asparaginase *Erwinia chrysanthemi*
ERWINAZE™

For Injection, Intramuscular Use

10,000 International Units/vial

PRESCRIBING INFORMATION

ERWINAZE™ is manufactured by
EUSA Pharma (USA), Inc
Langhorne, PA 19047
License: 1829
Customer Service: 1-800-833-3533
www.eusapharma.com

EUSAPharma

E606-1011A1

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ERWINAZE™ safely and effectively. See full prescribing information for ERWINAZE.

ERWINAZE (asparaginase *Erwinia chrysanthemi*)
for injection, intramuscular use
Initial U.S. Approval: 2011

----------INDICATIONS AND USAGE----------

ERWINAZE (asparaginase *Erwinia chrysanthemi*) is an asparagine-specific enzyme indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to *E. coli*-derived asparaginase. (1)

----------DOSAGE AND ADMINISTRATION----------

- To substitute for a dose of pegaspargase:
  The recommended dose is 25,000 International Units/m^2 administered intramuscularly three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of pegaspargase. (2.1)
- To substitute for a dose of native *E. coli* asparaginase:
  The recommended dose is 25,000 International Units/m^2 administered intramuscularly for each scheduled dose of native *E. coli* asparaginase. (2.1)
- Limit the volume of reconstituted ERWINAZE at a single injection site to 2 mL; if reconstituted dose to be administered is greater than 2 mL, use multiple injection sites. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

- 10,000 International Units lyophilized powder per vial

----------CONTRAINDICATIONS----------

- History of serious hypersensitivity reactions to ERWINAZE, including anaphylaxis (4)
- History of serious pancreatitis with prior L-asparaginase therapy (4)
- History of serious thrombosis with prior L-asparaginase therapy (4)
- History of serious hemorrhagic events with prior L-asparaginase therapy (4)

----------WARNINGS AND PRECAUTIONS----------

- If the following occur, discontinue ERWINAZE:
  Serious hypersensitivity reactions, including anaphylaxis (5.1)
  Severe or hemorrhagic pancreatitis (5.2)
- Glucose intolerance can occur and, in some cases, may be irreversible. Perform appropriate monitoring and treat hyperglycemia with insulin, as necessary (5.3)
- Thrombosis, hemorrhage: discontinue ERWINAZE until resolved (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (greater than >1%) are: serious hypersensitivity reactions, including anaphylaxis, pancreatitis, abnormal transaminases, coagulation abnormalities including thrombosis and hemorrhage, nausea and vomiting, and hyperglycemia.

To report SUSPECTED ADVERSE REACTIONS, contact EUSA Pharma (USA), Inc. at 800-833-3533 and/or FDA at 800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: November, 2011

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ERWINAZE (asparaginase *Erwinia chrysanthemi*) for Injection - FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ERWINAZE (asparaginase *Erwinia chrysanthemi*) is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to *E. coli*-derived asparaginase.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

To substitute for a dose of pegaspargase:

The recommended dose is 25,000 International Units/m^2 administered intramuscularly three times a week (Monday/Wednesday/Friday) for six doses for each planned dose of pegaspargase.

To substitute for a dose of native *E. coli* asparaginase:

The recommended dose is 25,000 International Units/m^2 administered intramuscularly for each scheduled dose of native *E. coli* asparaginase within a treatment.

2.2 Preparation Instructions

(1) Visually inspect the ERWINAZE powder for foreign particulate matter and discoloration prior to reconstitution. Discard vial if present.
(2) Reconstitute the contents of each vial by slowly injecting 1 or 2 mL of preservative-free sterile sodium chloride (0.9%) injection (USP) against the inner vial wall.
(3) Do not forcefully inject solution for reconstitution directly onto or into the powder. When reconstituted with 1 mL the resultant concentration is 10, 000 International Units per mL. When reconstituted with 2 mL the resultant concentration is 5,000 International Units per mL.
(4) Dissolve contents by gentle mixing or swirling. Do not shake or invert vial.
(5) When reconstituted, ERWINAZE should be a clear, colorless solution. Discard the reconstituted solution if any visible particles or protein aggregates are present.
(6) Calculate the dose needed and the volume needed to obtain the calculated dose.
(7) Withdraw the volume containing the calculated dose from the vial into a polypropylene syringe within 15 minutes of reconstitution. Do not freeze or refrigerate reconstituted solution and administer within 4 hours or discard.

[see *How Supplied (16)*].

2.3 Administration Instructions

(1) Inject ERWINAZE solution intramuscularly.
(2) Limit the volume of reconstituted ERWINAZE at a single injection site to 2 mL; if reconstituted dose to be administered is greater than 2 mL, use multiple injection sites.
(3) If a partial vial is used, do not save or reuse the unused drug for later administration. Discard unused portions.

3 DOSAGE FORMS AND STRENGTHS

Lyophilized powder 10,000 International Units per vial

4 CONTRAINDICATIONS

- History of serious hypersensitivity reactions to ERWINAZE, including anaphylaxis.
- History of serious pancreatitis with prior L-asparaginase therapy
- History of serious thrombosis with prior L-asparaginase therapy
- History of serious hemorrhagic events with prior L-asparaginase therapy

5 WARNINGS AND PRECAUTIONS

5.1 Serious hypersensitivity reactions, including anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis have occurred after the use of ERWINAZE in 5% of patients in clinical trials *[see Adverse Reactions (6.1)]*.

Administer this product in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis. If a serious hypersensitivity reaction occurs, discontinue ERWINAZE and initiate appropriate therapy.

5.2 Pancreatitis

Pancreatitis has been reported with ERWINAZE therapy in 4% of patients in clinical trials *[see Adverse Reactions (6.1)]*.

Evaluate patients with symptoms compatible with pancreatitis to establish a diagnosis. Discontinue ERWINAZE for severe or hemorrhagic pancreatitis manifested by abdominal pain > 72 hours and amylase elevation ≥ 2.0 x ULN. Severe pancreatitis is a contraindication to additional asparaginase administration. In the case of mild pancreatitis, hold ERWINAZE until the signs and symptoms subside and amylase levels return to normal. After resolution, treatment with ERWINAZE may be resumed.

5.3 Glucose Intolerance

Glucose intolerance has been reported with ERWINAZE therapy in 2% of patients in clinical trials, and, in some cases, may be irreversible *[see Adverse Reactions (6.1)]*. Monitor glucose levels in patients at baseline and periodically during treatment. Administer insulin therapy as necessary in patients with hyperglycemia.

5.4 Thrombosis and Hemorrhage

Serious thrombotic events, including sagittal sinus thrombosis have been reported with both *E. coli* and *Erwinia*-derived L-asparaginase therapy. The following coagulation proteins were decreased in the majority of patients after a 2-week course of ERWINAZE: fibrinogen, protein C activity, protein S activity, and anti-thrombin III. Discontinue ERWINAZE for a thrombotic or hemorrhagic event until symptoms resolve; after resolution, treatment with ERWINAZE may be resumed.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Serious hypersensitivity reactions, including anaphylaxis [see *Warnings and Precautions* (5.1)]
- Pancreatitis [see *Warnings and Precautions (5.2)*]
- Glucose intolerance *[see Warnings and Precautions (5.3)*]
- Thrombosis and hemorrhage [see *Warnings and Precautions (5.4)*]

The most common adverse reactions (incidence > 1%) with ERWINAZE treatment are serious hypersensitivity reactions, including anaphylaxis, pancreatitis, abnormal transaminases, coagulation abnormalities including thrombosis and hemorrhage, nausea and vomiting, and hyperglycemia.

6.1 Clinical Studies

Because clinical trials are conducted under controlled, but widely varying conditions, adverse reaction rates observed in clinical trials of ERWINAZE cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.

The data presented below are based on information collected from Study 1, a single-arm, multi-center, open-label, safety and clinical pharmacology trial and the

ERWINAZE Master Treatment Protocol (EMTP), an expanded access program. Study 1 enrolled 58 patients treated on National Cancer Institute (NCI)-sponsored cooperative group ALL protocols who were unable to continue to receive pegaspargase due to hypersensitivity reactions. Patients received 6 doses of ERWINAZE 25,000 International Units/m^2 intramuscularly on a Monday, Wednesday, and Friday schedule as a replacement for each scheduled dose of pegaspargase remaining on their original treatment protocol. The Study 1 population included patients with a median age of 10 years (2 to 18 years), 59% were male, 78% were White, 10% were Black/African American, 5% were Asian, and 5% were Hispanic or Latino. In Study 1, the planned number of ERWINAZE courses ranged from 1 to 8. Most patients, 55% (32 of 58) completed all planned therapy. Nine patients stopped therapy prior to completion, four due to allergic reactions, and five due to physician or patient choice. The remaining patients were continuing to receive ERWINAZE at the time of Study data lock. All other chemotherapy was continued according to the patient's prescribed treatment regimen [see *Clinical Studies (14)*].

At the time of data cut-off, the EMTP trial had enrolled 843 patients with ALL or lymphoblastic lymphoma who received ERWINAZE after developing systemic hypersensitivity to an *E. coli*-derived asparaginase. Safety data were submitted for 574 patients with a median age of 9 years (1 to 66 years), 62% were male, 97% with leukemia, and 3% with lymphoma. Patients received ERWINAZE according to several schedules, and treatment center specifications with doses that ranged from 20,000 to 25,000 International Units/m^2. In the EMTP trial, the planned number of doses of ERWINAZE ranged from 3 to 48 doses. Seventy-five percent of patients (434 of 575) were able to receive all planned doses to complete their prescribed treatment regimen.

In Study 1, safety information included all reported adverse events with systematic collection of the following adverse events of special interest: allergy, pancreatitis, coagulopathy (hemorrhage, thrombosis or infarct), hyperbilirubinemia, hyperglycemia, hyperlipidemia, ketoacidosis, and CNS events (hemorrhage, thrombosis or infarction, cerebral venous thrombosis). EMTP safety data were derived from case report forms that collected adverse event information. The forms specifically requested information on occurrence of allergic reactions, thrombotic events, hemorrhagic events, hepatobiliary disorders, pancreatic disorders, and hyperglycemia.

The combined incidence of non-hematologic, non-infectious, adverse reactions (all Grades) occurring with ERWINAZE in Study 1 and the EMTP trial is provided in Table 1. The incidence of Grade 3 or greater non-hematologic, non-infectious adverse reactions occurring with ERWINAZE in each individual Study is provided in Table 2

Table 1: Per Patient Combined Incidence of Non-Hematologic and Non-Infectious Adverse Events N=630 (Study 1 + EMTP)

Type of Event	Specific Response	Total Patients (N / % of total)
Allergic Reactions	Systemic Allergic Reactions (Anaphylaxis, Hypersensitivity, Urticaria)	108 (17%)
	Local Reactions (injection site)	3 (< 1%)
Pancreatitis	Pancreatitis	24 (4%)
Clinical Coagulation Abnormalities	*Total*	*16 (3%)*
	Thrombotic	10 (2%)
	Hemorrhagic	5 (1%)
	Transient Ischemic Attack	1 (< 1%)
	Disseminated Intravascular Coagulation	1 (< 1%)
Liver Abnormalities	*Total*	*27 (4%)*
	Hyperbilirubinemia	8 (1%)
	Abnormal Transaminase	22 (3%)
Hyperglycemia	Hyperglycemia	15 (2%)
Hyperammonemia	Hyperammonemia	4 (1%)
Fever	Fever	16 (3%)
Gastrointestinal Symptoms Not Associated with Pancreatitis	Vomiting	15 (2%)
	Nausea	10 (2%)
	Abdominal Pain	6 (1%)
Headache	Headache	5 (1%)
Diarrhea	Diarrhea	5 (1%)
Seizure	Seizure	4 (1%)

Table 2: Per Patient Incidence of Non-Hematologic, Non-Infectious, Grade 3 and 4 Adverse Reactions

Description of Event	Study 1 N=58	EMTP N=572
Allergic Reaction / Hypersensitivity	5 (9%)	27 (5%)
Pancreatitis	0	4 (1%)
Hyperglycemia	0	11 (2%)
Clinical Coagulation Abnormalities - Thrombosis	0	6 (1%)
Clinical Coagulation Abnormalities - Hemorrhage	0	1 (< 1%)
Elevated Transaminases	1 (2%)	2 (< 1%)

6.2 Immunogenicity

There is a potential for immunogenicity with therapeutic proteins such as ERWINAZE. Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ERWINAZE with the incidence of antibodies to other products may be misleading.

There is insufficient information to characterize the incidence of antibodies to ERWINAZE.

7 DRUG INTERACTIONS

No formal drug interaction studies between ERWINAZE and other drugs have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy category C. There are no adequate and well-controlled studies of ERWINAZE in pregnant women. Animal reproduction studies have not been conducted with ERWINAZE. It is not known whether ERWINAZE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ERWINAZE should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether ERWINAZE is secreted in human milk. Because many drugs are secreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ERWINAZE, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

[See *Clinical Studies (14)*].

8.5 Geriatric Use

The safety and efficacy of ERWINAZE has not been studied in geriatric patients.

10 OVERDOSAGE

There are no known cases of overdose with ERWINAZE.

11 DESCRIPTION

ERWINAZE (asparaginase *Erwinia chrysanthemi*) contains an asparaginase specific enzyme derived from *Erwinia chrysanthemi*. L-asparaginase is a tetrameric enzyme consisting of four identical subunits, each having a molecular weight of about 35 kDa. The activity of ERWINAZE is expressed in terms of International Units.

ERWINAZE is supplied as a sterile, lyophilized, white powder in vials. Each vial contains 10,000 International Units of asparaginase *Erwinia chrysanthemi*, and the inactive ingredients glucose monohydrate (5.0 mg) and sodium chloride (0.5 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Asparaginase *Erwinia chrysanthemi* catalyzes the deamidation of asparagine to aspartic acid and ammonia, resulting in a reduction in circulating levels of asparagine. The mechanism of action of ERWINAZE is thought to be based on the inability of leukemic cells to synthesize asparagine due to lack of asparagine synthetase activity, resulting in cytotoxicity specific for leukemic cells that depend on an exogenous source of the amino acid asparagine for their protein metabolism and survival.

12.3 Pharmacokinetics

The pharmacokinetics of ERWINAZE has not been characterized. The serum trough concentrations of asparaginase *Erwinia chrysanthemi* were determined in 48 ALL patients aged ≥ 2 year to ≤ 18 years enrolled in Study 1 [see *Clinical Studies (14)*]. Following administration of ERWINAZE 25,000 International Units/m^2 intramuscularly on a Monday, Wednesday, and Friday schedule for 6 doses, 100% of patients in course 1 achieved serum trough asparaginase concentrations ≥ 0.1 International Units/mL at either 48-hour (n=35) or 72-hour (n=13) post dose 3. Eighty percent (28/35) of those evaluated at 48 hours and 38% (5/13) evaluated at 72 hours had serum asparaginase activity levels > 0.4 International Units/mL [see *Clinical Studies (14)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term carcinogenicity studies in animals have been performed with asparaginase *Erwinia chrysanthemi*. No studies that assess the mutagenic potential of asparaginase *Erwinia chrysanthemi* have been conducted. No studies that assess the effects of asparaginase *Erwinia chrysanthemi* on fertility have been performed.

14 CLINICAL STUDIES

The safety and efficacy of ERWINAZE was established in Study 1, a single-arm, multi-center, open-label, safety and clinical pharmacology trial. Additional safety data was obtained in the ERWINAZE Master Treatment Protocol (EMTP), an expanded access program [see *Adverse Reactions (6)]*. Study 1 enrolled patients treated on National Cancer Institute (NCI)-sponsored cooperative group ALL protocols who were unable to continue to receive pegaspargase due to hypersensitivity reactions. 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 International Units/ mL. Serum trough asparaginase activity ≥ 0.1 International Units/ 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. Patients received ERWINAZE 25,000 International Units/m^2 intramuscularly for two weeks (total 6 doses) as a replacement for each scheduled dose of pegaspargase remaining on their original treatment protocol.

Fifty-eight patients were enrolled in Study 1; of these 48 were evaluable for the main outcome measure based on availability of pharmacokinetic samples in course 1. The median age was 10 years (2 to 18 years); 59% were male, 78% were White, 10% were Black/African American, 5% were Asian, and 5% were Hispanic or Latino.

Study 1 met its main outcome measure of demonstrating that greater than 50% of the patients achieved the pre-specified trough asparaginase activity level of ≥ 0.1 International Units/ mL at 48 or 72 hours following the third dose. Results for the main outcome measure and for an exploratory analysis using a higher cut-off (trough serum asparaginase activity levels ≥ 0.4 International Units/mL are presented in Table 3 [see *Clinical Pharmacology (12.3)*].

Table 3: Proportion of Patients in Study 1 with Sustained Asparaginase Activity

Trough sampling time post Dose 3	Main Outcome Proportion (n/N) and 95% CI with asparaginase activity ≥ 0.1 IU/mL	Exploratory Analysis Proportion (n/N) and 95% CI with asparaginase activity ≥ 0.4 IU/mL
48-hour	100% (35/35) 95% CI: 90%, 100%	80% (28/35) 95% CI: 64%, 90%
72-hour	100% (13/13) 95% CI: 77%, 100%	38% (5/13) 95% CI: 18%, 65%

16 HOW SUPPLIED / STORAGE AND HANDLING

ERWINAZE is a sterile, white lyophilized powder supplied in a clear 3 mL glass vial. Each carton of ERWINAZE (NDC 57902-249-05) contains 5 vials. Each single vial (NDC 57902-249-01) contains 10,000 International Units of asparaginase *Erwinia chrysanthemi.*

Store unused or unopened vials and cartons at 36°F to 46°F (2°C to 8°C). Protect from light. Do not use ERWINAZE after the expiration date on the vial.

17 PATIENT COUNSELING INFORMATION

- Instruct patients on the risk of allergic reactions, including anaphylaxis. Describe the symptoms of allergic reactions, including anaphylaxis, and instruct the patient to seek medical advice immediately if they experience such symptoms.
- Instruct patients on the risk of pancreatitis and to seek medical advice immediately if they experience abdominal pain.
- Instruct patients on the risk of hyperglycemia and glucose intolerance. Advise patients to seek medical advice if they experience excessive thirst or any increase in the volume or frequency of urination.
- Instruct patients on the risk of thrombosis and hemorrhage and to seek medical advice immediately if they experience headache, arm or leg swelling, shortness of breath, and chest pain.

Manufactured by EUSA Pharma (USA), Inc
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