ERWINASE® SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ERWINASE®, 10,000 Units/mL, Lysophilafile for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Crisantaspase (hyprograsin from Eriwina chrysanthemi) Enzyme L-asparaginase, 10,000 Units/mL. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lysophilafile for solution for injection. White lyophilised powder in a vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Enriwase 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 may 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 Enriwase as the enzymes are immunologically different.

4.2 Pharmacology and method of administration

Enriwase solution can be given by intravenous injection or by intramuscular or subcutaneous injection. For all patients the usual dose is 10,000 Units body surface area (200 Units/kg 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 Eriwina asparaginase. Previous episode of acute pancreatitis related to L-asparaginase therapy.

4.4 Special warnings and precautions for use

Warnings: Anaphylactic reactions have been observed after the use of Enriwase. 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.

4.5 Interactions with other medicinal products and other forms of interaction

Asparaginase may not be mixed with any other drugs prior to administration. Combination of L-asparaginase and drugs affecting liver function may increase the risk of a change in liver parameters (e.g., increase in ASAT, ALAT, bilirubin).

Concomitant use of prednisolone or L-asparaginase may decrease the effect of prednisolone. L-asparaginase and asparaginase levels are suppressed. Do not use methotrexate with, or following L-asparaginase, while asparaginase levels are below normal.

Concomitant use of prednisolone and L-asparaginase may increase the risk of a change in clotting parameters (e.g. decrease in factor VIII and APTT levels). Administration of warfarin concurrently with or immediately before treatment with L-asparaginase may be associated with increased toxicity and increased risk of bleeding.

4.6 Pregnancy and lactation

Pregnancy: There are no adequate data from the use of Crisantaspase (Eriwina L-asparaginase) in pregnant women. Limited reports in humans of the use of E coli asparaginase in combination with other antineoplastic treatments during pregnancy did not provide sufficient data to conclude. However, based on effects on embryofetal development shown in preclinical studies (see section 5.2), Enriwase should not be used during pregnancy unless clearly necessary.

Lactation: It is not known whether Crisantaspase (Eriwina L-asparaginase) is excreted in human breast milk. The excretion of Crisantaspase (Eriwina L-asparaginase) has not been studied in animals. Because potential serious adverse reactions may occur in nursing infants, breast-feeding is contraindicated.

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.
- Coagulation abnormalities (e.g., thrombosis), due to platelet dysfunction, are the second most frequent class of adverse reactions. Thrombi of peripheral, pulmonary or central nervous system blood vessels have been reported, potentially fatal or with residual disability affects dependant 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 <1% of cases. There have also been isolated reports of pseudomembranous enteritis occurring within 4 to 6 weeks of treatment with L-asparaginase.

4.9 Overdose

4.10 Mechanism of recovery

None known.

5. USE IN SPECIFIC POPULATIONS

5.1 Adolescents

None known.

5.2 Effects on laboratory parameters

None known.

5.3 Contraception

None known.

5.4 Effects on reproductive capacity

None known.

6. HOW TO USE

6.1 Administration of the medicinal product

Enriwase can be administered intravenously, intramuscularly or subcutaneously. Details are given in the summary of product characteristics (section 4.2).

6.2 Duration of treatment

The duration of treatment will depend on the response of the disease to therapy. The duration of treatment will depend on the response of the disease to therapy.

6.3 Stopping the treatment

The treatment should be stopped immediately if any significant fall in platelet count, or any evidence of coagulation abnormalities is noted.

6.4 Readministration after an interval

None known.

7. IMPROVED UNDERSTANDING OF THE MEDICINAL PRODUCT

None known.

8. USE IN SPECIAL POPULATIONS

None known.

9. PARTICULARS

9.1 Nature and composition

Crisantaspase is a glycoprotein enzyme produced by Eriwina chrysanthemi. It is a minor leucine peptidase that specifically hydrolysates asparagine, the major nitrogen source in mammalian cells.

9.2 Preclinical safety data

None known.

9.3 Preclinical pharmacology

None known.

9.4 Preclinical toxicology

None known.

9.5 Pharmaceutical properties

None known.

9.6 Molecular properties

None known.

9.7 Stability

None known.

9.8 Effect of temperature

None known.

9.9 Effects of freezing

None known.

10. QUALITY

The quality of the medicinal product is guaranteed by the manufacturer.

11. STABILITY

None known.

12. INCOMPATIBILITIES

None known.

13. PACKAGING AND STORAGEN

None known.

14. MARKETING AUTHORISATION HOLDER

Breon Pharmaceuticals Ltd

15. DISTRIBUTION

15.1 WITHIN THE UNITED KINGDOM

15.2 OUTSIDE THE UNITED KINGDOM

15.3 IMPORTATION

15.4 DISTRIBUTORS

15.5 MARKETING REPRESENTATIVES

16. MARKETING AUTHORISATION

None known.

17. PATIENT INFORMATION LEAFLET

Your medicine is called

ERWINASE®

Main ingredient

Crisantaspase, commonly known as Enriwase L-asparaginase

Contents of each bottle

Enriwase L-asparaginase enzyme 10,000 Units

Other Ingredients:

Sodium chloride 0.5mg

Glucose monohydrate 5.0 mg

What it looks like

Enriwase comes as a white powder in a glass bottle to which a special seal solution is added so it can be injected.

Type of medicine

Enriwase is an anti-blood-cell-cancer medicine.

Marketing Authorisation Holder

Health Protection Agency

Centre for Emergency Preparedness and Response

Porton Down, Salisbury, SP4 0JQ

United Kingdom

Manufacturer

Breon Pharmaceuticals Ltd

Hay on Wye, Hereford, HR3 5PG

United Kingdom

Uses

Enriwase is used for the treatment of certain types of blood-cell cancer including Acute Lymphoblastic Leukaemia, Acute Myeloid Leukaemia and Lymphoblastic Lymphoma.

When shouldn't you be given this medicine?

1. If you have had a bad reaction to treatment with Enriwase.

2. If you are having a baby, trying to have a baby or if you are breast-feeding.

Warnings and additional information

Enriwase is a substance which your body may become sensitive to after repeated treatments. We recommend to your doctor that Enriwase should not be mixed with other medicines although you will probably be given other medicines before, during or after Enriwase treatment as part of your course of therapy.

Treatment with Enriwase can sometimes affect the results of certain blood or urine tests. Your doctor will be aware of this.

If you are diabetic, you should note that both bottle of Enriwase contains 5 mg glucose.
ERWINASE®
(Erwinia L-asparginase)
10,000 Units
Powder for solution for injection

Dosage
Your doctor will have the latest information from the Medical Research Council on the recommended dosage of Erwinase. The standard dose is 6000 Units for each square meter of your body surface area, three times a week for three weeks. Further doses may be given at the doctor's discretion.

Side Effects
During your treatment with Erwinase, you may suffer from some side effects including high temperature, feeling or being sick and signs of nervous system changes. This may appear as drowsiness and confusion. If you develop swelling of the face and/or throat or difficulty breathing you may require emergency treatment and should seek medical advice immediately. Other side effects can include abdominal pain and changes in blood tests due to acute pancreatitis or blood infection and severe sensitivity.

Storage
Erwinase will be stored in a refrigerator (+2°C to +6°C) by the hospital and should not be used after the expiry date printed on the label. This Patient Information Leaflet was last updated on September 2008.

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e-mail: medinfouk@eusapharma.com

Erwinase is a registered trademark of the Health Protection Agency.

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

6.2 Incapacities
See section 4.5 "Interactions with other medicinal products and other forms of interaction".

6.3 Shelf-life
Small-pilot 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 +6°C).

6.5 Nature and contents of container
Type 1 clear glass/natural glass vials of 3 ml nominal capacity, closed with a 13 mm hexagonal friction-stopping and aluminium overcaps, 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. Slightly shake the reconstituted solution to dissolve the powder. Do not inject directly into the powder. Allow the contents to dissolve by gentle mixing or swabbing maintaining the vial in an upright position. Avoid hand formation due to excessive or vigorous shaking.

The solution should be used 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. In case of delay of more than 15 minutes between reconstitution and administration is unacceptable, the solution should be withdrawn into a glass or polypropylene syringe for the period of the delay. The solution should be used within 2 hours.

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

7. MARKETING AUTHORISATION HOLDER
Health Protection Agency
Centre for Emergency Preparedness and Response
Porton Down, Salisbury SP4 0PG
United Kingdom.

8. MARKETING AUTHORISATION NUMBER
PL 2017/0001

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
First authorization: 19 July 1995
Latest renewal: 25 May 2006

10. DATE OF REVISION OF THE SPC
March 2009

Local representative:
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EUSA Pharma

4.8 Overdosage
No specific measures are recommended.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamics properties
Pharmacodynamic group: other antineoplastic agents
ATC code: L01XX
Asparagine is a known product of two proteins, the asparaginase and protein synthesis. It is helpful in its absence, thereby inducing RNA and DNA synthesis with a resulting half to cellular proliferation.
Cellular cells associated with Acute Lymphoblastic Leukemia (ALL) Acute Myeloid Leukemia (AML) and Non-Hodgkin’s Lymphoma especially the lymphoblastic forms and are lacking asparaginase synthetase activity and are dependent upon exogenous asparagine.
The anti-therapy activity of asparagine is the result of the sustained depletion of exogenous asparagine. L-asparagine catalyzes the deamination of asparagine to aspartic and with the release of ammonia. The biochemical reaction may be depicted schematically as follows:

Asparagine + NH₄Cl → Aspartic acid + NH₄Cl

Asparagine has also been noted that asparagine, in addition to its asparagine activity, has significant glutamine activity. It catalyzes the deamination of glutamine in glutaric acid with the release of ammonia as follows:

Glutamine + NH₄Cl → Glutamic acid + NH₄Cl

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

5.2 Pharmacokinetics properties
Peak levels of Erwinase are achieved 6 hours after injection. The half in enzyme levels follows first order kinetics with a half life of 1 to 3 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 range.

6.2 Incapacities
See section 4.5 "Interactions with other medicinal products and other forms of interaction".

6.3 Shelf-life
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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 human insulin.

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

7. MARKETING AUTHORIZATION HOLDER
Health Protection Agency
Centre for Emergency Preparedness and Response
Porton Down, Salisbury SP4 0PG
United Kingdom.

8. MARKETING AUTHORIZATION NUMBER
PL 2017/0001

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
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Latest renewal: 25 May 2006

10. DATE OF REVISION OF THE SPC
March 2009

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EUSA Pharma
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**CSK QC Approved**

Date: 13/05/09

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**Customer Approved**

Date: 15/05/09

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**Chesapeake**

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