

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Erwinase 10,000 Units. Powder for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Crisantaspase (Asparaginase from *Erwinia chrysanthemi*; *Erwinia* L-asparaginase), 10,000 Units/vial.

Excipients with known effect:

Glucose monohydrate: 5 mg / vial

Sodium chloride: 0.5 mg / vial

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection.

White solid in a vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Erwinase is used in combination with other antineoplastic agents to treat acute lymphoblastic leukaemia.

Patients receiving treatment with L-asparaginase from *Escherichia coli* and who develop hypersensitivity to that enzyme may be able to continue treatment with Erwinase as the enzymes are immunologically distinct.

4.2 Posology and method of administration

Erwinase solution can be given by intravenous, intramuscular or subcutaneous injection.

Reference to current recognised acute lymphoblastic leukaemia protocols should be made for information on dose, route and frequency of treatment.

4.3 Contraindications

Previous allergic reaction to *Erwinia* asparaginase.

Previous episode of acute pancreatitis related to L-asparaginase therapy.

Pregnancy and breast-feeding (see section 4.6 Fertility, Pregnancy and Lactation).

4.4 Special warnings and precautions for use

Special Warnings

Erwinase should only be administered by consultant haematologists/oncologists with adequate laboratory facilities for monitoring its use.

Asparaginase is a bacterial protein and repeated use can therefore, lead to sensitisation reactions.

Posterior Reversible Encephalopathy Syndrome (PRES) may occur rarely during treatment with any asparaginase (see section 4.8). This syndrome is characterised in magnetic resonance imaging (MRI) by reversible (from a few days to months) lesions/oedema, primarily in the posterior region of the brain. Symptoms of PRES essentially include elevated blood pressure, seizures, headaches, changes in mental state and acute visual impairment (primarily cortical blindness or homonymous hemianopsia). It is unclear whether the PRES is caused by asparaginase, concomitant treatment or the underlying diseases. PRES is treated symptomatically, including measures to treat any seizures. Discontinuation or dose reduction of concomitantly administered immunosuppressive medicinal products may be necessary. Expert advice should be sought.

Special precautions for use

Erwinase should preferably be given without interruption. If, however, an interruption cannot be avoided, treatment should be resumed with a low dose, 300 Units/m²/day (10 Units/kg/day), and increased to the full dose over five days if tolerated. Anaphylaxis is rare but facilities should be made available for its management during administration.

L-asparaginase has been reported to have immunosuppressive activity in animal experiments. Accordingly, the possibility that use of the drug in man may predispose to infection should be considered.

Careful monitoring before and during therapy is necessary:

- Serum amylase, lipase and/or insulin levels should be monitored to exclude hyperglycaemia and severe pancreatitis. Hyperglycaemia may be treated with insulin, if needed.
- Routine clotting screening may be performed before treatment initiation. If significant symptomatic coagulopathy occurs withhold L-asparaginase treatment until resolved then continue according to protocol.
- Hepatic function tests should be monitored regularly during therapy.
- Renal function tests and serum uric acid levels should be monitored.

4.5 Interaction with other medicinal products and other forms of interaction

Asparaginase must not be mixed with any other drugs prior to administration.

Concomitant use of L-asparaginase and drugs affecting liver function may increase the risk of a change in liver parameters (e.g. increase of ASAT, ALAT, and bilirubin).

L-asparaginase may diminish or abolish methotrexate's effect on malignant cells; this effect persists as long as plasma asparagine levels are suppressed. Do not use methotrexate with, or following L-asparaginase, while asparagine levels are below normal.

Concomitant use of prednisone and L-asparaginase may increase the risk of a change in clotting parameters (e.g. a decrease in fibrinogen and ATIII levels).

Administration of vincristine concurrently with or immediately before treatment with L-asparaginase may be associated with increased toxicity and increased risk of anaphylaxis.

4.6 Fertility, pregnancy and lactation

Pregnancy: There are no adequate data from the use of Crisantaspase (*Erwinia* L-asparaginase) in pregnant women.

Limited reports in humans of the use of *E.coli* asparaginase in combination with other antineoplastics during pregnancy do not provide sufficient data to reach any conclusions. However, based on effects on embryonal/foetal development shown in pre-clinical studies (see section 5.3 Preclinical Safety Data),

Erwinase should not be used during pregnancy unless clearly indicated. Lactation: It is not known whether Crisantaspase (*Erwinia* L-asparaginase) is excreted in human breast milk. The excretion of Crisantaspase (*Erwinia* L-asparaginase) has not been studied in animals. Because potential serious adverse reactions may occur in nursing infants, breast-feeding is contraindicated.

Fertility: No fertility data are available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The two most frequent adverse reactions are Hypersensitivity, including urticaria, laryngeal oedema, bronchospasm, hypotension or even anaphylactic shock. In case of systemic hypersensitivity reaction, treatment should be discontinued immediately and withdrawn.

Coagulation abnormalities (e.g. thrombosis), due to protein synthesis impairment, are the second most frequent class of adverse reactions.

Thrombosis of peripheral, pulmonary or central nervous system blood vessels have been reported, potentially fatal or with residual delayed effects dependent upon the location of the occlusion. Other risk factors contributing to coagulation abnormalities include the disease itself, concomitant steroid therapy and central venous catheters.

Undesirable effects are generally reversible.

Tabulated list of adverse reactions

Adverse effects reported spontaneously and in the literature, from patients treated with L-asparaginase as part of their chemotherapy regimen, are listed in the table below. Adverse effects are categorised by system organ class and frequency.

Frequency definitions: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$) and very rare ($<1/10,000$). When no valid estimate of the incidence rate for an adverse event from available data can be calculated, the frequency of such ADR has been classified as "Not known".

System organ class	Reactions					
	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known
Infections and infestations					Infections, lifethreatening sepsis.	
Blood and lymphatic system disorders	Coagulopathies - abnormal clotting factor, decreased antithrombin III, protein C, protein S or blood fibrinogen ⁽¹⁾ .	Coagulopathies associated with bleeding or thrombotic complications, hypocoagulable state, asymptomatic coagulopathy.			Neutropenia, febrile neutropenia, thrombocytopenia.	Bone marrow depression, anaemia, leukopenia.
Immune systems disorders		Hypersensitivity.	Anaphylactic reaction.			
Metabolic and nutrition disorders		Increased serum amylase or lipase.	Hyperlipidaemia ⁽¹⁾ , hyperglycaemia.	Diabetic ketoacidosis.		Hyperammonaemia ⁽³⁾ .
Nervous system disorders		Lethargy, somnolence, confusional state, dizziness, neurotoxicity*, grand mal convulsion ⁽²⁾ , partial seizures ⁽²⁾ , headache.		Aphasia, paresis, encephalopathy ⁽³⁾ , depressed level of consciousness, coma. Posterior reversible encephalopathy syndrome (PRES)		
Cardiac disorders				Myocardial infarction – secondary to other adverse events (e.g. thrombosis, pancreatitis).		

System organ class	Reactions					
	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (<1/10,000)	Not known
Vascular disorders		Pulmonary, venous or cerebral thrombosis, pallor.				Haemorrhage, hypertension, flushing ⁽⁴⁾ , hypotension ⁽⁴⁾ .
Respiratory, thoracic and mediastinal disorders		Dyspnoea ⁽⁴⁾ .	Laryngeal oedema ⁽⁴⁾ , respiratory arrest, hypoxia, rhinitis, bronchospasm ⁽⁴⁾ .			
Gastro-intestinal disorders		Diarrhoea, acute Pancreatitis.			Haemorrhagic or necrotising pancreatitis*, dysphagia.	Nausea, vomiting, abdominal pain.
Hepato-biliary disorders		Increased blood bilirubin, ALT, AST, blood alkaline phosphatase or blood cholesterol, hepatotoxicity.		Hepatic failure.		Hepatomegaly, cholestatic jaundice, hypoalbuminaemia, hepatic steatosis.
Skin and subcutaneous tissue disorders		Rash, urticaria, pruritis, erythema, facial oedema, lip swelling ⁽⁴⁾ .				
Musculoskeletal and connective tissue disorders					Myalgia, reactive arthritis.	Pain in extremity.
Renal and urinary disorders						Renal impairment.

System organ class	Reactions					
	Very common ($\geq 1/10$)	Common ($\geq 1/100$ to $< 1/10$)	Uncommon ($\geq 1/1,000$ to $< 1/100$)	Rare ($\geq 1/10,000$ to $< 1/1,000$)	Very rare ($< 1/10,0000$)	Not known
General disorders and administration site conditions		Pyrexia, chills, peripheral oedema, injection site reaction (including injection site pain, erythema, haematoma or oedema), pain.				

* See description of selected adverse reactions.

1 - As a consequence of inhibition of protein synthesis.

2 - Convulsions may be associated with cases of thrombosis or metabolic encephalopathy.

3 - As a consequence of excessive ammonia production induced by the action of L-asparaginase on endogenous asparagine and glutamine.

4 - These symptoms are commonly associated with hypersensitivity reactions.

Description of selected adverse reactions

Pancreatic disorders – acute pancreatitis occurs in <10% of cases. There have been isolated reports of pseudocyst formation up to 4 months after last treatment, so appropriate testing (e.g. ultrasound) may need to be considered beyond last treatment. In very rare cases, haemorrhagic or necrotising pancreatitis occurs, with fatal consequences. L-asparaginase can affect endocrine pancreatic function. Hyperglycaemia is the most commonly reported undesired effect and is readily controlled with administration of insulin. Rare cases of diabetic ketoacidosis have been reported.

Nervous system and cardiac disorders are often secondary to other adverse effects (e.g. thromboembolism) or synergistic to the effects of other chemotherapy drugs (e.g. delayed methotrexate clearance). In rare cases, a posterior reversible encephalopathy syndrome (PRES) has been observed during therapy with asparaginase-containing regimens.

Paediatric population

The frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Other special populations

No special individual populations of patients have been identified in which the safety profile differs from that defined above.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

HPRa Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517.

Website: www.hpra.ie;

E-mail: medsafety@hpra.ie.

4.9 Overdose

Apart from acute allergic reactions or anaphylactic shock, L-asparaginase can cause chronic intoxication, characterised by impaired liver or kidney function.

The administration of L-asparaginase should be stopped immediately and symptomatic treatment commenced straight away.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents

ATC code: L01XX02

Neoplastic cells associated with Acute Lymphoblastic Leukaemia (ALL) are asparagine-dependent. Reduction of plasma asparagine levels achieved by administration of L-asparaginase produces an anti-neoplastic effect.

5.2 Pharmacokinetic properties

The half-life of Erwinase after i.v. infusion is 6.4 ± 0.5 hours.

The half-life of Erwinase after i.m. infusion is about 16 hours.

L-asparaginase penetrates through to the cerebrospinal fluid to a small degree and is also found in lymph.

Serum trough asparaginase activity ≥ 0.1 IU/mL has been demonstrated to correlate with asparagine depletion (asparagine < 0.4 mcg/mL or $3 \mu\text{M}$) and to serum levels that predict clinical efficacy.

With repeated use, the drug may be bound by specific antibodies and eliminated.

IM study:

The serum trough concentrations of crisantaspase were determined in 48 ALL patients aged ≥ 2 year to ≤ 18 years enrolled in a single-arm study, multi-centre, open-label, safety and clinical pharmacology trial AALL07P2. The main outcome measure was determination of the proportion of patients who achieved a serum trough asparaginase level greater than or equal to 0.1 IU/mL.

Following intramuscular administration at a dose of 25,000 IU/m² for the first course, serum asparaginase activity is maintained above 0.1 IU/mL at 48 hours post-dose in 92.5% of patients, and at least at 0.1 IU/mL after 72 hours in 88.5% of patients.

IV Study:

The serum trough asparaginase activity was determined in 24 ALL patients aged ≥ 1 year to ≤ 17 years enrolled in a single-arm, multi-centre, open-label, pharmacokinetic study 100EUSA12. The primary objective of the study was to determine the proportion of patients with 2-day nadir (trough) serum asparaginase activity levels (48-hour levels taken after the fifth dose) that were ≥ 0.1 IU/mL in the first 2 weeks of Erwinase treatment (three times per week IV) in patients with ALL/LBL who had developed hypersensitivity to native E. coli asparaginase, pegaspargase, or calaspargase pegol.

Following intravenous administration over 1 hour at a dose of 25,000 IU/m² for the first course, serum asparaginase activity was maintained ≥ 0.1 IU/mL at 48 hours post-dose 5 (primary endpoint) in 83% of patients, and ≥ 0.1 IU/mL 72 hours post dose 6 (secondary endpoint) in 43% of patients.

5.3 Preclinical safety data

Acute toxicity:

LD₅₀ i.p. in mice: 5×10^5 IU/kg

LD₅₀ i.p. in rabbits: 12,000 IU/kg

LD₅₀ i.p. in rats: 3,200 IU/kg

Subacute and chronic toxicity:

No pathological effects were observed at doses of up to 1,000 IU/kg/day in rabbits, up to 5,000 IU/kg/day in dogs and up to 10,000 IU/kg/day in Rhesus monkeys (for comparison: the recommended daily doses correspond to approximately 200 IU/kg). In rats and mice, subdural bleeding and renal tubuli damage occurred at very high doses.

Reproduction toxicity:

The product has been shown to be able to cross the placenta in rabbits, and embryotoxicity studies with Erwinia L-asparaginase have given evidence of teratogenic potential in rabbits. Animal studies provide evidence of injury to the embryo (malformation, foetal death). In view of asparagine depletion, teratogenic effects are anticipated.

Carcinogenicity:

No genotoxicity or carcinogenicity studies have been conducted on Erwinia sp. asparaginase. Asparaginase from *Erwinia chrysanthemi* is an enzyme, for which the structure and well documented activity do not suggest any carcinogenic or mutagenic potential. *In vitro*, no karyotype changes occurred, only a deceleration or arrest of the rate of mitosis (cytostatic effect).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Glucose Monohydrate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. See section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction.

6.3 Shelf life

Shelf life of product as packed for sale

3 years.

Shelf-life following reconstitution according to directions

15 minutes in the original container, 4 hours in a polypropylene syringe.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 4 hours when stored below 25°C unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store between 2°C and 8°C.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I clear neutral glass vials of 3 ml nominal capacity, closed with 13 mm bromobutyl stoppers and aluminium overseals containing a white lyophilised solid. Pack size of 5 vials.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The contents of each vial should be reconstituted in 1 ml to 2 ml of sodium chloride (0.9%) solution for injection. Slowly add the reconstitution solution against the inner vial wall, do not squirt directly onto or into the powder. Allow the content to dissolve by gentle mixing or swirling maintaining the vial in an upright position. Avoid froth formation due to excessive or vigorous shaking.

The solution should be clear without any visible particles. Fine crystalline or thread-like wisps of protein aggregates may be visible if shaking is excessive resulting in visible foaming. If there is any visible particles or protein aggregates present the reconstituted solution should be rejected.

The solution should be administered within 15 minutes of reconstitution. If a delay of more than 15 minutes between reconstitution and administration is unavoidable, the solution should be withdrawn into a polypropylene syringe for the period of the delay. The solution should be used within 4 hours and stored below 25°C.

Erwinase is not a cytotoxic drug (such as vincristine or methotrexate) and does not require the special precautions needed for manipulating such agents. Nevertheless, when preparing or administering Erwinase the fact should be taken into account that it can be sensitising.

It should be handled in the same way as other therapeutic enzymes such as hyaluronidase.

Inhalation of the powder or the solution should be avoided. In the event of it coming into contact with the skin or mucous membranes, in particular with the eyes, these should be rinsed with plenty of water for at least 15 minutes.

Any unused product or waste material should be disposed in accordance with local requirements

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

PA 1020/002/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 1998
Date of last renewal: 18 September 2013

10. DATE OF REVISION OF THE TEXT

September 2016