

Zemaira[®]

New Zealand

NAME OF THE MEDICINE

Human Alpha₁-Proteinase Inhibitor, powder for injection

DESCRIPTION

Zemaira[®] is supplied as a sterile, white, lyophilised powder to be administered by the intravenous route. The specific activity of Zemaira[®] is ≥ 0.7 mg of functional Alpha₁-Proteinase Inhibitor (A₁-PI) per milligram of total protein. The purity is $\geq 90\%$ A₁-PI. Following reconstitution with 20 mL of Sterile Water for Injections, each vial contains approximately 1000 mg of functionally active A₁-PI, 45 mg sodium phosphate monobasic, 47 mg sodium chloride, 22 mg sodium hydroxide and 564 mg mannitol. Zemaira[®] contains no preservatives.

The Zemaira[®] manufacturing process includes pasteurisation (60 °C for 10 hours) and nanofiltration to reduce the potential for pathogen transmission.

PHARMACOLOGY

Pharmacodynamics

A₁-PI is understood to be the primary antiprotease in the lower respiratory tract, where it inhibits neutrophil elastase (NE). Intravenous infusion of A₁-PI increases antigenic and functional (anti-neutrophil elastase capacity: ANEC) serum levels and lung epithelial lining fluid (ELF) levels of A₁-PI.

Pharmacokinetics

In a pharmacokinetic analysis, 15 subjects had a pre-infusion median antigenic A₁-PI serum level of 4.9 μM . Median time to maximum serum concentration (t_{max}) was 15 minutes with dose-dependent maximum serum levels (C_{max}) between 16.1 and 67.4 μM (medians 18.6 μM , 34.1 μM , and 56.3 μM for the dose groups 30, 60 and 120 mg/kg). Area under the curve (AUC) values also demonstrated a dose-dependent increase. The median terminal half-life ($t_{1/2\beta}$) for the 15 subjects was 5.2 days (range: 2.4 to 6.8 days) and appeared not to be dose-dependent. The median magnitude of functional A₁-PI serum concentrations relative to antigenic concentrations was 94.6% (range: 89.6% to 105.5%). The percentage of functional A₁-PI was similar across dose levels and time points. The concentrations of antigenic A₁-PI in ELF were about 10% of the serum A₁-PI concentrations and showed a dose-dependent increase, demonstrating diffusion into the lung.

In a clinical trial, 30 A₁-PI deficient subjects received 60 mg/kg of Zemaira[®] once weekly for 24 weeks. The mean (range and standard deviation) of the steady state trough serum antigenic A₁-PI serum levels was 17.7 μM (range 13.9 to 23.2). In all patients, steady state trough levels were above the target threshold of 11 μM .

CLINICAL TRIALS

Four clinical studies have been conducted for Zemaira[®] – two single dose studies to determine the pharmacokinetics, dose-ranging and to establish comparative bioavailability (see *Pharmacokinetics*). In addition two clinical trials to establish efficacy and safety have been conducted with Zemaira[®]. The four studies treated a total of 89 subjects with Zemaira[®] (23 subjects were enrolled in more than one of the trials).

The first trial was an open-label, uncontrolled 26-week study designed to demonstrate that a weekly dose of 60 mg/kg Zemaira[®] administered intravenously was able to maintain trough serum antigenic and functional A₁-PI levels above 11 µM. Only nine patients were enrolled and treated as the study was terminated early due to commencement of the second trial.

Following discussion with the FDA a second trial was initiated. A randomised, controlled (RCT) 24-week study designed to compare the biochemical efficacy, safety and tolerability of Zemaira[®] with Prolastin[®] in 44 subjects with A₁-PI deficiency and clinical evidence of emphysema. The study had two phases, a 10-week blinded phase that compared Zemaira[®] and Prolastin[®], and a 14-week open phase in which all subjects received weekly infusions of Zemaira[®]. Each product was administered as an intravenous infusion of 60 mg/kg once weekly; the dose at which comparable bioavailability had been demonstrated.

The results of these studies were consistent with each other showing that trough serum antigenic and functional A₁-PI levels were maintained at steady state above the protective threshold of 11 µM for the duration of the trials. In the RCT while there was a trend to reduction in antigenic A₁-PI from week 7 to week 24 (with a plateau of about 16 µM reached at 20 weeks) functional A₁-PI levels showed no downward trend, suggesting that no loss of biochemical efficacy is expected with long term Zemaira[®] therapy. In addition levels of the complex A₁-PI:NE from ELF obtained by bronchoalveolar lavage in patients from the RCT show that for both products A₁-PI reaches the lower lung in an active form and has the capacity to complex with its physiologic substrate, NE.

Sixty-nine (69) of the 89 subjects treated with Zemaira[®] (78%) and 20 of the 32 Prolastin[®] – treated subjects (63%) reported at least one treatment emergent adverse event (AE) in the four clinical trials. Most AEs were mild to moderate in severity and all drug related AEs were non-serious. A listing of AEs observed during the clinical studies is provided in Table 2 (see **ADVERSE EFFECTS**).

No case of viral transmission or seroconversion occurred during any of the clinical trials.

INDICATIONS

Zemaira[®] is indicated for chronic augmentation and maintenance therapy in individuals with alpha₁-proteinase inhibitor (A₁-PI) deficiency and clinical evidence of emphysema.

CONTRAINDICATIONS

Zemaira[®] is contraindicated in individuals with a known hypersensitivity to any of the components of the product.

Zemaira[®] must not be given to individuals with a history of anaphylaxis or severe systemic response to A₁-PI products.

Individuals with selective IgA deficiencies who have known antibodies against IgA (anti-IgA antibodies) should not receive Zemaira[®], since these patients may experience severe reactions, including anaphylaxis, to IgA that may be present in Zemaira[®].

PRECAUTIONS

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, dyspnoea, wheezing, faintness, hypotension and anaphylaxis. If these symptoms occur, they should be advised to discontinue use of the product immediately and contact their physician.

In case of shock, the current medical standards for shock treatment should be observed.

As with any colloid solution, there may be an increase in plasma volume following intravenous administration of Zemaira[®]. Caution should therefore be taken in patients at risk for circulatory overload. In addition, there may be a risk of unspecific general reactions and/or response of the circulatory system, e.g. nausea, malaise, decrease in blood pressure and vasodilatation, following intravenous administration of Zemaira[®].

Zemaira[®] contains 1.7 mmol (or 40 mg) total sodium per vial. This is to be taken into consideration for patients on a controlled sodium diet. Zemaira[®] also contains 0.37 mmol (or 36 mg) of phosphate per vial.

Infusion rates and the patient's clinical state should be monitored closely during infusion. The patient should be observed for signs of infusion-related reactions.

No data are available for the use in patients with lung disease in whom severe congenital A₁-PI deficiency has not been established.

Pathogen safety

This product is made from human plasma. Products made from human plasma may contain infectious agents such as viruses and theoretically Creutzfeldt-Jakob disease (CJD) agents, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain viral markers.

In addition, virus inactivation/removal procedures are included in the manufacturing process. The current process and procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and non-enveloped viruses, such as hepatitis A (HAV) and human parvovirus B19.

Despite these measures, such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

Any case of infection associated with the use of the product should be reported, together with details of batches given, to the Sponsor.

Effects on fertility

No animal reproduction studies have been conducted with Zemaira[®]. Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development.

Use in pregnancy

The use of Zemaira[®] in human pregnancy has not been established in controlled clinical trials. Zemaira[®] should be given to a pregnant woman only if clearly needed.

Use in lactation

No information is available. Zemaira[®] should be given to a lactating woman only if clearly needed.

Paediatric use

A₁-PI deficiency with clinical evidence of emphysema is not usually evident until the third or fourth decade of life. Therefore paediatric use of Zemaira[®] is not foreseen. Safety and effectiveness in the paediatric population has not been established.

Use in the elderly

The use of Zemaira[®] in the elderly has not been established in specifically designed clinical studies.

Carcinogenicity

Specific studies have not been conducted.

Genotoxicity

Specific studies have not been conducted.

Interactions with other medicines

Formal interaction studies of Zemaira[®] with other medicinal products have not been performed.

Effect on laboratory tests

Zemaira[®] is a physiological constituent of human plasma so no specific effects on laboratory tests are anticipated.

No effects on the ability to drive and use machines have been observed.

ADVERSE EFFECTS

Adverse effects based on experience from clinical studies and on postmarketing experience are provided in the tables below. The following frequency categories have been assigned:

Very common: $\geq 1/10$

Common: $\geq 1/100$ and $< 1/10$

Uncommon: $\geq 1/1000$ and $< 1/100$

Rare: $\geq 1/10,000$ and $< 1/1000$

Very rare: $< 1/10,000$

*Unknown: Cannot be reliably estimated from the available data

*Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not possible to reliably estimate the frequency of these reactions.

The following adverse drug reactions have been reported during post marketing surveillance for Zemaira®.

Table 1:

System, Organ, Class (SOC)	Events	Frequency Category
Infections and Infestations	Respiratory tract infection	Unknown
Immune system disorders	Hypersensitivity	Unknown
Nervous system disorders	Headache, lethargy, Paraesthesia, dizziness	Unknown
Vascular disorders	Flushing, Blood pressure fluctuation	Unknown
Respiratory, thoracic and mediastinal disorders	COPD, Dyspnoea, Oropharyngeal pain, Respiratory tract congestion	Unknown
Gastrointestinal disorders	Nausea, Abdominal distension, Diarrhoea	Unknown
Skin and subcutaneous tissue disorders	Pruritus, Urticaria, Rash,	Unknown
Musculoskeletal and connective tissue disorders	Myalgia, Arthralgia, Pain in extremity	Unknown
General disorders and administration site conditions	Asthenia, Chest discomfort, Chest pain, Fatigue, Influenza like illness, Malaise, Pyrexia, Oedema.	Unknown

The following adverse events have been observed in clinical studies, independent from the assessment of the causal relation with the therapy:

Table 2:

System, Organ, Class (SOC)	Events	Frequency Category
Infections and infestations	Upper respiratory tract infection, Sinusitis,	Common
	Headache, Dizziness, Paraesthesia	Common
Nervous system disorders	Headache, Dizziness, Paraesthesia	Common
	Migraine	Uncommon
Vascular disorders	Haemorrhage, Vasodilatation	Uncommon
Respiratory, thoracic and mediastinal disorders	Lung disorder, Dyspnoea, Cough increased, Bronchospasm,	Uncommon

	Oropharyngeal pain, COPD	
Gastrointestinal disorders	Abdominal pain, Diarrhoea, Dyspepsia, Nausea	Uncommon
Skin and subcutaneous tissue disorders	Pruritus,	Common
	Ecchymosis, Rash	Uncommon
Musculoskeletal and connective tissue disorders	Myalgia, Back pain, Musculoskeletal chest pain	Uncommon
General disorders and administration site conditions	Asthenia, Injection site pain	Common
	Pain, Chest pain, Injection site reaction, Pyrexia	Uncommon

DOSAGE AND ADMINISTRATION

The recommended dose for Zemaira[®] is 60 mg/kg body weight administered once weekly, by intravenous infusion.

Reconstitution and withdrawal must be carried out using aseptic techniques. After reconstitution the product is administered intravenously at a rate of approximately 0.08 mL/kg/min as determined by the comfort of the patient. The recommended dosage of 60 mg/kg body weight will take approximately 15 minutes to infuse.

The solution should be clear or slightly opalescent. The reconstituted product should be inspected visually for particulate matter and discoloration prior to administration. Do not use solutions, which are cloudy or contain residues (deposits/particles).

Zemaira[®] does not contain an antimicrobial preservative. It must, therefore, be used immediately after reconstitution. If product is not used immediately after reconstitution, protect from light and use within 3 hours. Any unused solution should be discarded appropriately. Use in one patient on one occasion only. Do not use if the product has been frozen.

Do not mix with other medicinal products in the same infusion line.

It is strongly recommended that every time Zemaira[®] is administered to a patient, the name and batch number of the product be recorded in order to maintain a link between the patient and the batch of the product.

Reconstitution

Bring both product vial and diluent vial to room temperature prior to reconstitution.

Remove the plastic caps from the vials. Aseptically cleanse the stoppers with antiseptic solution and allow them to dry.

The transfer device (figure 1) provided in the package is comprised of a white double end for the diluent vial and a green single orifice end for the product vial. Incorrect use of the transfer device will result in loss of vacuum and prevent transfer of the diluent, thereby preventing reconstitution of the product.

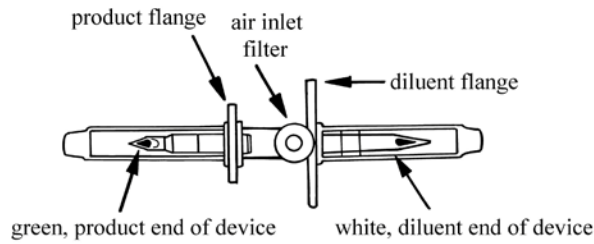


Figure 1.

The transfer device is sterile. Do not touch the exposed ends of the spike after removing the protective covers.

Remove the protective cover from the white end of the transfer device and insert it into the centre of the stopper of the upright diluent vial first (figure 2).



Figure 2.

Remove the protective cover from the green end of the transfer device. Invert the diluent vial with the attached transfer device and insert the green end of the transfer device into the centre of the rubber stopper of the upright product vial (figure 3). The transfer device should rest on the surface of the stopper so that the diluent flows into the product vial.



Figure 3.

Direct the solvent, which will be drawn in by vacuum, over the entire surface of the Zemaira[®] powder.

Do not allow the air inlet filter to face downward. Care should be taken not to lose the vacuum, as this will prolong reconstitution of the product.

When diluent transfer is complete, withdraw the transfer device and diluent vial and gently swirl the product vial until the powder is completely dissolved. Avoid shaking causing formation of foam. A clear to slightly opalescent solution will result.

After reconstitution the physico-chemical stability has been demonstrated for three hours at room temperature (up to max. 25 °C). If it is not administered immediately, storage should not exceed three hours at room temperature.

Pooling Vials

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

The reconstituted solution should be administered using a standard infusion set including a commercially available 5 micron filter.

OVERDOSAGE

Consequences of an overdose are not known.

PRESENTATION AND STORAGE CONDITIONS

Zemaira® is presented in packs containing:

- 1 vial with powder for solution for infusion: A₁-PI 1000mg
- 1 vial with 20 ml Sterile Water for Injections
- 1 vented transfer device

Store below 25°C. This product must not be frozen. Freezing may damage the diluent container. Do not use after the expiry date. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Medicine

Zemaira[®] has been granted provisional consent under section 23 of the Medicines Act 1981.

Date of Preparation: 23 June 2011

Zemaira[®] Registered trademark of CSL Group of Companies

Prolastin[®] (alpha₁-proteinase inhibitor, human) Registered trademark of Talecris Biotherapeutics Inc.

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