A comprehensive support program
to help your Alpha-1 patients with personalized assistance

Starting ZEMAIRA

ZEMAIRA QuickAccessSM
• Free product and up to $3,000 in co-pay assistance
• Eligible patients may receive up to 4 weeks of ZEMAIRA at no cost

Affording ZEMAIRA

CSL Behring AssuranceSM
• Free product for eligible patients who experience a lapse or gap in commercial insurance coverage

Patient Assistance ProgramSM
• Support for both uninsured and underinsured patients

Financial assistance
• Connect patients with financial assistance support

Connect your patients with other Alphas through our partnership with AlphaNet

For more information about ZEMAIRA and starting treatment for your patients, call ZEMAIRA CareZ today. Experienced case managers are ready to assist you.

1-866-ZEMAIRA (1-866-936-2472)

Important Safety Information

Alpha1-Proteinase Inhibitor (Human), ZEMAIRA® is indicated for chronic augmentation and maintenance therapy for adults with alpha1-proteinase inhibitor (A1-PI) deficiency and emphysema. The effect of augmentation therapy with ZEMAIRA or any A1-PI product on pulmonary exacerbations and progression of emphysema in A1-PI deficiency has not been demonstrated in randomized, controlled clinical studies.

Please see full Important Safety Information on back and enclosed full prescribing information for ZEMAIRA.
Starting ZEMAIRA

1. **Step 1 | Have your patients enroll in ZEMAIRA CareZ®**
   - Complete and sign the ZEMAIRA referral form

   **Remember to:**
   - Provide all patient demographics and insurance information. For prompt processing, please make sure all information is complete
   - Check the ZEMAIRA QuickAccess program box for early access to sample product
   - Check the AlphaNet box to connect patients with other Alphas for education and support

2. **Step 2 | Approximately 24 hours after receipt of a completed referral form, CareZ will:**
   - Confirm receipt of the referral with your practice
   - Call your patients to introduce all the CareZ program services
   - Provide your patients with a CareZ welcome kit

3. **Step 3 | Within 72 hours upon receipt of a completed referral form, access information for ZEMAIRA will be provided**
   - CareZ will inform your practice of the results of the benefits investigation
   - CareZ will initiate care with specialty pharmacy or infusion clinic

If you have questions about ZEMAIRA and/or starting your patients on ZEMAIRA, call CareZ today.
Experienced case managers are ready to assist you.
1-866-ZEMAIRA (1-866-936-2472)

**Important Safety Information**
ZEMAIRA is contraindicated in patients with a history of severe systemic reactions to the product or to A1-PI protein, including anaphylaxis. Due to the risk of severe hypersensitivity, ZEMAIRA is also contraindicated in immunoglobulin A-deficient patients with antibodies against IgA.

Please see full Important Safety Information on back and enclosed full prescribing information for ZEMAIRA.
Affording ZEMAIRA

CareZ provides a variety of patient support services regardless of insurance coverage or financial situation

<table>
<thead>
<tr>
<th>Commercial insurance</th>
<th>State- or federally funded insurance</th>
<th>Uninsured or underinsured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Patient Assistance Program</td>
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<td>Sample Program</td>
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<td>ZEMAIRA® Signature SavingsSM Co-pay Program</td>
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<td>ZEMAIRA QuickAccess</td>
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</tbody>
</table>

Connecting with Alphas

AlphaNet
Our partnership with AlphaNet, Inc. keeps your patients connected to other Alphas who understand the challenges of living with Alpha-1.

Maintaining your health

My Steps for Healthy Living
The My Steps for Healthy Living program is a self-paced walking program designed for all Alphas to reinforce the potential therapeutic benefits of an active Alpha-1 lifestyle.

Please see full Important Safety Information on back and enclosed full prescribing information for ZEMAIRA.
CareZ is the single point of contact for access, reimbursement, and ongoing support for you and your Alpha-1 patients

Starting ZEMAIRA
- Simple referral process

Affording ZEMAIRA
- Experienced reimbursement case managers are standing by to assist with:
  - Navigating access to ZEMAIRA by working with your patients’ insurance provider to:
    - Determine coverage
    - Enroll your patients in appropriate financial assistance programs

Community and lifestyle
- AlphaNet Coordinators provide nonmedical peer-to-peer counseling

If you have questions about ZEMAIRA and/or starting your patients on ZEMAIRA, call CareZ today. Experienced case managers are ready to assist you. 1-866-ZEMAIRA (1-866-936-2472)

Important Safety Information
Alpha1-Proteinase Inhibitor (Human), ZEMAIRA® is indicated for chronic augmentation and maintenance therapy for adults with alpha1-proteinase inhibitor (A1-PI) deficiency and emphysema. The effect of augmentation therapy with ZEMAIRA or any A1-PI product on pulmonary exacerbations and progression of emphysema in A1-PI deficiency has not been demonstrated in randomized, controlled clinical studies.

ZEMAIRA is not indicated for lung disease patients in whom severe A1-PI deficiency has not been established.

ZEMAIRA is contraindicated in patients with a history of severe systemic reactions to the product or to A1-PI protein, including anaphylaxis. Due to the risk of severe hypersensitivity, ZEMAIRA is also contraindicated in immunoglobulin A-deficient patients with antibodies against IgA.

Use caution in administering ZEMAIRA to patients who have experienced anaphylaxis or severe systemic reactions to another A1-PI product. Patients with selective or severe IgA deficiency can develop antibodies to IgA and are at greater risk of such reactions. If anaphylactic or severe anaphylactoid reactions occur during infusion, discontinue immediately.

In pre-licensure clinical studies, the following adverse reactions were reported in at least 5% of subjects receiving ZEMAIRA: headache, sinusitis, upper respiratory infection, bronchitis, asthenia, increased cough, fever, injection-site hemorrhage, rhinitis, sore throat, and vasodilation.

ZEMAIRA is derived from human plasma. The risk of transmission of 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.
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).

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).

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, 76 mL, or 95 mL of Sterile Water for Injection, USP. The amount of functional A1-PI is printed on the vial label and carton (3).

- History of anaphylaxis or severe systemic reactions to ZEMAIRA or A1-PI protein (4).
- Immunoglobulin A (IgA)-deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity (4).

- Observe any signs of hypersensitivity such as tachycardia, hypotension, confusion, syncope, oxygen consumption decrease, and pharyngeal edema when administering ZEMAIRA to patients with known hypersensitivity to an A1-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 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 (5.3).

- 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 occurring in at least 5% of subjects receiving ZEMAIRA in all pre-licensure 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.

See 17 for PATIENT COUNSELING INFORMATION.  
Revised: April 2019
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. ZEMAIRA increases antigenic and functional (anti-neutrophil elastase capacity [ANEC]) serum levels and lung epithelial lining fluid (ELF) levels of A1-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 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. ZEMAIRA is not indicated as therapy for lung disease patients in whom severe A1-PI deficiency has not been established.

2 DOSEAGE 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 an aseptic technique to maintain product sterility.
- Total reconstitution time for a 4g or 5g vial should be obtained within 10 minutes.
- Total reconstitution time for a 1g vial should be obtained within 5 minutes.
- Inspect the reconstituted solution prior to administration. The solution should be clear, colorless to slightly yellow, and free from visible particles.
- 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 lid (Fig. 1). Do not remove the transfer set from 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 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, 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.
4 CONTRAINdications
- ZEMAIRA is contraindicated in patients with a history of anaphylaxis or severe systemic reactions to ZEMAIRA or Aβ-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 Aβ-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 deficiency or an Aβ-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 plasma donors for prior exposure to certain viruses, testing for the presence of certain current virus infections, and including virus inactivation/removal 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 infectious risk to 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 reaction (AR) 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-1-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 9 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 in 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></th>
<th>Number of Subjects* (Events per Subject-Year†)</th>
<th>Number of Infusions § (% of all Infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEMAIRA</td>
<td>(n=66, SY=28.72)</td>
<td>ZEMAIRA (n=1296) Prolastin (n=160)</td>
</tr>
<tr>
<td>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)</td>
<td>54 (5.6) 16 (3.8) 160 (12.3) 31 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13 (0.7) 5 (1.3) 19 (1.5) 5 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>10 (0.5) 1 (0.3) 13 (1.0) 1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Infection</td>
<td>10 (0.4) 1 (0.3) 10 (0.8) 1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5 (0.2) 0 (0.0) 6 (0.5) 0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>5 (0.2) 2 (0.5) 5 (0.4) 2 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Cough Increased</td>
<td>5 (0.2) 1 (0.5) 5 (0.4) 2 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>4 (0.1) 0 (0.0) 4 (0.3) 0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Injection Site Hemorrhage</td>
<td>4 (0.1) 0 (0.0) 4 (0.3) 0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4 (0.1) 0 (0.0) 4 (0.3) 0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Sore Throat</td>
<td>4 (0.1) 0 (0.0) 4 (0.3) 0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Vasodilation</td>
<td>4 (0.1) 1 (0.3) 4 (0.3) 1 (0.6)</td>
<td></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% 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 clinical trials of ZEMAIRA.

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

<table>
<thead>
<tr>
<th></th>
<th>Number of Subjects* (Events per Sub-ject-Year†)</th>
<th>Number of Infusions § (% of all Infusions)</th>
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<td>Rhinitis</td>
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<td>Sore Throat</td>
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<td>Vasodilation</td>
<td>4 (0.1) 1 (0.3) 4 (0.3) 1 (0.6)</td>
<td></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.
‡ 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.

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]: 1.56 [0.46 – 3.45]). 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>Serious COPD Exacerbations*</th>
<th>EAR</th>
<th>EAR</th>
<th>EAR</th>
<th>EAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEMAIRA (N = 93)</td>
<td>0</td>
<td>0</td>
<td>1.26 (0.46 - 3.45)</td>
<td></td>
</tr>
<tr>
<td>Placebo (N = 87)</td>
<td>0</td>
<td>0</td>
<td>1.58 (0.68 - 3.66)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RAPID Study (Years 1 – 2)</th>
<th>Early Start (N = 76)</th>
<th>Delayed Start (N = 64)</th>
<th>Early: Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZEMAIRA</td>
<td>0.25 (0.18 - 0.33)</td>
<td>0.16 (0.10 - 0.25)</td>
<td>1.26 (0.46 - 3.45)</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.15 (0.10 - 0.22)</td>
<td>0.12 (0.07 - 0.18)</td>
<td>1.26 (0.46 - 3.45)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extension Study (Years 3-4)</th>
<th>Early Start (N = 64)</th>
<th>Delayed Start (N = 76)</th>
<th>Early: Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Start</td>
<td>0.25 (0.18 - 0.33)</td>
<td>0.16 (0.10 - 0.25)</td>
<td>1.26 (0.46 - 3.45)</td>
</tr>
<tr>
<td>Early: Delayed</td>
<td>0.15 (0.10 - 0.22)</td>
<td>0.12 (0.07 - 0.18)</td>
<td>1.26 (0.46 - 3.45)</td>
</tr>
</tbody>
</table>

| N = total number of safety subjects, n = number of subjects within a category, % = n/N*100, CI = Confidence Interval. | | | |

8.2 Lactation
Risk Summary
No animal reproduction studies have been conducted with Zema 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 Zema will cause harm to the fetus when given at recommended doses. However, Zema 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.

8.4 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-1-antiproteinase, to be reconstituted and administered by the intravenous route. ZEMAIRA contains active 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 a functional assay is ≥90% of the labeled amount.

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>Lymph node pain</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
</tr>
<tr>
<td>General disorders and administration side conditions</td>
<td>Chills, infusion site reactions, facial, periorbital, lip and extremity swelling, chest pain</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Hypoesthesia, paresthesia, dizziness</td>
</tr>
<tr>
<td>Skin disorders</td>
<td>Hyperhidrosis, pruritus, rash including exfoliative and generalized, urticaria</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Flushing</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
No animal reproduction studies have been conducted with Zema 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 Zema will cause harm to the fetus when given at recommended doses. However, Zema 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.

<table>
<thead>
<tr>
<th>8.2 Lactation</th>
<th>Risk Summary</th>
</tr>
</thead>
</table>
No animal reproduction studies have been conducted with Zema 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 Zema will cause harm to the fetus when given at recommended doses. However, Zema 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.

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

<table>
<thead>
<tr>
<th>Manufacturing Step</th>
<th>HIV-1</th>
<th>BVDV</th>
<th>WNV</th>
<th>PRV</th>
<th>HAV</th>
<th>CPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enveloped Viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Enveloped Viruses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heat treatment†</td>
<td>≥6.8</td>
<td>≥5.2</td>
<td>≥5.3</td>
<td>4.4</td>
<td>≥5.4</td>
<td>na</td>
</tr>
<tr>
<td>Neutralization</td>
<td>≥5.5</td>
<td>≥5.4</td>
<td>≥5.5</td>
<td>≥6.3</td>
<td>≥5.3</td>
<td>≥6.4</td>
</tr>
<tr>
<td>Cumulative Virus Reduction (log10)</td>
<td>≥12.3</td>
<td>≥10.6</td>
<td>≥16.7</td>
<td>≥10.7</td>
<td>≥10.7</td>
<td>≥6.4</td>
</tr>
</tbody>
</table>

* Studies using B19V, which are considered experimental in nature, have demonstrated a virus reduction factor of 1.9 log10.
† At 60ºC for 10 hours.
12.2 Pharmacodynamics

Weekly repeated infusions of A-PI at a dose of 60 mg/kg lead to serum A-PI levels above the historical target threshold of 11 µM. The clinical benefit of the increased blood levels of A-PI at the recommended dose has not been established for any A-PI product.

12.3 Pharmacokinetics

A double-blind, randomized, active-controlled, crossover pharmacokinetic study was conducted in 13 males and 5 females with A-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 A-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 (AUCinf)</td>
<td>144 ± (27) µM x day</td>
</tr>
<tr>
<td>Maximum concentration (C_max)</td>
<td>44.1 (±10.8) µM</td>
</tr>
<tr>
<td>Terminal half-life (t1/2)</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.

The clinical efficacy of ZEMAIRA or any A-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.