ERWINASE®
(Erwinia L-asparaginase)

1. Name of the Medicinal Product

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 asparagine 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 Posology and method of administration

Erwinase solution can be given by intravenous injection or by intramuscular or subcutaneous injection.
For all patients the usual dose is 6,000 Units/m² 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.

4.3 Contra-indications

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.

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 Interactions 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 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).

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”.

<table>
<thead>
<tr>
<th>Infections and infestations:</th>
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<tbody>
<tr>
<td><strong>Very rare:</strong> Infections and life-threatening sepsis.</td>
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</table>

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<tr>
<th>Blood and lymphatic system disorders:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very Common:</strong> Coagulation abnormalities - decreased levels of clotting factor, antithrombin III, protein C, protein S and fibrinogen&lt;sup&gt;(1)&lt;/sup&gt;.</td>
</tr>
<tr>
<td><strong>Common:</strong> Coagulation abnormalities associated with bleeding or thrombotic complications, hypofibrinogenemia, asymptomatic coagulopathy.</td>
</tr>
<tr>
<td><strong>Very Rare:</strong> Neutropenia, febrile neutropenia and thrombocytopenia.</td>
</tr>
<tr>
<td><strong>Not known:</strong> Haemorrhage.</td>
</tr>
</tbody>
</table>
**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.

**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.

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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.
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:

\[
\begin{align*}
\text{Asparagine} & \xrightarrow{\text{Erwinia L-asparaginase}} \text{Aspartate} + \text{NH}_3 \\
\end{align*}
\]

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:

\[
\begin{align*}
\text{Glutamine} & \xrightarrow{\text{Erwinia L-asparaginase}} \text{Glutamate} + \text{NH}_3 \\
\end{align*}
\]

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

5.2 Pharmacokinetic properties

Peak levels of Erwinase are achieved in blood in 1 to 2 hours. The fall in enzyme levels follows first order kinetics with a half-life of 7 to 13 hours.

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 "Instructions for use/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 Instructions for use/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. Marketing Authorisation Holder

Health Protection Agency  
Centre for Emergency Preparedness and Response  
Porton Down, Salisbury, SP4 0JG  
United Kingdom

8. Marketing Authorisation Number

PL 20170/0001

9. Date of First Authorisation/Renewal of the authorisation

First authorisation: 19 July 1985  
Latest renewal: 25 May 2006

10. Date of Revision of the SPC

March 2009

Local representative:

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