Alpha-1 Is A Family Affair

Alpha₁-antitrypsin (A₁AT) deficiency is a hereditary condition that may affect you and your loved ones¹.

Learn more about Alpha-1 and free testing inside

Important Safety Information

Alpha₁-Proteinase Inhibitor (Human), ZEMAIRA® is indicated to raise the plasma level of alpha₁-proteinase inhibitor (A₁-PI) in patients with A₁-PI deficiency and related emphysema. The effect of this raised level on the frequency of pulmonary exacerbations and the progression of emphysema have not been established in clinical trials.

Please see full Important Safety Information inside and enclosed full prescribing information for ZEMAIRA.
What is Alpha-1?

• Alpha-1 is the common name for the hereditary condition known as alpha\textsubscript{1} antitrypsin (A\textsubscript{1}AT) deficiency\textsuperscript{2}

• A\textsubscript{1}AT is a protein in the blood that protects your lungs from damage due to excessive inflammation caused by infection or inhaled irritants, such as tobacco smoke\textsuperscript{2}

• Alpha-1 occurs when there is a low level or insufficient amount of A\textsubscript{1}AT protein in the blood\textsuperscript{2}

What are common risk factors for Alpha-1?

If you have one or more of the following risk factors, you should be tested for Alpha-1\textsuperscript{3}:

• A family history of Alpha-1

• One of these conditions: COPD, emphysema, irreversible asthma

• Unexplained liver disease

• A family history of lung or liver disease

• The skin disease panniculitis

American Thoracic Society recommends testing for everyone with COPD or any of these risk factors.\textsuperscript{3}

Important Safety Information

Because ZEMAIRA is made from human blood, the risk of transmitting infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent and its variant (vCJD), cannot be completely eliminated.

Please see full Important Safety Information inside and enclosed full prescribing information for ZEMAIRA.
In a person with Alpha-1, the $\text{A}_1\text{AT}$ levels are lower than they are in a person who does not have Alpha-1.²

**Alpha-1 lungs**

When there is a low level or deficiency of $\text{A}_1\text{AT}$ in the blood, your lungs cannot be fully protected.²

This image depicts $\text{A}_1\text{AT}$ levels in a person without Alpha-1 (healthy lung) and in a person who has Alpha-1 (deficient lung).

In a person with Alpha-1, the $\text{A}_1\text{AT}$ levels are lower than they are in a person who does not have Alpha-1.⁴
Important Safety Information

Alpha_1-Proteinase Inhibitor (Human), ZEMAIRA® is indicated to raise the plasma level of alpha_1-proteinase inhibitor (A_1-PI) in patients with A_1-PI deficiency and related emphysema. The effect of this raised level on the frequency of pulmonary exacerbations and the progression of emphysema have not been established in clinical trials.

ZEMAIRA may not be suitable for everyone; for example, people with known hypersensitivity to components used to make ZEMAIRA, those with a history of anaphylaxis or severe systemic response to A_1-PI products, and those with certain IgA deficiencies. If you think any of these may apply to you, ask your doctor.

Early signs of hypersensitivity reactions to ZEMAIRA include hives, rash, tightness of the chest, unusual breathing difficulty, wheezing, and feeling faint. Immediately discontinue use and consult with physician if such symptoms occur.

In clinical studies, the following adverse reactions were reported in at least 5% of subjects receiving ZEMAIRA: headache, sinusitis, upper respiratory infection, bronchitis, fatigue, increased cough, fever, injection-site bleeding, nasal symptoms, sore throat, and swelled blood vessels.

Because ZEMAIRA is made from human blood, the risk of transmitting infectious agents, including viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent and its variant (vCJD), cannot be completely eliminated.

Please see enclosed full prescribing information for ZEMAIRA.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.
How is Alpha-1 inherited?

Alpha-1 is a hereditary condition, meaning it is passed on from parents to their children through DNA, or genes.¹

\[\begin{align*}
Z & = \text{Normal gene} \\
M & = \text{Abnormal gene (Mild to moderate symptoms)} \\
S & = \text{Abnormal gene (Severe symptoms)} \\
\end{align*}\]

Alpha-1 is a lifelong journey

The good news is that experienced counselors can help you and your family every step of the way.

Contact an Alpha-1 counselor at the Alpha-1 Genetic Counseling Service (1-800-785-3177).
Why is family testing for Alpha-1 important?

- First-degree relatives (parents, children, siblings) of patients diagnosed with Alpha-1 should be tested\(^5\)
- Testing can help your family treat and manage Alpha-1 for generations to come\(^5\)

**DNA, Advanced Alpha-1 Screening™ can identify Alpha-1 genes that other tests can’t find**

- Simple finger-stick blood test
- Only 1 blood spot (an average of 4 to 6 drops of blood) needed
- Results within 3 to 5 days

References:

Please see full Important Safety Information inside and enclosed full prescribing information for ZEMAIRA.
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**, Alpha1-Proteinase Inhibitor (Human) lyophilized powder for reconstitution for intravenous use  
Initial U.S. Approval: 2003

---

**INDICATIONS AND USAGE**

Dosage and Administration (2.1)  
4/2019

---

**RECENT MAJOR CHANGES**

Dosage and Administration (2.1)  
4/2019

---

**INDICATIONS AND USAGE**

- ZEMAIRA is an alpha1-proteinase inhibitor (A1-PI) indicated for chronic augmentation and maintenance therapy in adults with A1-PI deficiency and clinical evidence of emphysema (1).
- The effect of augmentation therapy with ZEMAIRA or any A1-PI product on pulmonary exacerbations and on the progression of emphysema in A1-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 A1-PI deficiency has not been established (1).

---

**DOSE 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 A1-PI product (2).
- Administer through a suitable 5 micron infusion filter (not supplied) at room temperature within 3 hours after reconstitution (2.2).
- Do not mix with other medicinal products. Administer through a separate dedicated infusion line (2.2).
- Administer 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).

---

Full Prescribing Information Contents*:

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
   2.1 Preparation and Reconstitution
   2.2 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
   5.1 Hypersensitivity to Other A1-PI Products
   5.2 Hypersensitivity to IgA
   5.3 Transmissible Infectious Agents
6 ADVERSE REACTIONS
   6.1 Clinical Trials Experience
   6.2 Immunogenicity
   6.3 Postmarketing Experience
7 USE IN SPECIFIC POPULATIONS
   8.1 Pregnancy
   8.2 Lactation
   8.4 Pediatric Use
   8.5 Geriatric Use
8 USE IN SPECIFIC POPULATIONS
9 DESCRIPTION
10 CLINICAL PHARMACOLOGY
   12.1 Mechanism of Action
   12.2 Pharmacodynamics
   12.3 Pharmacokinetics
11 NONCLINICAL TOXICOLOGY
   13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
   13.2 Animal Toxicology and/or Pharmacology
12 CLINICAL STUDIES
13 REFERENCES
14 HOW SUPPLIED/STORAGE AND HANDLING
15 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.
The effect of augmentation therapy with ZEMAIRA or any A1-PI product on pulmonary individuals with ZEMAIRA are not available.

Clinical data demonstrating the long-term effects of chronic augmentation therapy of maintenance therapy in adults with A1-PI deficiency and clinical evidence of emphysema exacerbations and on the progression of emphysema in A1-PI deficiency has not been demonstrated in randomized, controlled clinical studies.

ZEMAIRA is not indicated as therapy for lung disease patients in whom severe A1-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 A1-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 according to the instructions provided below.
- Reconstitute ZEMAIRA using aseptic technique to maintain product sterility.
- Total reconstitution time for a 1g vial should be obtained within 5 minutes.
- Total reconstitution time for a 4g or 5g vial should be obtained within 10 minutes.
- Reconstituted ZEMAIRA may be stored at room temperature. Do not freeze the reconstituted solution.

Follow the steps provided below for the preparation and reconstitution of ZEMAIRA:

1. Ensure that the ZEMAIRA vial and Sterile Water for Injection vial are at room temperature.
2. Remove the plastic flip-top cap from the Sterile Water for Injection vial.
3. Wipe the rubber stopper of the Sterile Water for Injection vial with antiseptic solution and allow it to dry.
4. Open the Mix2Vial® filter transfer set by peeling off the blister package.
5. Place the Sterile Water for Injection vial on an even, clean surface and hold the vial tight. Take the transfer set together with the blister package and vertically pierce the Sterile Water for Injection vial with the blue tip of the transfer set (Fig. 2).
6. Carefully remove the blister package from the transfer set by holding at the rim, and pulling vertically upwards. Make sure that you only pull away the blister package and not the transfer set (Fig. 3).
7. Remove the plastic flip-top cap from the ZEMAIRA vial.
8. Wipe the rubber stopper of the ZEMAIRA vial with antiseptic solution and allow it to dry.
9. Place the ZEMAIRA vial on an even and firm surface. Invert the Sterile Water for Injection vial with the transfer set attached and vertically pierce the ZEMAIRA vial with the clear tip of the transfer set (Fig. 4). The Sterile Water for Injection will automatically flow into the ZEMAIRA vial.
   Note: Ensure all water has transferred into the ZEMAIRA vial.
10. Follow steps below to remove entire transfer set from ZEMAIRA vial:
   - With one hand tightly grasp the ZEMAIRA vial as shown in Fig. 5.
   - With the other hand tightly grasp Sterile Water for Injection vial and blue transfer set.
   - Bend the entire transfer set to the side until it disconnects from the ZEMAIRA vial (Fig. 5).
   - Discard the Sterile Water for Injection vial with the entire transfer set.
11. Gently swirl the ZEMAIRA vial until the powder is completely dissolved (Fig. 6). DO NOT SHAKE. Take care not to touch the rubber vial stopper.

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 ZEMAIRA 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, 4000 mg, or 5000 mg of functionally active A1-PI as a white to off-white lyophilized powder for reconstitution with 20 mL of Sterile Water for Injection, USP. The amount of functional A1-PI is printed on the vial label and carton.
5 Warnings and Precautions

5.1 Hypersensitivity to Other A1-PI Products
Observe any signs of hypersensitivity such as tachycardia, hypotension, confusion, syncope, oxygen consumption decrease, and pharyngeal edema when administering ZEMAIRA to patients with known IgA as reactivity to an A1-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.

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 blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. The risk of infectious agent transmission has been reduced by screening, placebo-dosing 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 blood, 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 reported following administration of ZEMAIRA in pre-licensure 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 pre-licensure clinical trials were headache, sinusitis, upper respiratory infection, bronchitis, asthma, cough increased, fever, injection site hemorrhage, rhinitis, sore throat, and vasodilation.

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

In post-licensure trials, the exposure adjusted incidence rate (EAIR) of serious exacerbations of chronic obstructive pulmonary disease (COPD) among subjects was higher during the RAPID Extension trial as compared to the rate observed during the preceding RAPID trial [see Adverse Reactions (6.1)].

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.

The following clinical trials were conducted with ZEMAIRA:
- Controlled, double-blind trial in 44 subjects, who received a weekly 60 mg/kg body weight dose of either ZEMAIRA (30 subjects) or Prolastin® (a commercially available Alpha,-Proteinase Inhibitor Human product) (14 subjects) for 10 weeks, followed by an open-label phase in which 43 subjects received ZEMAIRA weekly for 14 weeks;
- Open-label trial in 12 subjects who received a weekly 60 mg/kg body weight dose of ZEMAIRA for 26 weeks, followed by a 7-week to 22-week extension;
- 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;
- 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; and
- Post-Licensure Randomized, Placebo-Controlled Trial of Augmentation Therapy in Alpha-1 Protease Inhibitor Deficiency (RAPID), in 180 subjects who received a weekly 60 mg/kg body weight dose of either ZEMAIRA (93 subjects) or placebo (87 subjects) for 24 months (referred to as years 1 and 2 and Table 3).
- Post-Licensure Open-label extension of the RAPID trial involving 140 subjects who had completed blinded treatment with ZEMAIRA or placebo for 24 months in the RAPID trial and who entered the extension trial and received open-label ZEMAIRA for up to an additional 24 months (referred to as years 3 and 4 in Table 3). 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 pre-licensure clinical trials of ZEMAIRA.

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

<table>
<thead>
<tr>
<th>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).</th>
<th>Number of Subjects (Events per Subject-Year)</th>
<th>Number of Infusions (% of all Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEMAIRA (n=66, SY=28.72)</td>
<td>Prolastin (n=32, SY=3.83)</td>
<td>ZEMAIRA (n=1296)</td>
</tr>
<tr>
<td>ARs</td>
<td>54 (5.6)</td>
<td>16 (3.8)</td>
</tr>
<tr>
<td>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 or for which causality assessment was missing or indeterminate).</td>
<td>4 (0.2)</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

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% of subjects, expressed as events per subject-year, and the corresponding number of ARs of the same type, expressed as % of all infusions, for each treatment in clinical trials of ZEMAIRA.

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

<table>
<thead>
<tr>
<th>ARs (AEs assessed by investigator)</th>
<th>Number of Subjects (Events per Subject-Year)</th>
<th>Number of Infusions (% of all Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEMAIRA (n=66, SY=28.72)</td>
<td>Prolastin (n=32, SY=3.83)</td>
<td>ZEMAIRA (n=1296)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (0.7)</td>
<td>5 (1.3)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>10 (0.5)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>10 (0.4)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5 (0.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Asthma</td>
<td>5 (0.2)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Cough Increased</td>
<td>5 (0.2)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Injection Site Hemorrhage</td>
<td>4 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Sore Throat</td>
<td>4 (0.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>4 (0.1)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

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.

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.

Chronic Obstructive Pulmonary Disease (COPD) Exacerbations

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 RAPID study 25 serious exacerbations of COPD were reported in 15 ZEMAIRA subjects vs. 17 such events in 9 placebo subjects, corresponding to rates of 0.146 exacerbations per subject-year with ZEMAIRA and 0.115 exacerbations per subject-year with placebo, (ratio ZEMAIRA:Placebo [95% confidence interval]: 1.256 [0.457 - 3.454]).

Subjects who were randomized to ZEMAIRA in the 2-year RAPID trial who then entered and received open-label ZEMAIRA in the 2 year RAPID extension trial were in the “Early Start” group. Subjects who were randomized to placebo in the 2-year RAPID trial who then entered and received open-label ZEMAIRA in the 2 year RAPID extension trial were in the “Delayed Start” group. During the RAPID extension trial 37 serious exacerbations of COPD were reported in 19 subjects (25%) in the Early Start group, corresponding to rates of 0.25 exacerbations per subject-year. In comparison, 20 serious exacerbations were reported in 11 subjects (17%) in the Delayed Start group corresponding to rates of 0.16 exacerbations per subject-year (ratio Early: Delayed [95% confidence interval]: 1.58 [0.68 – 3.66], Table 3). Among the Early Start subjects who entered the RAPID extension trial (N = 76), the exposure adjusted incidence rate of serious exacerbations during the RAPID extension trial (years 3-4) was 0.25 compared to 0.12 for those subjects during the earlier RAPID trial (years 1-2), (ratio RAPID Extension:RAPID: 2.10 [95% confidence interval: 1.21 - 3.67]). Among the Delayed Start subjects who entered the RAPID extension trial (N = 64), the exposure adjusted incidence rate of serious exacerbations during the RAPID extension trial (years 3-4) was 0.16 compared to 0.10 for those subjects during the earlier RAPID trial (years 1-2), (ratio RAPID Extension:RAPID: 1.56 [95% confidence interval: 0.80 – 3.03]).

Table 3. Comparison of Exposure-Adjusted Incidence Rates (EAIR) for Serious COPD Exacerbations Occurring in the RAPID study between ZEMAIRA and Placebo subjects and in the RAPID Extension Studies between Early Start and Delayed Start subjects

<table>
<thead>
<tr>
<th>Treatment Ratio for EAIR (95% CI)*</th>
<th>Early: Delayed</th>
<th>EAIR (95% CI)</th>
<th>Placebo (N = 87)</th>
<th>ZEMAIRA: Placebo</th>
<th>EAIR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RAPID Study</strong> (Years 1 – 2)</td>
<td></td>
<td>Early Start†</td>
<td>0.15 (0.10-0.25)</td>
<td>0.12 (0.07-0.18)</td>
<td>1.26 (0.46-3.45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Delayed Start‡ (N = 64)</td>
<td>0.16 (0.10-0.25)</td>
<td>1.58 (0.68-3.66)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Early: Delayed</td>
<td>0.25 (0.18-0.35)</td>
<td>20 11 17.2</td>
<td>0.16 (0.10-0.25)</td>
</tr>
<tr>
<td><strong>Extension Study</strong> (Years 3-4)</td>
<td></td>
<td>Early: Delayed</td>
<td>25 15 37 19</td>
<td>20 11 17.2</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. ARs Reported During the Postmarketing Use of ZEMAIRA

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term/Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Hypersensitivity, pruritus, rash including exfoliative and generalized, urticaria</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Hypoesthesia, paresthesia, dizziness</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Skin disorders</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary

No animal reproduction studies have been conducted with ZEMAIRA and its safety for use in human pregnancy has not been established in controlled clinical trials. Since alpha-1-proteinase inhibitor is an endogenous human protein, it is considered unlikely that ZEMAIRA will cause harm to the fetus when given at recommended doses. However, ZEMAIRA should be given with caution to pregnant women. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation Risk Summary

There is no information regarding the excretion of ZEMAIRA in human milk, the effect on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ZEMAIRA and any potential adverse effects on the breastfed infant from ZEMAIRA or from the underlying maternal condition.

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 to off-white, lyophilized preparation of purified alpha-1-proteinase inhibitor (human) (A1-PI), also known as alpha,-antitrypsin, to be reconstructed and 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 (total A1-PI/total protein) is ≥90% A1-PI. Each vial contains approximately 1000 mg, 4000 mg or 5000 mg of functionally active A1-PI. The measured amount per vial of functionally active A1-PI as determined by its capacity to neutralize human neutrophil elastase (NE) is printed on the vial label and carton.

Table 5. Cumulative (Log10) Virus Inactivation/Removal in ZEMAIRA

<table>
<thead>
<tr>
<th>Virus</th>
<th>Enveloped Viruses</th>
<th>Non-Enveloped Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td>BVDV</td>
<td>WNV</td>
</tr>
<tr>
<td>Heat treatment†</td>
<td>≥6.8</td>
<td>≥5.2</td>
</tr>
<tr>
<td>Nanofiltration</td>
<td>≥5.5</td>
<td>≥5.4</td>
</tr>
</tbody>
</table>

Table 5. Cumulative (Log10) Virus Inactivation/Removal in ZEMAIRA

<table>
<thead>
<tr>
<th>Virus</th>
<th>Enveloped Viruses</th>
<th>Non-Enveloped Viruses</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1</td>
<td>BVDV</td>
<td>WNV</td>
</tr>
<tr>
<td>Heat treatment†</td>
<td>≥6.8</td>
<td>≥5.2</td>
</tr>
<tr>
<td>Nanofiltration</td>
<td>≥5.5</td>
<td>≥5.4</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus type 1, a model for HIV-1 and HIV-2. BVDV, bovine viral diarrhea virus, a model for HIV. WNV, West Nile virus. PRV, pseudorabies virus, a non-specific model for large DNA viruses, e.g., herpes. HA, hepatitis A virus. CVF, canine parvovirus, model for B19V.

† At 60°C for 10 hours.

Virus, uncertain size, it is not always possible to reliably estimate the frequency of these reactions due to an insufficient number of subjects.
12.1 Mechanism of Action
A polymorphism in the PI-α gene is a common, hereditary, autosomal, co-dominant disorder that is usually fatal in its severe form. Low blood levels of A1-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, PIZZ individuals, whose serum A1-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 A1-PI levels are above or below 11 µM. Not all individuals with severe genetic variants of A1-PI deficiency have emphysema. Augmentation therapy with alpha1-proteinase inhibitor (human) is indicated only in patients with severe congenital A1-PI deficiency who have clinically evident emphysema. A 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. 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 clinically symptomatic 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. Increasing the levels of functional protease inhibitor by intravenous infusion is an approach to therapy for patients with A1-PI deficiency. However, the efficacy of augmentation therapy in the prevention of emphysema has not been demonstrated in randomized, controlled clinical trials. 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 A1-PI product actually protects the lower respiratory tract from progressive emphysematous changes has not been evaluated. Individuals with endogenous levels of A1-PI below 11 µM, in general, manifest a significantly increased risk for development of emphysema above the general population background risk. Although the maintenance of blood serum levels of A1-PI (antigenically measured) above 11 µM has been historically postulated to provide therapeutically relevant anti-neutrophil elastase protection, this has not been proven. Individuals with severe A1-PI deficiency have been shown to have increased neutrophil and NE concentrations in lung epithelial lining fluid compared to normal PI MM individuals, and some PIZ individuals with A1-PI above 11 µM have emphysema attributed to A1-PI deficiency. These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of A1-PI during augmentation therapy.

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 NE. Normal healthy individuals produce sufficient A1-PI to control the NE produced by activated neutrophils and are thereby subject to more rapid proteolysis of the alveolar walls leading to chronic lung disease. ZEMAIRA serves as an A1-PI augmentation therapy in this patient population, acting to increase and maintain serum levels and ELF levels of A1-PI.

12.2 Pharmacodynamics
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 µM. The clinical benefit of the increased blood levels of A1-PI at the recommended dose has not been established for any A1-PI product.

12.3 Pharmacokinetics
A double-blind, randomized, active-controlled, crossover pharmacokinetic study was conducted in 13 males and 5 females with A1-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 6 shows the mean results for the ZEMAIRA pharmacokinetic parameters.

Table 6. Pharmacokinetic Parameters for Antigenic A1-PI in 18 Subjects Following a Single 60 mg/kg Dose of ZEMAIRA

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Mean (SD)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under the curve (AUC&lt;sub&gt;0-21&lt;/sub&gt;)</td>
<td>144 (±27.7) µM x day</td>
</tr>
<tr>
<td>Maximum concentration (C&lt;sub&gt;max&lt;/sub&gt;)</td>
<td>44.1 (±10.8) µM</td>
</tr>
<tr>
<td>Terminal half-life (t&lt;sub&gt;1/2&lt;/sub&gt;)</td>
<td>5.1 (±2.4) days</td>
</tr>
<tr>
<td>Total clearance</td>
<td>603 (±129) mL/day</td>
</tr>
<tr>
<td>Volume of distribution at steady state</td>
<td>3.8 (±1.3) L</td>
</tr>
</tbody>
</table>

* n=18 subjects.

In a double-blind, randomized, active-controlled, crossover pharmacokinetic study, 44 subjects received a 60 mg/kg 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.

14 CLINICAL STUDIES
Clinical trials were conducted pre-licensure 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 A1-PI deficiency, and 3% had the MZ phenotype. At screening, serum A1-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 A1-PI above 11 µM (80 µg/dL) and increases A1-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 A1-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 antigenic A1-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 A1-PI related analytes in ELF were measured: antigenic A1-PI, A1-PI:NE complexes, free NE, and functional A1-PI (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 (Table 7). 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 A1-PI analytes showed any clinically significant differences between the ZEMAIRA and Prolastin treatment groups.

Table 7. Change in ELF From Baseline to Week 11 in a Subgroup Analysis

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Treatment</th>
<th>Mean Change From Baseline</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1-PI (nM)</td>
<td>ZEMAIRA*</td>
<td>1358.3</td>
<td>822.6 to 1894.0</td>
</tr>
<tr>
<td></td>
<td>Prolastin†</td>
<td>949.9</td>
<td>460.0 to 1439.7</td>
</tr>
<tr>
<td>ANEC (nM)</td>
<td>ZEMAIRA</td>
<td>-588.1</td>
<td>-2032.3 to 856.1</td>
</tr>
<tr>
<td></td>
<td>Prolastin</td>
<td>497.5</td>
<td>-392.3 to 1387.2</td>
</tr>
<tr>
<td>A1-PI:NE Complexes (nM)</td>
<td>ZEMAIRA</td>
<td>118.0</td>
<td>39.9 to 196.1</td>
</tr>
<tr>
<td></td>
<td>Prolastin</td>
<td>287.1</td>
<td>49.8 to 524.5</td>
</tr>
</tbody>
</table>

* n=10 subjects.
† n=5 subjects.

The clinical efficacy of ZEMAIRA or any A1-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

16 HOW SUPPLIED/STORAGE AND HANDLING
How Supplied
ZEMAIRA is supplied in a single use vial containing the amount of functionally active A1-PI printed on the vial label and carton.

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Kit NDC Number</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000 mg of functionally active A1-PI</td>
<td>0053-7203-02</td>
<td>• ZEMAIRA in a single-use vial [NDC 0053-7213-01]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 95 mL vial of Sterile Water for Injection, USP [NDC 0053-7653-12]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• One Mix2Vial filter transfer set for reconstitution</td>
</tr>
</tbody>
</table>

Storage and Handling
- When stored up to 25°C (77°F), ZEMAIRA is stable for the period indicated by the expiration date on its vial label and carton.
- 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, the variant Creutzfeldt-Jakob disease (vCJD) agent and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent [see Warnings and Precautions (5.3)].
- Inform patients that administration of ZEMAIRA has been demonstrated to raise the plasma level of A1-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.
- Dizziness may occur following the administration of ZEMAIRA; therefore, patients...