double-blind, controlled clinical trial to evaluate the safety and efficacy of Zemaira, 44 subjects were randomized to receive 60 mg/kg of either Zemaira or Prolastin once weekly for 10 weeks. After 10 weeks, subjects in both groups received Zemaira for an additional 14 weeks. Subjects were followed for a total of 24 weeks to complete the safety evaluation *[see Adverse Reactions (6.1)]*. The mean trough serum A_1-PI levels at steady state (Weeks 7-11) in the Zemaira-treated subjects were statistically equivalent to those in the Prolastin-treated subjects within a range of ±3 µM. Both groups were maintained above 11 µM. The mean (range and standard deviation [SD]) of the steady state trough serum antigenic A_1-PI level for Zemaira-treated subjects was 17.7 µM (range 13.9 to 23.2, SD 2.5) and for Prolastin-treated subjects was 19.1 µM (range 14.7 to 23.1, SD 2.2). The difference between the Zemaira and the Prolastin groups was not considered clinically significant and may be related to the higher specific activity of Zemaira.

In a subgroup of subjects enrolled in the trial (10 Zemaira-treated subjects and 5 Prolastin-treated subjects), bronchoalveolar lavage was performed at baseline and at Week 11. Four A_1-PI related analytes in ELF were measured: antigenic A_1-PI, A_1-PI:NE complexes, free NE, and functional A_1-PI (ANEC). A blinded retrospective analysis, which revised the prospectively established acceptance criteria showed that within each treatment group, ELF levels of antigenic A_1-PI and A_1-PI:NE complexes increased from baseline to Week 11 (Table 6). 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 trial period as baseline values in the Zemaira-treated subjects were unexpectedly high. No A_1-PI analytes showed any clinically significant differences between the Zemaira and Prolastin treatment groups.

Table 6: Change in ELF From Baseline to Week 11 in a Subgroup Analysis

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

CI, confidence interval.

* n=10 subjects.

† n=5 subjects.

The clinical efficacy of Zemaira or any A_1-PI product in influencing the course of pulmonary emphysema or pulmonary exacerbations has not been demonstrated in adequately powered, randomized, controlled clinical trials.

15 REFERENCES

1. Turino GM, Barker AF, Brantly ML, et al. Clinical features of individuals with PI*SZ phenotype of α_1-antitrypsin deficiency. *Am J Respir Crit Care Med.* 1996;154:1718-1725.
2. Stoller JK, Brantly M, et al. Formation and current results of a patient-organized registry for α_1-antitrypsin deficiency. *Chest.* 2000;118(3):843-848.
3. McElvaney NG, Stoller JK, et al. Baseline characteristics of enrollees in the National Heart, Lung, and Blood Institute Registry of α_1-Antitrypsin Deficiency. *Chest.* 1997;111:394-403.
4. Crystal RG. α_1-antitrypsin deficiency, emphysema, and liver disease; genetic basis and strategies for therapy. *J Clin Invest.* 1990;85:1343-1352.
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8. Gadek JE, Crystal RG. α_1-antitrypsin deficiency. In: Stanbury JB, Wyngaarden JB, Frederickson DS, et al., eds. *The Metabolic Basis of Inherited Disease*. 5th ed. New York, NY: McGraw-Hill; 1983:1450-1467.
9. American Thoracic Society. Guidelines for the approach to the patient with severe hereditary alpha-1-antitrypsin deficiency. *Am Rev Respir Dis.* 1989;140:1494-1497.
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16 HOW SUPPLIED/STORAGE AND HANDLING

Zemaira is supplied in a single use vial containing the amount of functionally active A_1-PI printed on the label.

The product presentation includes a package insert and the following components:

Presentation	Carton NDC Number	Components
1000 mg of functionally active A_1-PI	0053-7201-02	• Zemaira in a single-use vial [NDC 0053-7211-01] • 20 mL vial of Sterile Water for Injection, USP [NDC 0053-7653-20] • One vented transfer device

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 the diluent vial.

17 PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reactions to Zemaira (including hives, generalized urticaria, tightness of the chest, dyspnea, wheezing, faintness, hypotension, and anaphylaxis). Advise patients to discontinue use of Zemaira and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur *[see Warnings and Precautions (5.2)]*.
- Inform patients that because Zemaira is made from human blood, it may carry a risk of transmitting infectious agents (e.g., viruses and, theoretically, the CJD agent) *[see Warnings and Precautions (5.3)]*.
- Inform patients that administration of Zemaira has been demonstrated to raise the plasma level of A_1-

PI, but that the effect of this augmentation on the frequency of pulmonary exacerbations and on the rate of progression of emphysema has not been established by clinical trials.

Prolastin is a registered trademark of Talecris Biotherapeutics, Inc.

Manufactured by:
CSL Behring LLC
Kankakee, IL 60901 USA
US License No. 1767

US Patent No. 8,124,736

PRINCIPAL DISPLAY PANEL - Vial Label

NDC 0053-7211-01

Alpha$_1$-Proteinase Inhibitor (Human)

Zemaira®

Store up to 25°C (77°F).

Rx only
IV use only

Manufactured by:
CSL Behring LLC
Kankakee, IL 60901 USA
US License No. 1767

PRINCIPAL DISPLAY PANEL - Vial Carton

NDC 0053-7201-02
One single dose vial
with diluent

Alpha$_1$-Proteinase Inhibitor (Human)

Zemaira®

For Intravenous Administration Only.

Dosage and Administration: see enclosed package insert.

Reconstitute with accompanying volume of Sterile Water for Injection, USP.
See insert for directions under **Reconstitution.**

Administer at room temperature within 3 hours of reconstitution.

CSL Behring

NDC 0053-7201-02

Alpha$_1$-Proteinase Inhibitor (Human)
Zemaira®

Contains no preservative.

This product is prepared from large pools of human plasma which may contain the causative agents of hepatitis and other viral diseases. See package insert **Warnings and Precautions.**

Following reconstitution with 20 mL of Sterile Water for Injection, USP, the Zemaira® solution contains 73 to 89 mM sodium, 33 to 42 mM chloride, 15 to 20 mM phosphate, and 121 to 168 mM mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

CSL Behring

NDC 0053-7201-02
One single dose vial
with diluent

Alpha$_1$-Proteinase Inhibitor (Human)
Zemaira®

For Intravenous Administration Only.

Dosage and Administration: see enclosed package insert.

Reconstitute with accompanying volume of Sterile Water for Injection, USP. See insert for directions under **Reconstitution.**

Administer at room temperature within 3 hours of reconstitution.

CSL Behring

Die 6402

NDC 0053-7201-02
One single dose vial
with diluent

Alpha$_1$-Proteinase Inhibitor (Human)
Zemaira®

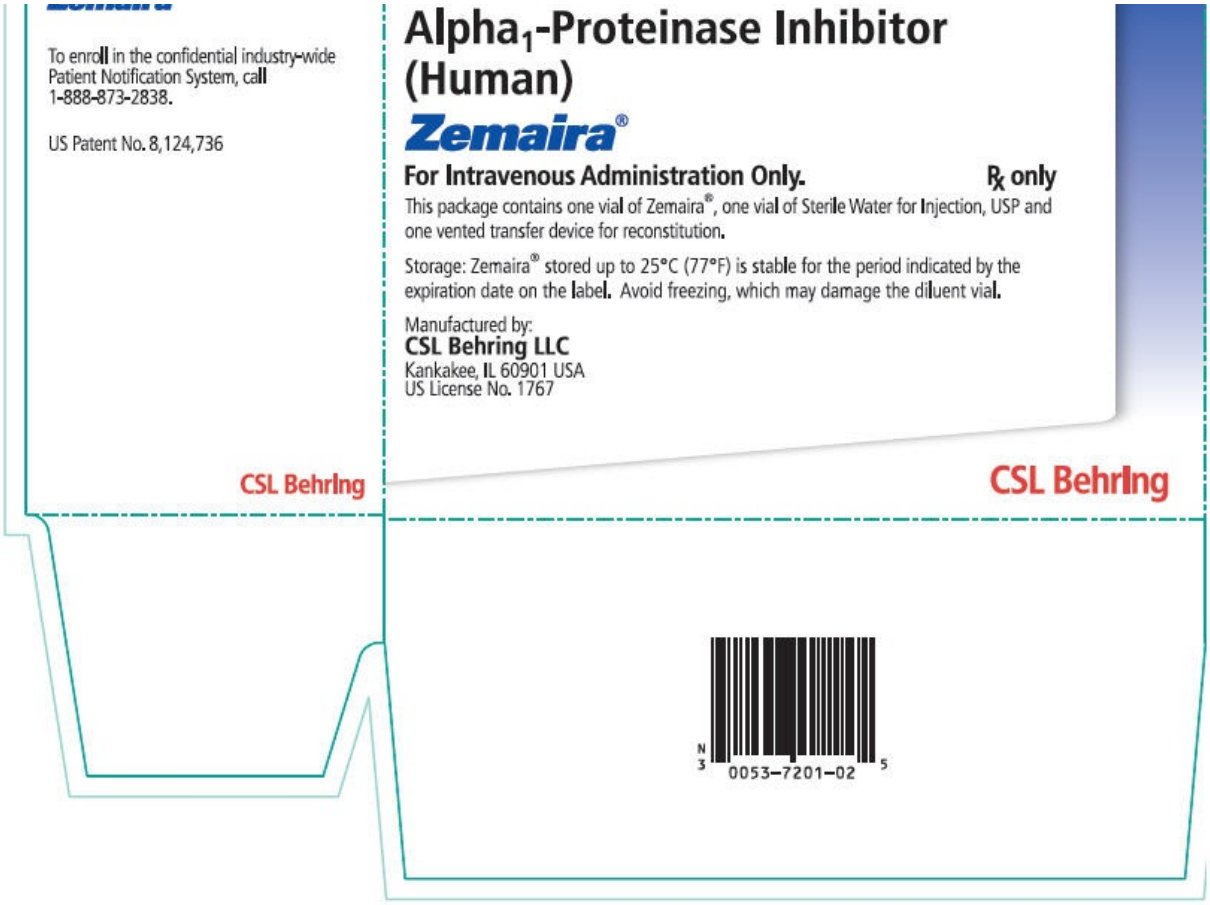
LOT:
EXP:
mg/Vial:

13230-03

NDC 0053-7201-02

Alpha$_1$-Proteinase Inhibitor (Human)
Zemaira®

NDC 0053-7201-02
One single dose vial
with diluent



ZEMAIRA

alpha-1-proteinase inhibitor human kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:0053-7201

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0053-7201-02	1 in 1 CARTON		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL, SINGLE-DOSE	20 mL
Part 2	1 VIAL, SINGLE-DOSE	20 mL

Part 1 of 2

ALPHA-1-PROTEINASE INHIBITOR HUMAN

alpha-1-proteinase inhibitor human injection, powder, lyophilized, for solution

Product Information

Item Code (Source)	NDC:0053-7211		
Route of Administration	INTRAVENOUS	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
alpha-1-proteinase inhibitor human (alpha-1-proteinase inhibitor human)	alpha-1-proteinase inhibitor human	1000 mg in 20 mL

Inactive Ingredients

Ingredient Name	Strength
Sodium Chloride	119 mmol in 20 mL
Sodium Phosphate	17 mmol in 20 mL
Mannitol	144 mmol in 20 mL
hydrochloric acid	
sodium hydroxide	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0053-7211-01	20 mL in 1 VIAL, SINGLE-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125078	07/08/2003	

Part 2 of 2

DILUENT

water injection

Product Information

Item Code (Source)	NDC:0053-7653		
Route of Administration	INTRAVENOUS	**DEA Schedule**	

Inactive Ingredients

Ingredient Name	Strength
Water	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0053-7653-20	20 mL in 1 VIAL, SINGLE-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125078	07/08/2003	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125078	07/08/2003	

Labeler - CSL Behring LLC (058268293)

Establishment

Name	Address	ID/FEI	Business Operations
CSL Behring LLC		058268293	MANUFACTURE

Revised: 5/2013 CSL Behring LLC