

# CODING AND REIMBURSEMENT GUIDE

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ZEMAIRA<sup>®</sup> (Alpha<sub>1</sub>-Proteinase Inhibitor [Human])

# CODING INFORMATION: ZEMAIRA® (ALPHA<sub>1</sub>-PROTEINASE INHIBITOR [HUMAN])

**Disclaimer:** The codes being provided are from a complex and evolving medical coding system. The treating physician is solely responsible for diagnosis coding and determination of the appropriate ICD-10-CM codes that describe the patient's condition and are supported by the medical record. All codes provided are for informational purposes and are not an exhaustive list. The CPT, HCPCS, ICD-10-CM, and ICD-10-PCS codes provided are based on AMA or CMS guidelines. The billing party is solely responsible for coding of services (eg, CPT Coding). Because government and other third-party payer coding requirements change periodically, please verify current coding requirements directly with the payer being billed.

## ICD-10-CM Diagnosis Code for Alpha-1 Antitrypsin Deficiency<sup>1</sup>

ICD-10-CM Code	Description
E88.01	Alpha-1-antitrypsin (AAT) deficiency
Some payers will only cover treatment for Alpha-1 antitrypsin deficiency when the patient also has documented panlobular emphysema. <b>Code only if applicable:</b>	
J43.1	Panlobular emphysema [panacinar emphysema]

## HCPCS Codes<sup>2</sup>:

The following drug code has been assigned by the Centers for Medicare & Medicaid Services National Level II HCPCS coding system and can be used for ZEMAIRA. Providers are advised to verify correct code(s) with the payer.

HCPCS Code	Description
J0256	Injection, alpha 1 proteinase inhibitor (human), not otherwise specified, 10 mg

ZEMAIRA is supplied in a single-dose vial containing approximately 1000 mg, 4000 mg, or 5000 mg of functionally active A<sub>1</sub>-PI as a white to off-white lyophilized powder for reconstitution with Sterile Water for Injection, USP. The amount of functional A<sub>1</sub>-PI is printed on the vial label and carton.

**Note:** When using the HCPCS code, include the drug NDC for ZEMAIRA, and the total number of units printed on the carton. If the number of units is not a multiple of the 10 mg units provided in the long HCPCS descriptor for J0256, provider shall round up to the nearest whole number to express the number as a multiple.<sup>3</sup>

## JW and JZ Modifier<sup>3</sup>:

For Medicare, providers are required to use the JW modifier for claims with unused drugs or biologicals from single use vials that are appropriately discarded. The amount discarded must be documented in the patient's medical record.

Effective July 1, 2023, Medicare requires the JZ modifier on all claims for single-dose containers where there are no discarded amounts. Providers are advised to verify requirements with non-Medicare payers.

## "Special Payment Instructions" for J0256<sup>4</sup>:

Status indicators (SI) describe how particular HCPCS codes and APCs are paid under the Outpatient Prospective Payment System (OPPS). J0256 for ZEMAIRA has **Status Indicator K**, which is defined as non-pass-through drugs/implantable biologicals including therapeutic radiopharmaceuticals.

As a result, when administered in an outpatient facility, payment for ZEMAIRA is separate from payment for administration under the OPPS, because it exceeds the per day cost threshold for separately payable drugs. These payment rates are published quarterly on the Centers for Medicare and Medicaid Services (CMS) website at <https://www.cms.gov/Medicare/Coding/HCPCSReleaseCodeSets/HCPCS-Quarterly-Update>.

## ZEMAIRA National Drug Code (NDC)

Certain payers may require separate prior authorizations if patient's dose requires use of multiple kit sizes. For example, a patient receiving a 6000 mg dose may need both a 5000 mg and a 1000 mg vial, which could require separate prior authorizations. Payers may also require NDC #s on claims, which will require billing each kit size on separate lines of the claim form. Providers are advised to verify requirements with the payer.

ZEMAIRA Kit NDC #	Presentation	Billing Format
0053-7201-02	1000 mg of functionally active A <sub>1</sub> -PI	00053-7201-02
0053-7202-02	4000 mg of functionally active A <sub>1</sub> -PI	00053-7202-02
0053-7203-02	5000 mg of functionally active A <sub>1</sub> -PI	00053-7203-02

RED "0" is required for some claims file formats (11-digit, 5-4-2 formatting). Use if applicable.

## CPT Administration Codes

If the provider performs administration services in conjunction with a ZEMAIRA infusion, the following administration codes may be billed for this service. Providers are advised to verify correct code(s) with the payer:

**Please verify current coding requirements directly with the payer being billed.**

CPT Code	Description
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour <sup>5</sup>
<b>OR</b>	
96374	Intravenous push, single or initial substance/drug <sup>6</sup>
<b>NOTE:</b> An IV push is defined as: (a) injection in which the individual who administers the drug/substance is continuously present to administer the injection and observe the patient, or (b) an infusion of 15 minutes or less.	
<b>NOTE:</b> The recommended dosage of 60 mg/kg body weight will take approximately 15 minutes to infuse (based on an "average" 75 kg, 165 lb patient). Individual experiences may vary.	
S9346	Home infusion therapy, alpha-1 proteinase inhibitor (eg, prolastin); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem <sup>7</sup>
<b>Note from HCPCS Level II Manual: Noncovered by Medicare</b>	
<b>Note from CPT National Correct Coding Initiative (NCCI) Policy Manual for Medicare Services:</b> Drug administration CPT code 96365 and 96366 have been valued to include the work and practice expenses of CPT code 99211. Therefore, CPT code 99211 is not reportable with CPT code 96372. Other non-facility based evaluation and management codes may be separately reportable with modifier 25 if the physician provides a significant and separately identifiable E&M service.	


Payers may allow administration of ZEMAIRA by HCPs in facility outpatient settings, as well as in the home. The benefit category for coverage (medical or pharmacy), may differ depending on site of care, and should be checked before claim submission.

For Medicare beneficiaries, administration of intravenous (IV) drugs requires the supervision of a healthcare professional (HCP). Both ZEMAIRA and its administration are covered as a Part B (Medical) service when performed in a facility-based outpatient setting. Note that payers other than Medicare may require patients to meet additional medical necessity criteria for approval of facility-based services.

For Medicare beneficiaries, when ZEMAIRA is given at home, the drug may be covered under either Part B or Part D, depending on circumstances.

**For reimbursement support, please call ZEMAIRA Connect at 1-866-ZEMAIRA or 1-866-936-2472.**

# CLAIM FORM EXAMPLE



## HEALTH INSURANCE CLAIM FORM

APPROVED BY NATIONAL UNIFORM CLAIM COMMITTEE (NUCC) 02/12

CARRIER

<input type="checkbox"/> PICA		<input type="checkbox"/> PICA	
1. MEDICARE <input type="checkbox"/> (Medicare#)		1a. INSURED'S LD. NUMBER (For Program in Item 1)	
2. PATIENT'S NAME (Last Name, First Name, Middle Initial)		4. INSURED'S NAME (Last Name, First Name, Middle Initial)	
3. PATIENT'S BIRTH DATE MM DD YY SEX M <input type="checkbox"/> F <input type="checkbox"/>		7. INSURED'S ADDRESS (No., Street)	
5. PATIENT'S ADDRESS (No., Street)		6. PATIENT RELATIONSHIP TO INSURED Self <input type="checkbox"/> Spouse <input type="checkbox"/> Child <input type="checkbox"/> Other <input type="checkbox"/>	
CITY STATE		CITY STATE	
ZIP CODE TELEPHONE (Include Area Code) ( )		ZIP CODE TELEPHONE (Include Area Code) ( )	
9. OTHER INSURED'S NAME (Last Name, First Name, Middle Initial)		8. RESERVED FOR NUCC USE	
a. OTHER INSURED'S POLICY OR GROUP NUMBER		10. IS PATIENT'S CONDITION RELATED TO:	
b. RESERVED FOR NUCC USE		a. EMPLOYMENT? (Current or Previous) YES <input type="checkbox"/> NO <input type="checkbox"/>	
c. RESERVED FOR NUCC USE		b. AUTO ACCIDENT? YES <input type="checkbox"/> NO <input type="checkbox"/> PLACE (State) _____	
d. INSURANCE PLAN NAME OR PROGRAM NAME		c. OTHER ACCIDENT? YES <input type="checkbox"/> NO <input type="checkbox"/>	
12. PATIENT'S OR AUTHORIZED PERSON'S SIGNATURE I authorize the release of any medical or other information necessary to process this claim. I also request payment of government benefits either to myself or to the party who accepts assignment below.		11. INSURED'S POLICY GROUP OR FECA NUMBER	
SIGNED _____ DATE _____		13. INSURED'S OR AUTHORIZED PERSON'S SIGNATURE I authorize payment of medical benefits to the undersigned physician or supplier for services described below.	
14. DATE OF CURRENT ILLNESS, INJURY, or PREGNANCY (LMP) MM DD YY QUAL.		16. DATES PATIENT UNABLE TO WORK IN CURRENT OCCUPATION FROM MM DD YY TO MM DD YY	
17. NAME OF REFERRING PROVIDER OR OTHER SOURCE		18. HOSPITALIZATION DATES RELATED TO CURRENT SERVICES FROM MM DD YY TO MM DD YY	
19. ADDITIONAL CLAIM INFORMATION (Designated by NUCC)		20. OUTSIDE LAB? YES <input type="checkbox"/> NO <input type="checkbox"/> \$ CHARGES	
21. DIAGNOSIS OR NATURE OF ILLNESS OR INJURY Relate A-L to service line below (24E) ICD Ind.		22. RESUBMISSION CODE ORIGINAL REF. NO.	
24A (shaded)		23. PRIOR AUTHORIZATION NUMBER	
24. A. DATE(S) OF SERVICE From MM DD YY To MM DD YY		B. PLACE OF SERVICE	
C. EMG		D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS MODIFIER	
E. DIAGNOSIS POINTER		F. \$ CHARGES	
G. DAYS OR UNITS		H. EFSDT Family Plan	
I. ID. QUAL.		J. RENDERING PROVIDER ID. #	
25. FEDERAL TAX ID. NUMBER SSN EIN		26. PATIENT'S ACCOUNT NO.	
27. ACCEPT ASSIGNMENT? (For govt. claims, see back) YES <input type="checkbox"/> NO <input type="checkbox"/>		28. TOTAL CHARGE \$	
29. AMOUNT PAID \$		30. Rsvd for NUCC Use	
31. SIGNATURE OF PHYSICIAN OR SUPPLIER INCLUDING DEGREES OR CREDENTIALS (I certify that the statements on the reverse apply to this bill and are made a part thereof.)		32. SERVICE FACILITY LOCATION INFORMATION	
SIGNED _____ DATE _____		33. BILLING PROVIDER INFO & PH # ( )	
a. NPI		b. NPI	

NUCC Instruction Manual available at: [www.nucc.org](http://www.nucc.org)

PLEASE PRINT OR TYPE

APPROVED OMB-0938-1197 FORM 1500 (02-12)

PATIENT AND INSURED INFORMATION

PHYSICIAN OR SUPPLIER INFORMATION

Please see full Important Safety Information on page 6 and full prescribing information for ZEMAIRA on page 7.

# CLAIM FORM EXAMPLE (CONTINUED)

## Field 19: Additional Claim Information

HCPCS code (J0256) can be used for other alpha-1 proteinase inhibitors besides ZEMAIRA. Therefore, when billing ZEMAIRA, the provider must include additional information about this specific product in a free-text field (eg, Field 19 or its electronic equivalent).

Payers typically require: drug name, NDC, route of administration, and amount used for treatment. For example:

ZEMAIRA NDC 00053-7201-02; Intravenous, 1000 mg of functionally active A<sub>1</sub>-PI

ZEMAIRA NDC 00053-7202-02; Intravenous, 4000 mg of functionally active A<sub>1</sub>-PI

ZEMAIRA NDC 00053-7203-02; Intravenous, 5000 mg of functionally active A<sub>1</sub>-PI

NDC Code: Note that the 10-digit NDC code for ZEMAIRA is converted to an 11-digit billing format by inserting a zero in the first segment. The NDC code on the package is XXXX-XXXX-XX; the 11-digit billing format is 0XXXX-XXXX-XX.

## Field 21: Diagnosis or Nature of Illness of Injury

Enter the ICD-10-CM diagnosis code(s) that best describes the reason the patient is receiving care.

## Field 24A (Shaded Area): NDC

For Medicaid claims, and for Medicare claims that will cross over to Medicaid as the secondary payer, the NDC in a specific format is required in the shaded area above the line on which ZEMAIRA is reported in Field 24A. **Various state Medicaid plans and Medicare may have different reporting formats for this information.**

Usually, the provider will need to supply the NDC in 11-digit format preceded by the modifier N4 (N40XXXX-XXXX-XX). This is typically followed by the NDC unit of measure (F2 [mg]) and the numeric quantity of the NDC that was dispensed.

Other payers may require different information. Check with the payer for specific requirements.

## Field 24D: CPT/HCPCS

HCPCS coding for ZEMAIRA should use:

**J0256:** Injection, alpha 1 proteinase inhibitor (human), not otherwise specified, 10 mg

**For Medicare beneficiaries**, the following code may not be payable.

- S9346—Home infusion therapy, alpha-1 proteinase inhibitor (eg, prolastin); administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

**The code selected is based on the documented service provided to the patient.**

## Field 24E: Diagnosis Pointer

Enter the number(s) from Field 21 that best describes the medical necessity for the service.

## Field 24G: Days or Units

**J0256:** Injection, alpha 1 proteinase inhibitor (human), not otherwise specified, 10 mg

Requirements for Field 24G vary by payer. For example, some payers rely on the information in Field 19 for this data and request a placeholder of "1" in Field 24G. Other payers may require 1 unit per unit of drug used in the care of the patient.

# INDICATIONS AND IMPORTANT SAFETY INFORMATION

ZEMAIRA®, Alpha<sub>1</sub>-Proteinase Inhibitor (Human), is indicated for chronic augmentation and maintenance therapy for adults with alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI) deficiency and emphysema. The effect of augmentation therapy with ZEMAIRA or any A<sub>1</sub>-PI product on pulmonary exacerbations and progression of emphysema in A<sub>1</sub>-PI deficiency has not been demonstrated in randomized, controlled clinical studies.

ZEMAIRA is not indicated for lung disease patients in whom severe A<sub>1</sub>-PI deficiency has not been established.

ZEMAIRA is contraindicated in patients with a history of severe systemic reactions to the product or to A<sub>1</sub>-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 A<sub>1</sub>-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 full prescribing information for ZEMAIRA on page 7.**

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](http://www.fda.gov/medwatch).

**References:** **1.** National Center for Health Statistics (US Department of Health and Human Services) International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM). Comprehensive Listing ICD-10-CM Files: 2024 release of ICD-10-CM. <https://www.cdc.gov/nchs/icd/comprehensive-listing-of-icd-10-cm-files.htm>. Accessed September 15, 2023. **2.** U.S. Centers for Medicare & Medicaid Services (US Department of Health and Human Services). HCPCS Quarterly Update. <https://www.cms.gov/medicare/coding-billing/healthcare-common-procedure-system/quarterly-update>. Accessed September 15, 2023. **3.** Billing and Coding: JW and JZ Modifier Billing Guidelines. Article A55932. <https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=55932>. Accessed September 15, 2023. **4.** MLN Matters MM10923, October 2018 Update of the Hospital Outpatient Prospective Payment System (OPPS). US Department of Health and Human Services, Centers for Medicare and Medicaid Services, Medicare Learning Network. <https://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/MLNMattersArticles/downloads/MM10923.pdf>. Accessed September 15, 2023. **5.** 2023 CPT Code 96365. American Academy of Professional Coders website. <https://www.aapc.com/codes/cpt-codes/96365>. Accessed September 15, 2023. **6.** 2023 CPT Code 96374. American Academy of Professional Coders website. <https://www.aapc.com/codes/cpt-codes/96374>. Accessed September 15, 2023. **7.** HCPCS Codes. Temporary National Codes (Non-Medicare). Codify by AAPC. <https://www.aapc.com/codes/hcpcs-codes/S9346>. Accessed September 15, 2023.

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**CSL Behring**

## 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<sub>1</sub>-Proteinase Inhibitor (Human)  
lyophilized powder for reconstitution for intravenous use  
Initial U.S. Approval: 2003

### INDICATIONS AND USAGE

- ZEMAIRA is an alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI) indicated for chronic augmentation and maintenance therapy in adults with A<sub>1</sub>-PI deficiency and clinical evidence of emphysema (1).
- The effect of augmentation therapy with ZEMAIRA or any A<sub>1</sub>-PI product on pulmonary exacerbations and on the progression of emphysema in A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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-dose vial containing approximately 1000 mg, 4000 mg, or 5000 mg of functionally active A<sub>1</sub>-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<sub>1</sub>-PI is printed on the vial label and carton (3).

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### CONTRAINDICATIONS

- History of anaphylaxis or severe systemic reactions to ZEMAIRA or A<sub>1</sub>-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<sub>1</sub>-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/med-watch](http://www.fda.gov/med-watch).

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Revised: September 2022

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# CSL Behring

## ZEMAIRA®

### Alpha<sub>1</sub>-Proteinase Inhibitor (Human)

#### FULL PRESCRIBING INFORMATION

#### 1 INDICATIONS AND USAGE

ZEMAIRA is an alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI) indicated for chronic augmentation and maintenance therapy in adults with A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-PI product on pulmonary exacerbations and on the progression of emphysema in A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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).

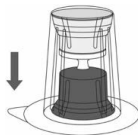


Fig. 2

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.

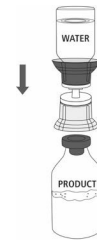


Fig. 4

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 dose 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-dose vial containing approximately 1000 mg, 4000 mg, or 5000 mg of functionally active A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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](http://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<sub>1</sub>-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 <sup>a</sup> (Events per Subject-Year <sup>a</sup> )		Number of Infusions <sup>a</sup> (% of all Infusions)	
	ZEMAIRA (n=66, SY <sup>b</sup> =28.72)	Prolastin (n=32, SY <sup>b</sup> =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)

<sup>a</sup> Based on unique subjects. If a subject experienced more than one AR, the subject was only counted once.

<sup>b</sup> 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.

<sup>c</sup> If there were multiple occurrences of ARs following a single infusion, only one occurrence was counted.

<sup>d</sup> 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 <sup>a</sup> (Events per Subject-Year <sup>a</sup> )		Number of Infusions <sup>a</sup> (% of all Infusions)	
	ZEMAIRA (n=66, SY <sup>b</sup> =28.72)	Prolastin (n=32, SY <sup>b</sup> =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)

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

<sup>b</sup> 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.

<sup>c</sup> If more than one of the same type of an event occurred after an infusion, only one event was counted.

<sup>d</sup> 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*	Epi-episode			EAIR (95% CI)	Epi-episode			EAIR 95% CI	Treatment Ratio for EAIR (95% CI)*
	n	%			n	%			
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)	
Extension Study (Years 3-4)	Early Start <sup>†</sup> (N = 76)				Delayed Start <sup>‡</sup> (N = 64)				Early: Delayed
	37	19	25.0	0.25 (0.18 - 0.35)	20	11	17.2	0.16 (0.10 - 0.25)	

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<sup>1</sup> 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.

<sup>†</sup> 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).

<sup>‡</sup> 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<sub>1</sub>PI 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<sub>1</sub>-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<sub>1</sub>-proteinase inhibitor (human) (A<sub>1</sub>-PI), also known as alpha<sub>1</sub>-antitrypsin, to be reconstituted and administered by the intravenous route. The specific activity of ZEMAIRA is ≥0.7 mg of functional A<sub>1</sub>-PI per milligram of total protein. The purity (total A<sub>1</sub>-PI/total protein) is ≥90% A<sub>1</sub>-PI. Each vial contains approximately 1000 mg, 4000 mg or 5000 mg of functionally active A<sub>1</sub>-PI. The measured amount per vial of functionally active A<sub>1</sub>-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<sup>4</sup> 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<sub>10</sub> reduction factor.

**Table 5. Cumulative (Log<sub>10</sub>) Virus Inactivation/Removal in ZEMAIRA**

Manufacturing Step	Virus Reduction Factor (Log <sub>10</sub> )					
	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
<b>Cumulative Virus Reduction (log<sub>10</sub>)</b>	<b>≥12.3</b>	<b>≥10.6</b>	<b>≥16.7</b>	<b>≥10.7</b>	<b>≥10.7</b>	<b>≥6.4</b>

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<sub>10</sub>.

† At 60°C for 10 hours.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

A<sub>1</sub>-PI deficiency is a chronic, hereditary, autosomal, co-dominant disorder that is usually fatal in its severe form. Low blood levels of A<sub>1</sub>-PI (i.e., below 11 µM) are most commonly associated with progressive, severe emphysema that becomes clinically apparent by the third to fourth decade of life. In addition, PiZZ individuals, whose serum A<sub>1</sub>-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<sub>1</sub>-PI levels are above or below 11 µM.<sup>2</sup> Not all individuals with severe genetic variants of A<sub>1</sub>-PI deficiency have emphysema. **Augmentation therapy with alpha<sub>1</sub>-proteinase inhibitor (human) is indicated only in patients with severe congenital A<sub>1</sub>-PI deficiency who have clinically evident emphysema.** A registry study showed 54% of A<sub>1</sub>-PI deficient subjects had emphysema.<sup>3</sup> Another registry study showed 72% of A<sub>1</sub>-PI deficient subjects had pulmonary symptoms.<sup>4</sup> Smoking is an important risk factor for the development of emphysema in patients with A<sub>1</sub>-PI deficiency.

Approximately 100 genetic variants of A<sub>1</sub>-PI deficiency can be identified electrophoretically, only some of which are associated with the clinical disease.<sup>5,6</sup> Ninety-five percent of clinically symptomatic A<sub>1</sub>-PI deficient individuals are of the severe PiZZ phenotype. Up to 39% of A<sub>1</sub>-PI deficient patients may have an asthmatic component to their lung disease, as evidenced by symptoms and/or bronchial hyperreactivity.<sup>3</sup> Pulmonary infections, including pneumonia and acute bronchitis, are common in A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-PI product actually protects the lower respiratory tract from progressive emphysematous changes has not been evaluated. Individuals with endogenous levels of A<sub>1</sub>-PI below 11 µM, in general, manifest a significantly increased risk for development of emphysema above the general population background risk.<sup>6,7,8,9</sup> Although the maintenance of blood serum levels of A<sub>1</sub>-PI (antigenically measured) above 11 µM has been historically postulated to provide therapeutically relevant anti-neutrophil elastase protection<sup>10</sup>, this has not been proven. Individuals with severe A<sub>1</sub>-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<sub>1</sub>-PI above 11 µM have emphysema attributed to A<sub>1</sub>-PI deficiency.<sup>2</sup> These observations underscore the uncertainty regarding the appropriate therapeutic target serum level of A<sub>1</sub>-PI during augmentation therapy.

Pulmonary disease, particularly emphysema, is the most frequent manifestation of A<sub>1</sub>-PI deficiency.<sup>6</sup> The pathogenesis of emphysema is understood to evolve as described in the "protease-antiprotease imbalance" model. A<sub>1</sub>-PI is now understood to be the primary antiprotease in the lower respiratory tract, where it inhibits NE.<sup>11</sup> Normal healthy individuals produce sufficient A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-PI augmentation therapy in this patient population, acting to increase and maintain serum levels and ELF levels of A<sub>1</sub>-PI.

### 12.2 Pharmacodynamics

Weekly repeated infusions of A<sub>1</sub>-PI at a dose of 60 mg/kg lead to serum A<sub>1</sub>-PI levels above the historical target threshold of 11 µM.

The clinical benefit of the increased blood levels of A<sub>1</sub>-PI at the recommended dose has not been established for any A<sub>1</sub>-PI product.

### 12.3 Pharmacokinetics

A double-blind, randomized, active-controlled, crossover pharmacokinetic study was conducted in 13 males and 5 females with A<sub>1</sub>-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<sub>1</sub>-PI in 18 Subjects Following a Single 60 mg/kg Dose of ZEMAIRA**

Pharmacokinetic Parameter	Mean (SD)*
Area under the curve (AUC <sub>0-∞</sub> )	144 (±27) µM x day
Maximum concentration (C <sub>max</sub> )	44.1 (±10.8) µM
Terminal half-life (t <sub>1/2β</sub> )	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<sub>1</sub>-PI deficiency, and 3% had the M<sub>ALTON</sub> phenotype. At screening, serum A<sub>1</sub>-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<sub>1</sub>-PI above 11 µM (80 mg/dL) and increases A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-PI related analytes in ELF were measured: antigenic A<sub>1</sub>-PI, A<sub>1</sub>-PI:NE complexes, free NE, and functional A<sub>1</sub>-PI (ANEC). A blinded retrospective analysis, which revised the prospectively established acceptance criteria showed that within each treatment group, ELF levels of antigenic A<sub>1</sub>-PI and A<sub>1</sub>-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<sub>1</sub>-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 <sub>1</sub> -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 <sub>1</sub> -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<sub>1</sub>-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

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

ZEMAIRA is supplied in a single-dose vial containing the amount of functionally active A<sub>1</sub>-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.

**Table 8: How Supplied**

Presentation	Kit NDC Number	Components
1000 mg of functionally active A <sub>1</sub> -PI	0053-7201-02	<ul style="list-style-type: none"> <li>• ZEMAIRA in a single-dose vial [NDC 0053-7211-01]</li> <li>• 20 mL vial of Sterile Water for Injection, USP [NDC 0053-7653-20]</li> <li>• One Mix2Vial filter transfer set for reconstitution</li> </ul>
4000 mg of functionally active A <sub>1</sub> -PI	0053-7202-02	<ul style="list-style-type: none"> <li>• ZEMAIRA in a single-dose vial [NDC 0053-7212-01]</li> <li>• 76 mL vial of Sterile Water for Injection, USP [NDC 0053-7653-80]</li> <li>• One Mix2Vial filter transfer set for reconstitution</li> </ul>

Presentation	Kit NDC Number	Components
5000 mg of functionally active A <sub>1</sub> -PI	0053-7203-02	<ul style="list-style-type: none"> <li>• ZEMAIRA in a single-dose vial [NDC 0053-7213-01]</li> <li>• 95 mL vial of Sterile Water for Injection, USP [NDC 0053-7653-12]</li> <li>• One Mix2Vial filter transfer set for reconstitution</li> </ul>

### 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.
- Discard any unused product and all used disposable supplies.

## 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<sub>1</sub>-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:  
**CSL Behring LLC**  
 Kankakee, IL 60901 USA  
 US License No. 1767

For patent information: <http://www.cslbehring.com/products/patents>

Prolastin is a registered trademark of Grifols Therapeutics Inc.

Mix2Vial® is a registered trademark of West Pharma. Services IL, Ltd., a subsidiary of West Pharmaceuticals Services, Inc.



## 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<sub>1</sub>-Proteinase Inhibitor (Human)  
lyophilized powder for reconstitution for intravenous use  
Initial U.S. Approval: 2003

### INDICATIONS AND USAGE

- ZEMAIRA is an alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI) indicated for chronic augmentation and maintenance therapy in adults with A<sub>1</sub>-PI deficiency and clinical evidence of emphysema (1).
- The effect of augmentation therapy with ZEMAIRA or any A<sub>1</sub>-PI product on pulmonary exacerbations and on the progression of emphysema in A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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-dose vial containing approximately 1000 mg, 4000 mg, or 5000 mg of functionally active A<sub>1</sub>-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<sub>1</sub>-PI is printed on the vial label and carton (3).

### CONTRAINDICATIONS

- History of anaphylaxis or severe systemic reactions to ZEMAIRA or A<sub>1</sub>-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<sub>1</sub>-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/med-watch](http://www.fda.gov/med-watch).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: September 2022

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CSL Behring  
**ZEMAIRA®**  
**Alpha<sub>1</sub>-Proteinase Inhibitor**  
**(Human)**

**FULL PRESCRIBING INFORMATION**

**1 INDICATIONS AND USAGE**

ZEMAIRA is an alpha<sub>1</sub>-proteinase inhibitor (A<sub>1</sub>-PI) indicated for chronic augmentation and maintenance therapy in adults with A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-PI product on pulmonary exacerbations and on the progression of emphysema in A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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).

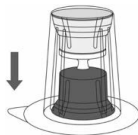


Fig. 2

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).

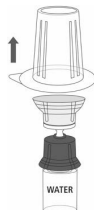


Fig. 3

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.

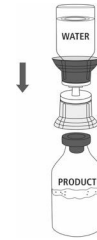


Fig. 4

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 dose 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-dose vial containing approximately 1000 mg, 4000 mg, or 5000 mg of functionally active A<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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<sub>1</sub>-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](http://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<sub>1</sub>-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 <sup>a</sup> (Events per Subject-Year <sup>a</sup> )		Number of Infusions <sup>a</sup> (% of all Infusions)	
	ZEMAIRA (n=66, SY <sup>b</sup> =28.72)	Prolastin (n=32, SY <sup>b</sup> =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)

<sup>a</sup> Based on unique subjects. If a subject experienced more than one AR, the subject was only counted once.

<sup>b</sup> 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.

<sup>c</sup> If there were multiple occurrences of ARs following a single infusion, only one occurrence was counted.

<sup>d</sup> 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 <sup>a</sup> (Events per Subject-Year <sup>a</sup> )		Number of Infusions <sup>a</sup> (% of all Infusions)	
	ZEMAIRA (n=66, SY <sup>b</sup> =28.72)	Prolastin (n=32, SY <sup>b</sup> =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)

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

<sup>b</sup> 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.

<sup>c</sup> If more than one of the same type of an event occurred after an infusion, only one event was counted.

<sup>d</sup> 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*	Epi-episode			EAIR (95% CI)	Epi-episode			EAIR 95% CI	Treatment Ratio for EAIR (95% CI)*
	n	%			n	%			
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)	
Extension Study (Years 3-4)	Early Start <sup>†</sup> (N = 76)				Delayed Start <sup>‡</sup> (N = 64)				Early: Delayed
	37	19	25.0	0.25 (0.18 - 0.35)	20	11	17.2	0.16 (0.10 - 0.25)	

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<sup>1</sup> 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.

<sup>†</sup> 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).

<sup>‡</sup> 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<sub>1</sub>PI 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<sub>1</sub>-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<sub>1</sub>-proteinase inhibitor (human) (A<sub>1</sub>-PI), also known as alpha<sub>1</sub>-antitrypsin, to be reconstituted and administered by the intravenous route. The specific activity of ZEMAIRA is ≥0.7 mg of functional A<sub>1</sub>-PI per milligram of total protein. The purity (total A<sub>1</sub>-PI/total protein) is ≥90% A<sub>1</sub>-PI. Each vial contains approximately 1000 mg, 4000 mg or 5000 mg of functionally active A<sub>1</sub>-PI. The measured amount per vial of functionally active A<sub>1</sub>-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<sup>4</sup> 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<sub>10</sub> reduction factor.

**Table 5. Cumulative (Log<sub>10</sub>) Virus Inactivation/Removal in ZEMAIRA**

Manufacturing Step	Virus Reduction Factor (Log <sub>10</sub> )					
	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
<b>Cumulative Virus Reduction (log<sub>10</sub>)</b>	<b>≥12.3</b>	<b>≥10.6</b>	<b>≥16.7</b>	<b>≥10.7</b>	<b>≥10.7</b>	<b>≥6.4</b>

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<sub>10</sub>.

† At 60°C for 10 hours.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

$A_1$ -PI deficiency is a chronic, hereditary, autosomal, co-dominant disorder that is usually fatal in its severe form. Low blood levels of  $A_1$ -PI (i.e., below 11  $\mu$ M) are most commonly associated with progressive, severe emphysema that becomes clinically apparent by the third to fourth decade of life. In addition, PiZZ individuals, whose serum  $A_1$ -PI levels range from approximately 9 to 23  $\mu$ M, 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  $\mu$ M.<sup>2</sup> Not all individuals with severe genetic variants of  $A_1$ -PI deficiency have emphysema. **Augmentation therapy with alpha<sub>1</sub>-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.<sup>3</sup> Another registry study showed 72% of  $A_1$ -PI deficient subjects had pulmonary symptoms.<sup>4</sup> 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.<sup>5,6</sup> 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.<sup>3</sup> 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  $\mu$ M, in general, manifest a significantly increased risk for development of emphysema above the general population background risk.<sup>6,7,8,9</sup> Although the maintenance of blood serum levels of  $A_1$ -PI (antigenically measured) above 11  $\mu$ M has been historically postulated to provide therapeutically relevant anti-neutrophil elastase protection<sup>10</sup>, 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  $\mu$ M have emphysema attributed to  $A_1$ -PI deficiency.<sup>2</sup> 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.<sup>6</sup> 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.<sup>11</sup> 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  $\mu$ M.

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 ( $\pm$ 27) $\mu$ M x day
Maximum concentration ( $C_{max}$ )	44.1 ( $\pm$ 10.8) $\mu$ M
Terminal half-life ( $t_{1/2\beta}$ )	5.1 ( $\pm$ 2.4) days
Total clearance	603 ( $\pm$ 129) mL/day
Volume of distribution at steady state	3.8 ( $\pm$ 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 treatment-related 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<sub>MALTON</sub> phenotype. At screening, serum  $A_1$ -PI levels were between 3.2 and 10.1  $\mu$ M (mean of 5.6  $\mu$ M). The objectives of the clinical trials were to demonstrate that ZEMAIRA augments and maintains serum levels of  $A_1$ -PI above 11  $\mu$ M (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  $\pm$ 3  $\mu$ M. Both groups were maintained above 11  $\mu$ M. 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  $\mu$ M (range 13.9 to 23.2, SD 2.5) and for Prolastin-treated subjects was 19.1  $\mu$ M (range 14.7 to 23.1, SD 2.2). The difference between the ZEMAIRA and the Prolastin groups was not considered clinically significant and may be related to the higher specific activity of ZEMAIRA.

In a subgroup of subjects enrolled in the 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.

## 15 REFERENCES

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## 16 HOW SUPPLIED/STORAGE AND HANDLING

ZEMAIRA is supplied in a single-dose vial containing the amount of functionally active A<sub>1</sub>-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.

**Table 8: How Supplied**

Presentation	Kit NDC Number	Components
1000 mg of functionally active A <sub>1</sub> -PI	0053-7201-02	<ul style="list-style-type: none"> <li>• ZEMAIRA in a single-dose vial [NDC 0053-7211-01]</li> <li>• 20 mL vial of Sterile Water for Injection, USP [NDC 0053-7653-20]</li> <li>• One Mix2Vial filter transfer set for reconstitution</li> </ul>
4000 mg of functionally active A <sub>1</sub> -PI	0053-7202-02	<ul style="list-style-type: none"> <li>• ZEMAIRA in a single-dose vial [NDC 0053-7212-01]</li> <li>• 76 mL vial of Sterile Water for Injection, USP [NDC 0053-7653-80]</li> <li>• One Mix2Vial filter transfer set for reconstitution</li> </ul>

Presentation	Kit NDC Number	Components
5000 mg of functionally active A <sub>1</sub> -PI	0053-7203-02	<ul style="list-style-type: none"> <li>• ZEMAIRA in a single-dose vial [NDC 0053-7213-01]</li> <li>• 95 mL vial of Sterile Water for Injection, USP [NDC 0053-7653-12]</li> <li>• One Mix2Vial filter transfer set for reconstitution</li> </ul>

### 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.
- Discard any unused product and all used disposable supplies.

## 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<sub>1</sub>-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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For patent information: <http://www.cslbehring.com/products/patents>

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