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/m² 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)

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)].

Administration of ERWINAZE results in antibody synthesis to L-asparaginase. The following IgG anti-asparaginase antibodies have been observed in patients receiving ERWINAZE.

5.2 Pancreatitis

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

5.3 Glucose Intolerance

Glucose intolerance can occur and, in some cases, may be irreversible. Perform appropriate monitoring and, in some cases, may be irreversible. Perform appropriate monitoring and, in some cases, may be irreversible. Perform appropriate monitoring and, in some cases, may be irreversible. Perform appropriate monitoring.

5.4 Thrombosis and Hemorrhage

Thrombosis and hemorrhage: discontinue ERWINAZE until resolved (5.4).

5.5 Anaphylaxis

Immediate hypersensitivity reactions, including anaphylaxis, have occurred. Administer epinephrine and other supportive measures as indicated.

6 ADVERSE REACTIONS

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 conditions, it is not possible to estimate the incidence of adverse events observed in the clinical trials of ERWINAZE that may not occur 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

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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Langhorne, PA 19047
Customer Service: 1-800-833-3533
www.eusapharma.com

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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.

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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×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

Thrombotic and hemorrhagic events, including deep vein thrombosis, pulmonary embolism, and petechiae on the oral mucosa, have been reported with ERWINAZE and are most commonly observed during the second and third treatment cycles.

6 ADVERSE REACTIONS

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 conditions, it is not possible to estimate the incidence of adverse events observed in the clinical trials of ERWINAZE that may not occur 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
coagulopathy (hemorrhage, thrombosis or infarct), hyperbilirubinemia, hyperglycemia.

In Study 1, safety information included all reported adverse events with systematic analysis performed on 547 patients treated with ERWINAZE. Seventy-five percent (434 of 575) of the patients treated with 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), hypothyroidism, hyperglycemia, hypothyroidism, hyperglycemia, hepatitis, lymphocytic lymphoma, and hypersensitivity. The combined incidence of non-hematologic, non-infectious, adverse reactions occurring in erwinase in each individual Study is provided in Table 2.

### Table 1: Per Patient Incidence of Non-Hematologic and Non-Infectious, Adverse Events N=830 (Study 1 + EMTP)

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Specific Response</th>
<th>Total Patients</th>
<th>N (%) of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Reactions</td>
<td>Systemic Allergic Reactions (Hyperglycemia, Hypersensitivity, Urticaria)</td>
<td>108 (17%)</td>
<td>16% (2%)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Pancreatitis</td>
<td>24 (4%)</td>
<td>24 (4%)</td>
</tr>
<tr>
<td>Clinical Coagulation Abnormalities</td>
<td>Total</td>
<td>16 (2%)</td>
<td>16 (2%)</td>
</tr>
<tr>
<td></td>
<td>Thrombotic</td>
<td>10 (2%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic</td>
<td>3 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td></td>
<td>Lymphocytic Lymphoma</td>
<td>1 (&lt; 1%)</td>
<td>1 (&lt; 1%)</td>
</tr>
<tr>
<td></td>
<td>Disseminated Intravascular Coagulation</td>
<td>1 (&lt; 1%)</td>
<td>1 (&lt; 1%)</td>
</tr>
<tr>
<td>Liver Abnormalities</td>
<td>Total</td>
<td>27 (4%)</td>
<td>27 (4%)</td>
</tr>
<tr>
<td></td>
<td>Hyperbilirubinemia</td>
<td>8 (1%)</td>
<td>8 (1%)</td>
</tr>
<tr>
<td></td>
<td>Abnormal Transaminase</td>
<td>22 (3%)</td>
<td>22 (3%)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
<td>15 (2%)</td>
<td>15 (2%)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Hypomagnesemia</td>
<td>4 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Fever</td>
<td>Fever</td>
<td>16 (2%)</td>
<td>16 (2%)</td>
</tr>
<tr>
<td>Gastrointestinal Symptoms Not Associated with Pancreatitis</td>
<td>Vomiting</td>
<td>15 (2%)</td>
<td>15 (2%)</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>10 (2%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain</td>
<td>6 (1%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Headache</td>
<td>Headache</td>
<td>5 (1%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Sniffing</td>
<td>Sniffing</td>
<td>5 (1%)</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>Seizure</td>
<td>4 (1%)</td>
<td>4 (1%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Description of Event</th>
<th>Study 1 N=88</th>
<th>EMTP N=572</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic Reaction / Hypersensitivity</td>
<td>5 (9%)</td>
<td>27 (5%)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0 (0%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>Hypervigilance</td>
<td>0 (0%)</td>
<td>11 (2%)</td>
</tr>
<tr>
<td>Clinical Coagulation Abnormalities - Thrombosis</td>
<td>0 (0%)</td>
<td>6 (1%)</td>
</tr>
<tr>
<td>Clinical Coagulation Abnormalities - Hemorrhage</td>
<td>0 (0%)</td>
<td>1 (&lt; 1%)</td>
</tr>
<tr>
<td>Elevated Transaminases</td>
<td>1 (2%)</td>
<td>2 (&lt; 1%)</td>
</tr>
</tbody>
</table>

### 6.2 Immunoresponse

The clinical immune response in immunotherapy with therapeutic proteins such as ERWINAZE. ERWINAZE immunity assay results are highly dependent on several factors including assay sensitivity, the time of sampling, assay methodology, sample handling, and timing of sampling, 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 significant drug interaction studies have been conducted with 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 excreted 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.

### OVERDOSAGE

There are no known cases of overdose with ERWINAZE.

### 9. DESCRIPTION

ERWINAZE (asparaginase Erwinia chrysanthemi) contains an asparaginase specific enzyme derived from Erwinia chrysanthemi. L-asparaginase is a tetrameric enzyme consisting of four 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 25,000 International Units of asparaginase Erwinia chrysanthemi and the inactive ingredients glucose monodextrose (5.0 mg) and sodium chloride (0.5 mg).

### 12. CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Asparaginase Erwinia chrysanthemi catalyzes the deamination 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 utilize asparagine as a nutrient 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 to 5 years or 18 years enrolled in Study 1 [see Clinical Studies (14)].

Following administration of ERWINAZE 25,000 International Units intramuscularly on a Monday, Wednesday, and Friday schedule for 6 doses, 100% of patients in course 1 achieved trough asparaginase concentrations ≥ 0.1 International Units/mL at either 48-hour (n=35) or 72-hour (n=31) post dose. Eighty percent (28/35) of those evaluated at 48 hours and 38% (5/13) 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 includes 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 Emergency Treatment Program (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. Patients received ERWINAZE according to several schedules, and treatment center specifications with doses that ranged from 20,000 to 25,000 International Units/mL. 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.

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 90% of the patients achieved serum trough asparaginase concentration ≥ 0.4 International Units/mL by day 4 of course 2 (10/15; 90%). The activity of ERWINAZE is expressed in terms of International Units.

Serum trough asparaginase activity ≥ 0.1 International Units/mL has been demonstrated to correlate with asparagine depletion (< 0.4 mcg/mL or 3 µM) and to serum levels that predict clinical efficacy. Patients received ERWINAZE 25,000 International Units intramuscularly for two weeks (total 6 doses) as a replacement for each scheduled dose of pegaspargase remaining on their original treatment protocol.

### 15. PATIENT COUNSELING INFORMATION

Instruct patients on the risk of thrombosis and hemorrhage and to seek medical advice immediately if they experience such symptoms.

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 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.

### 16. HOW SupPLIED / STORAGE and HANDLING

ERWINAZE is a sterile, white lyophilized powder supplied in a clear 3 mL glass vial. Each vial of ERWINAZE (NDC 57902-249-05) contains 25,000 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 if they experience abdominal pain.

- Instruct patients on the risk of hyperglycemia and glucose intolerance. Advise patients with diabetes to consult with their health care provider 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 if they experience headache, arm or leg swelling, shortness of breath, and chest pain.

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