New Zealand Datasheet

1. PRODUCT NAME
Erwinase® 10,000 Units/vial, Lyophilisate for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Crisantaspase (Asparaginase from Erwinia chrysanthemi;
Erwinia L-asparaginase), 10,000 Units/vial.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Lyophilisate for solution for injection.
White lyophilised powder in a vial.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Erwinase is used in combination with other anti-neoplastic agents to treat acute lymphoblastic leukaemia. It may also be used in other neoplastic conditions where depletion of asparagines might be expected to have a useful effect. 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 Dose and method of administration
For all patients the usual dose is 6,000 Units/m^2 body surface area (200 Units/kg of body weight), three times a week for three weeks.

Therapy may be further intensified according to protocol.

Reference to current Medical Research Council protocols on leukaemia therapy should be made for information on dose, route and frequency of treatment.

Method of administration
Erwinase solution can be given by intravenous injection or by intramuscular or subcutaneous injection.

4.3 Contraindications
Previous allergic reaction to Erwinia asparaginase.
Previous episode of acute pancreatitis related to L-asparaginase therapy.
Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use
Warnings: Anaphylactic reactions have been observed after the use of Erwinase. Facilities should be made available for management of an anaphylactic reaction, should it occur, during administration.

Careful observation is required on re-exposure to L-asparaginase after any time interval (e.g. between induction and consolidation), which may increase the risk of anaphylactic reactions occurring.

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.

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.

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, 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 did not provide sufficient data to conclude.

However, based on effects on embryonal/foetal development shown in pre-clinical studies (see section 5.3), Erwinase should not be used during pregnancy unless clearly necessary.

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 contra-indicated.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

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

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. thromboses), due to protein synthesis impairment, are the second most frequent class of adverse reactions. Thromboses of peripheral, pulmonary or central nervous system blood vessels have been reported, potentially fatal or with residual delayed affects 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.

Pancreatic disorders – acute pancreatitis occurs in <10% of cases. There have been isolated reports of pseudocyst formation up to four 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. Isolated cases of diabetic ketoacidosis have been reported.

Nervous system and cardiac disorders are often secondary to other adverse effects (e.g. thrombo-embolism) 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.

Undesirable effects are generally reversible.

Frequency definitions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000) and very rare (<1/10000).

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”.

Isolated cases reported in the literature or spontaneously have been classified as “Rare” or “Very Rare”.

Infections and infestations:	
Very rare:	Infections and life-threatening sepsis.
Blood and lymphatic system disorders:	
Very Common:	Coagulation abnormalities - decreased levels of clotting factor, antithrombin III, protein C, protein S and fibrinogen(1).
Common:	Coagulation abnormalities associated with bleeding or thrombotic complications, hypofibrinogenemia, asymptomatic coagulopathy.
Very Rare :	Neutropenia, febrile neutropenia and thrombocytopenia.
Not known:	Haemorrhage.
Immune system disorders:	
Common:	Hypersensitivity or systemic allergic reactions.
Uncommon:	Anaphylaxis.

Metabolic and nutrition disorders:	
Common :	Elevation of serum amylases and lipase.
Uncommon:	Hyperlipidaemia(1) and hyperglycaemia.
Rare:	Diabetic ketoacidosis.
Not known :	Hyperammonaemia(3).
Nervous system disorders:	
Common :	Lethargy, somnolence, confusion, dizziness, neurotoxicity, convulsions (grand mal, partial seizures)(2), headache.
Rare:	Dysphasia, dysphagia, paresis and encephalopathy(3), CNS depression and coma. Posterior Reversible Encephalopathy Syndrome (PRES).
Cardiac disorders:	
Rare:	Myocardial infarction – secondary to other adverse events (e.g. thrombosis, pancreatitis).
Vascular disorders:	
Common:	Thrombosis of peripheral, pulmonary or central nervous system blood vessels and pallor.
Not known :	Hypertension, flushing(4) and hypotension(4).
Respiratory, thoracic and mediastinal disorders:	
Common:	Dyspnoea(4).
Uncommon:	Laryngeal oedema(4), respiratory arrest, hypoxia, rhinitis and bronchospasm(4).
Gastrointestinal system disorders:	
Common :	Diarrhoea and acute pancreatitis.
Very rare:	Haemorrhagic or necrotising pancreatitis.
Not known :	Nausea, vomiting and abdominal pain.
Hepato-biliary disorders:	
Common:	Elevation of bilirubin, ALT, AST, alkaline phosphatase and cholesterol levels, liver toxicity.
Rare:	Hepatic failure.
Not known:	Hepatomegaly, jaundice (cholestatic), increased BSP retention.
Skin and sub-cutaneous tissue disorders:	
Common:	Rashes, urticaria, pruritis, erythema, facial oedema and swelling lips(4).
Musculoskeletal and connective tissue disorders:	
Very rare:	Myalgia and reactive arthritis.
Not known :	Pain in extremities.
General disorders:	
Common:	Pyrexia, chills, swelling of limbs and injection site reactions (including pain, erythema, purpura and swelling at injection site), generalised pain.

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.

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 the national reporting system listed.

4.9 Overdose

No specific measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

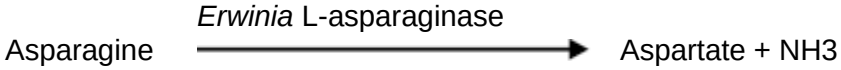
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents
ATC code: L01XX02

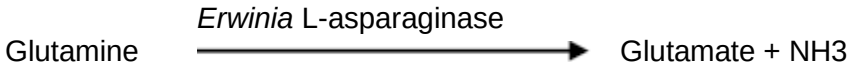
Asparagine is found incorporated into most proteins, and protein synthesis is halted in its absence, thereby inhibiting RNA and DNA synthesis with a resulting halt to cellular proliferation.

Neoplastic cells associated with Acute Lymphoblastic Leukaemia (ALL), Acute Myeloid Leukaemia (AML) and Non-Hodgkin's Lymphoma (especially the lymphoblastic form) are lacking asparagine synthetase activity and are dependent upon exogenous asparagine.

The anti-tumour activity of L-asparaginase is a result of the sustained depletion of exogenous asparagine. L-asparaginase catalyses the deamination of asparagine to aspartic acid with the release of ammonia. The biochemical reaction may be depicted schematically as follows:



It has also been noted that asparaginase, in addition to its asparaginase activity, has significant glutaminase activity. It catalyses the deamination of glutamine in glutamic acid with the release of ammonia as follows:



Glutamine may lead to alternative asparagine synthesis and therefore glutamine depletion may complement asparagines depletion. However, exact potential of this glutaminase activity remains unknown.

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 U/mL has been demonstrated to correlate with asparagine depletion (asparagine < 0.4 mcg/mL or 3 µM) 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 ≥2year 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 U/mL.

Following intramuscular administration at a dose of 25,000 U/m^2 for the first course, serum

asparaginase activity is maintained above 0.1 U/mL at 48 hours post-dose in 92.5% of patients, and at least at 0.1 U/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 U/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 U/m^2 for the first course, serum asparaginase activity was maintained ≥0.1 U/mL at 48 hours post-dose 5 (primary endpoint) in 83% of patients, and ≥0.1 U/mL 72 hours post dose 6 (secondary endpoint) in 43% of patients.

5.3 Pre-clinical safety data
Embryotoxicity studies with Erwinia L-asparaginase have given evidence of teratogenic potential in rabbits. In addition, pre-clinical experience with other asparaginase preparations has shown teratogenic potential in rats, mice and rabbits with doses in the therapeutic ranges.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium Chloride
Glucose Monohydrate

6.2 Incompatibilities
See section 4.5 "Interactions 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, 8 hours in a glass or polypropylene syringe. (See section 6.6 "Special precautions for disposal and other handling").

6.4 Special precautions for storage
Store in a refrigerator (+2°C to +8°C).

6.5 Nature and contents of container
Type 1 clear neutral glass vials of 3 ml nominal capacity, closed with 13 mm halobutyl freeze-drying stoppers and aluminium overseals, containing a white lyophilised solid.

Pack size: 5 vials.

6.6 Special precautions for disposal and other handling
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 contents 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. If there are 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 glass or polypropylene syringe for the period of the delay. The solution should be used within 8 hours.

Erwinase is not a cytotoxic drug (such as vincristine or methotrexate) and does not require the special precautions needed for manipulating such agents.

It should be handled in the same way as other therapeutic enzymes such as hyaluronidase.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

New Zealand Medical & Scientific Ltd
PO Box 132400,
Silvia Park
Auckland 1644
New Zealand
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9. DATE OF FIRST APPROVAL

First authorisation: 4 July 1991

10. DATE OF REVISION OF THE TEXT

14 November 2016

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Addition of: 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.
4.8	Addition of: In rare cases, a posterior reversible encephalopathy syndrome (PRES) has been observed during therapy with asparaginase-containing regimens. Nervous system disorders: Rare: Posterior Reversible Encephalopathy Syndrome (PRES).
5.2	Pharmacokinetics updated and addition of: 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 U/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.