Prescribing ZEMAIRA: An Instructional Guide

ZEMAIRA is indicated for chronic augmentation and maintenance therapy for adults with alpha$_1$-proteinase inhibitor (A_1-PI) deficiency and emphysema. No clinical data are available demonstrating the effect of augmentation therapy with ZEMAIRA or any A_1-PI product on the progression of emphysema in A_1-PI deficiency.

Please see full Prescribing Information.

Zemaira®
alpha$_1$-proteinase inhibitor (Human)

Completing the Prescription and Service Request Form

Patient Information

- Complete the patient's First Name, Last Name, DOB, ZIP, Gender, Phone, and Email

Patient Insurance Information

- If the patient does not have insurance, indicate on form
- If the patient does have insurance, the Primary Medical Insurance and ID # fields must be completed
- It is recommended that you attach copies of both sides of the patient's pharmacy and insurance card(s)

Medical Information and Prescribing Physician Information

- Select the appropriate diagnosis/ICD-10 code, indicate whether patient has previously received augmentation therapy, and describe his/her medical history
- Provide the following patient information: smoking history (including dates), drug allergies, concurrent medicines, vascular access points
- Attach/send the following documentation: signed medical history and physical, serum A_1AT with genotype, lung imaging, non-smoker or smoking cessation program attestation with MD and patient signatures
- Complete the Prescriber's Name, NPI #, Address, City, State, Phone Number, Fax Number, and Office Contact Name fields

Prescription Information and Prescriber Authorization

- Indicate dosage, which supplies (if any) are required, refill quantities, and any specific lab order you may have
- Under Section 6 (Prescriber Authorization Required), sign your name on the designated line. Also, indicate (with another signature) whether you will allow prescription substitution or would like the prescription dispensed as written

Patient Services Authorization and Release of Health Information

- If a patient wants to enroll in ZEMAIRA Connect, he or she must sign this section or contact ZEMAIRA Connect directly at 1-866-936-2472
  - Before patients elect or decline to enroll, they should read Section 7 on page 3
  - Please note that enrolling in ZEMAIRA Connect is not required for a patient to receive his or her prescription, but the patient must be enrolled to be eligible for financial assistance and other programs
  - To allow information regarding the ZEMAIRA prescription to be left on an answering machine or voicemail, initial the appropriate statement
- Please note that the patient's consent to Section 7 is mandatory in order for ZEMAIRA Connect to process the prescription
- If the patient is not present to sign the form, please fax the form to ZEMAIRA Connect so that the prescription process can begin

1 fill it out

and sign it.

2 fax it

to 1-855-829-5365.

- **A Fax Receipt Confirmation will be provided by ZEMAIRA Connect**
- **If any of the information is missing or incomplete, ZEMAIRA Connect will fax a Missing Information Form**

Also include patient:

- ✔ **Lab results**
- ✔ **Pulmonary function test**
- ✔ **History and physical (signed)**
- ✔ **Serum A_1AT with genotype**
- ✔ **Lung imaging**
- ✔ **Non-smoker or smoking cessation program attestation (signed)**

3 finished

ZEMAIRA Connect takes care of the rest! After verifying your new patient's eligibility, your ZEMAIRA Connect Case Manager will:

- ✔ **Complete a benefit investigation and coordinate access**
- ✔ **Confirm your patient's contact and prescription delivery information through a specialty pharmacy**

Zemaira® Connect℠

ZEMAIRA Prescription & Service Request Form

Fax completed form to 1-855-829-5365 | Phone: 1-866-ZEMAIRA (1-866-936-2472)

Zemaira® alpha$_1$-proteinase inhibitor (Human)

1 Patient Information

☐ Check here if information is included on additional pages

Patient first name _____ Middle initial ____ Last name _____ DOB ____/____/____ SSN (last 4 digits only) ____ ____ ____ ____ Gender ☐ M ☐ F

Street address _____ City _____ State _____ ZIP _____

Home phone _____ Mobile phone _____ Work phone _____ Email _____

Alternate caregiver first name _____ Last name _____ Phone number _____ Email _____ Relationship to patient _____

2 Patient Insurance Information — Please attach copies of both sides of all patient's medical and prescription insurance card(s), if available.

☐ Check if patient does not have insurance

Primary insurance name _____

Insurance phone _____ Policy # _____

Policyholder name _____ Policyholder DOB ____/____/____

Secondary insurance name _____

Insurance phone _____ Policy # _____

Policyholder name _____ Policyholder DOB ____/____/____

Pharmacy plan name _____ Group # _____ Policy # _____ Rx BIN # _____ Rx PCN # _____

I have read and agree to the attached Patient Authorization Section 7: Patient Services Authorization and Release of Health Information. (Signature and date may be required to receive certain services.)

Patient signature _____ Date _____

Initial Here

The initials to the left denote that I authorize ZEMAIRA Connect to leave information regarding my ZEMAIRA prescription, insurance coverage, and Specialty Pharmacy Provider on my voicemail or with alternate contact _____ (participation optional).

3 Medical Information — Please include a copy of patient's clinical notes, if available.

Diagnosis ☐ Alpha$_1$ Antitrypsin Deficiency E88.01 AND/OR ☐ Other ICD-10 _____ Phenotype _____ FEV1 _____ % predicted PFTs

Serum A$_1$AT level (At diagnosis) _____ mg/dL OR _____ µM Serum A$_1$AT level (Current) _____ mg/dL OR _____ µM

Treatment history Has patient ever received augmentation therapy? ☐ Yes ☐ No If yes, which therapy? _____

Medical history ☐ COPD ☐ Asthma ☐ Emphysema ☐ Other _____

Smoking history ☐ Yes ☐ No If yes, date stopped _____ ☐ NKDA ☐ Known drug allergies _____

Concurrent meds _____ **Vascular access** ☐ Peripheral ☐ Central ☐ Port

Please attach/send the following clinical documentation:

☐ History and physical (signed) ☐ Serum A$_1$AT with genotype ☐ Lung imaging ☐ Non-smoker or smoking cessation program attestation (signed)

4 Prescribing Physician Information

Prescriber's first name _____ Last name _____ Specialty _____ NPI # _____ Tax ID # _____ State license # _____

Office/clinic/institution name _____ Street address _____ City _____ State _____ ZIP _____

Office contact name _____ Office contact email _____

Office contact phone _____ Office contact fax _____

5 Prescription Information

Medication	Dose	Directions
ZEMAIRA	☐ Recommended dose is 60 mg/kg IV weekly. ☐ Other dose/frequency _____ Patient weight _____ kg (1 kg = 2.2 lb)	Rate protocol: As tolerated by patient, not to exceed 0.08 mL per kg per minute.

Supplies (please strike through if not required)

Dispense needles, 5 micron infusion filter, syringes, ancillary supplies, and home medical equipment necessary to administer medication.

Quantity/Refills

☐ Dispense 1-month supply. Refill x 1 year unless noted otherwise.
☐ Dispense 90-day supply. Refill x 1 year unless noted otherwise.
☐ Other _____

Lab Orders

Skilled nursing visit as needed to establish venous access, administer medication, and assess general status and response to therapy. Visit frequency based on prescribed orders.

*If nursing services will be required for therapy administration, the home health nurse will call for additional orders per state regulations.

**ALL fields must be completed to expedite prescription fulfillment.

If shipped to physician's office, physician accepts on behalf of patient for administration in office.

6 Prescriber Authorization Required

I have discussed with the above-named patient or the patient's legal guardian that CSL Behring sponsors a program through which CSL Behring will make a limited free supply of ZEMAIRA available to the patient. The patient desires to participate in this CSL Behring program and receive the free product. I certify that the requested product is medically necessary for this patient and that the patient has no treatment history with this product (or has not been treated with this product in the last 12 months).

I have received the necessary written authorization from the patient or the patient's legal guardian to release to CSL Behring and its contracted agents, working solely on behalf of patient, the medical and/or other patient information included in this form relating to the patient referenced above for the purposes of participating in programs and services offered through CSL Behring ZEMAIRA Connect, which may include any of the following: participating in the ZEMAIRA Trial program, seeking reimbursement through ZEMAIRA Connect, verifying insurance coverage and/or the evaluation of the patient's eligibility for alternate sources of funding patient support services, including materials fulfillment, and product fulfillment via specialty pharmacies.

If I have requested free trial product, I will not directly or indirectly sell, resell, trade, barter, or return for credit the requested product or seek reimbursement for them from any source whatsoever, including any public or private third-party program. The prescriber is to comply with his/her state-specific prescription requirements such as e-prescribing, state-specific prescription form, fax language, etc. Noncompliance with state-specific requirements could result in outreach to the prescriber. I authorize HUB to transmit this prescription by fax to the designated pharmacy provider.

Dispense as written: Prescriber signature _____ Date _____

(Physician attests this is his/her legal signature. NO STAMPS)

Substitution allowed: Prescriber signature _____ Date _____

ZEMAIRA Prescription & Service Request Form

Provide to patient after prescription form is signed

Zemaira®
alpha$_1$-proteinase inhibitor (Human)

7 Patient Services Authorization and Release of Health Information

By signing this authorization, I authorize my health plans, physicians and staff, other healthcare providers, and pharmacy providers (collectively, my "Providers") to disclose information, including but not limited to, personal health information about me or my minor child, including information related to my or my child's medical condition, treatment, care management, and health insurance coverage and claims, any prescription (including fill/refill information), and any other information disclosed in connection with the Services (as defined below) ("Personal Health Information"), to CSL Behring and its representatives, agents, and contractors, including CSL Behring's support program(s) (collectively "CSL Behring Entities") for the purposes of:

(1) establishing eligibility for insurance benefits including but not limited to coverage for prescription drugs;

(2) evaluation and enrollment in one or more financial assistance program(s) offered by CSL Behring Entities, such as a co-pay mitigation program and/or patient assistance programs (if one or more of such programs apply to my treatment with a CSL Behring therapy);

(3) enrollment in available patient services programs offered by CSL Behring Entities;

(4) communication about my treatment with me or my Providers, including by contacting me directly to facilitate the dispensing of medication and scheduling shipments and refill reminders;

(5) providing product support and adherence services through CSL Behring Entities;

(6) evaluating the effectiveness of CSL Behring's support program(s); and

(7) any other related support, education, and assistance services related to my treatment with CSL Behring therapy and/or living with my disease (collectively, the "Services").

Further, I authorize any of the CSL Behring Entities to contact me by mail, telephone and/or SMS/text message, or e-mail for relevant follow-up to any of the aforementioned Services. CSL Behring Entities include but are not limited to brand specific support through hub service providers, pharmacy service providers, nurse self-infusion training providers and/or nurse adherence providers, as well as other entities under contract with CSL Behring to support these or similar aspects of the Services. I understand that these CSL Behring Entities may collect Personal Health Information from me for the purposes listed above, and that such collection is subject to CSL Behring's Privacy Policy.

I understand that once my Personal Health Information or other personal information is disclosed to the CSL Behring Entities under this authorization, it may no longer be protected by state and/or federal privacy laws and may be further disclosed by the CSL Behring Entities. However, I understand that the CSL Behring Entities will disclose my Personal Health Information only for the limited purposes described above, or as I may further authorize in writing, or as permitted or required by law. I understand that data related to my enrollment in any CSL Behring program may be collected, analyzed and shared among CSL Behring Entities. I also understand that CSL Behring Entities may receive compensation from CSL Behring in connection with the Services.

I understand that my pharmacy Providers, including those Providers who dispense free trials as part of the Services or commercially-reimbursed doses of CSL Behring products, may disclose to the CSL Behring Entities certain Personal Health Information regarding the dispensing of my prescription and that such disclosure may result in remuneration to my pharmacy Provider(s). If necessary or if requested by my prescriber, I authorize CSL Behring Entities to forward my prescription to a dispensing pharmacy on my behalf.

I understand that I may refuse to sign this authorization. I understand, however, that if I do not sign this authorization, I may not be able to receive Services through CSL Behring Entities. I understand that my treatment with a CSL Behring therapy (other than participation in a free trial program), payment for treatment, insurance enrollment, or eligibility for insurance benefits are not conditioned upon my agreement to sign this authorization. I understand that Services provided by CSL Behring are not insurance and that CSL Behring has the right to rescind, revoke or amend any Service at any time without notice.

I understand that I am entitled to a copy of this authorization.

I understand that if CSL loans me durable medical equipment or other medical equipment through the Services, CSL reserves the right to seek reimbursement from me for all unreturned DME or equipment.

I understand that I may change my mind and cancel this authorization at any time by writing a letter requesting such cancellation to CSL Behring c/o Patient Services P.O. Box 61501 King of Prussia, PA 19406 or by calling the CSL Behring Customer Affairs toll free number 1-888-508-6978 and that this cancellation will end my participation in CSL Behring Services and will not apply to any information already used or disclosed through this authorization before notice of the cancellation is received by CSL Behring Entities. This authorization expires five (5) years from the date signed, or earlier, if required by state law. CSL Behring will not retain this data beyond the maximum period allowed by law.

I understand that, under certain circumstances, by law I may have certain rights regarding CSL Behring's use of my or my minor child's data. I may have the right to receive information about what data CSL Behring has collected about me or my minor child. I may have the right to ask CSL Behring to delete certain personal information about me or my minor child, but only when CSL Behring does not have a legal reason for retaining such personal information. I understand that if I exercise these rights, I will be asked to verify my identity, that if someone else will exercise my rights on my behalf, that they will need to prove that they have your permission to do so. I understand that to exercise my rights, I may contact CSL Behring through https://privacyinfo.csl.com/ or toll free by phone at (833) 704-0018. For more information about how CSL Behring handles personal information, I understand that I can view CSL Behring's privacy policy at https://www.cslbehring.com/privacy-policy.

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

1020 First Avenue, PO Box 61501, King of Prussia, PA 19406-0901 USA
www.CSLBehring.com **www.ZEMAIRA.com** ZMR-0021-APR21

CSL Behring
Biotherapies for Life®

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)
lyophilized powder for reconstitution for intravenous use
Initial U.S. Approval: 2003

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1) 4/2019

----------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 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).

----------DOSAGE FORMS AND STRENGTHS----------

ZEMAIRA is supplied in a single-use vial containing approximately 1000 mg, 4000 mg, or 5000 mg of functionally active A_1-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 A_1-PI is printed on the vial label and carton (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----------

- 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 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 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).

----------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 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**

FULL PRESCRIBING INFORMATION: CONTENTS*

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

CSL Behring

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

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

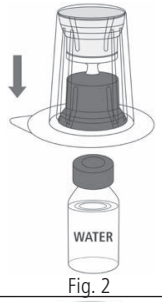
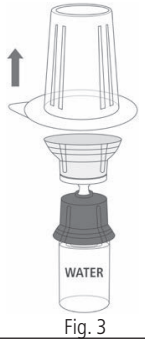
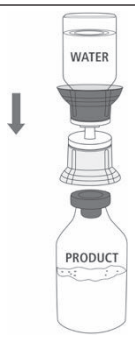
For intravenous use after reconstitution only.

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 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.
- 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.	 Fig. 1
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).	 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).	 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.	 Fig. 4
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.	 Fig. 5
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.	 Fig. 6

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 A_1-PI as a white to off-white 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

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 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.

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 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, asthenia, 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

	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 or for which causality assessment was missing or indeterminate).	4 (0.2)	1 (1.0)	6 (0.5)	1 (0.6)

* 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

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.

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

Serious COPD Exacerbations*	Episode	n	%	EAIR (95% CI)	Episode	n	%	EAIR 95% CI	Treatment Ratio for EAIR (95% CI)*
RAPID Study (Years 1 – 2)	ZEMAIRA (N = 93)				Placebo (N = 87)				ZEMAIRA: Placebo
	25	15	16.1	0.15 (0.10-0.22)	17	9	10.3	0.12 (0.07-0.18)	1.26 (0.46 - 3.45)
Extension Study (Years 3-4)	Early Start† (N = 76)				Delayed Start‡ (N = 64)				Early: Delayed
	37	19	25.0	0.25 (0.18 – 0.35)	20	11	17.2	0.16 (0.10 – 0.25)	1.58 (0.68 – 3.66)

N = total number of safety subjects, n = number of subjects within a category, % = (n/N)*100, CI = Confidence Interval. Subject time at risk: ZEMAIRA = 171.14 years, Placebo = 147.75 years, Early Start Group = 146.46 years, Delay Start Group = 124.71 years.

EAIR = Exposure-Adjusted Incidence Rate (events/subject time at risk). The point estimates and confidence intervals for EAIR values were calculated using negative binomial models.

* Episode = Serious exacerbations of COPD identified by investigators as meeting the Anthonisen criteria[1] plus Serious Adverse Event (SAE) terms COPD, Condition Aggravated, Bronchitis, Lower Respiratory Tract Infection, Pneumonia.

Serious exacerbation events that overlap or occur within 1 day of one another were counted as single exacerbation episodes.

† Early Start Group subjects were randomized to ZEMAIRA during the double-blind RAPID trial (years 1-2) and received open-label ZEMAIRA during the RAPID extension trial (years 3-4).

‡ Delayed Start Group subjects were randomized to Placebo during the double-blind RAPID trial (years 1-2) and received open-label ZEMAIRA during the RAPID extension trial (years 3-4).

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 4 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 4. 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, chest pain
Nervous system disorders	Hypoesthesia, paresthesia, dizziness
Skin disorders	Hyperhidrosis, pruritus, rash including exfoliative and generalized, urticaria
Vascular disorders	Flushing

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) (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, 4000 mg or 5000 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, 76 mL or 95 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 ≤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 5 shows the virus clearance capacity of the ZEMAIRA manufacturing process, expressed as mean $\log_{10}$ reduction factor.

Table 5. 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, e.g., 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 60ºC 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.[2] 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.[3] Another registry study showed 72% of A_1-PI deficient subjects had pulmonary symptoms.[4] 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.[5,6] 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.[3] 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.[6,7,8,9] 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[10], 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.[2] 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.[6] 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.[11] 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 6 shows the mean results for the ZEMAIRA pharmacokinetic parameters.

Table 6. 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 x day
Maximum concentration (C_{max})	44.1 (±10.8) µM
Terminal half-life ($t_{1/2\beta}$)	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 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 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 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 A_1-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

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.

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16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

The product presentations include a package insert and the following components. Not made with natural rubber latex.

Presentation	Kit 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 Mix2Vial filter transfer set for reconstitution
4000 mg of functionally active A_1-PI	0053-7202-02	• ZEMAIRA in a single-use vial [NDC 0053-7212-01] • 76 mL vial of Sterile Water for Injection, USP [NDC 0053-7653-80] • One Mix2Vial filter transfer set for reconstitution
5000 mg of functionally active A_1-PI	0053-7203-02	• ZEMAIRA in a single-use vial [NDC 0053-7213-01] • 95 mL vial of Sterile Water for Injection, USP [NDC 0053-7653-12] • One Mix2Vial filter transfer set for reconstitution

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 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.
- Dizziness may occur following the administration of ZEMAIRA; therefore, patients should rest for a while immediately following an infusion.

Manufactured by:
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