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 (IM) or intravenous (IV) use
Initial U.S. Approval: 2011

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.1)	12/2014
Warnings and Precautions (5)	12/2014
Warnings and Precautions (5.1)	03/2014
Warnings and Precautions (5.3)	03/2014

----------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 for each planned dose of pegaspargase is 25,000 International Units/m^2 administered intramuscularly or intravenously 3 times a week (Monday/Wednesday/Friday) for 6 doses. (2.1)
- To substitute for a dose of native *E. coli* asparaginase: The recommended dose is 25,000 International Units/m^2 administered intramuscularly or intravenously for each scheduled dose of native *E. coli* asparaginase. (2.1)

----------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 (incidence 1% or greater) are: systemic hypersensitivity, hyperglycemia, transaminases abnormal, fever, pancreatitis, local reactions, vomiting, nausea, thrombosis, hyperbilirubinemia, abdominal pain/discomfort, and diarrhea.

To report SUSPECTED ADVERSE REACTIONS, contact Jazz Pharmaceuticals, Inc. at 1-800-520-5568 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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

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

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

When administering ERWINAZE intravenously, consider monitoring nadir (pre-dose) serum asparaginase activity (NSAA) levels and switching to intramuscular administration if desired NSAA levels are not achieved [*see Clinical Pharmacology (12.3)*].

2.2 Preparation and Handling 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. Inspect the solution after reconstitution and discard 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. For intravenous use, slowly inject the reconstituted ERWINAZE into an IV infusion bag containing 100 mL of normal saline acclimatized to room temperature. Do not shake or squeeze the IV bag.
8. If a partial vial is used, do not save or reuse the unused drug for later administration. Discard unused portions.
9. Do not freeze or refrigerate reconstituted solution and administer within 4 hours or discard [*see How Supplied/Storage and Handling (16)*].

2.3 Administration Instructions

ERWINAZE solution can be administered by intramuscular injection or by intravenous infusion.

- For intramuscular use, 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.
- For intravenous use, infuse ERWINAZE in 100 mL of normal saline over 1 hour. Do not infuse other intravenous drugs through the same intravenous line while infusing ERWINAZE.

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 Hypersensitivity Reactions

Grade 3 and 4 hypersensitivity reactions after the use of ERWINAZE have occurred 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 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 in 5% of patients receiving ERWINAZE in clinical trials [*see Adverse Reactions* (*6.1*)]. In some cases glucose intolerance may be irreversible. 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 and pulmonary embolism 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 by intramuscular administration: 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:

- Hypersensitivity reactions [*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% or greater) with ERWINAZE treatment are systemic hypersensitivity, hyperglycemia, transaminases abnormal, fever, pancreatitis, local reactions, vomiting, nausea, thrombosis, hyperbilirubinemia, abdominal pain/discomfort, and diarrhea.

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 (intramuscular administration), the ERWINAZE Master Treatment Protocol (EMTP), an expanded access program (both intramuscular, intravenous, and other or unknown administration), and Study 2, a single-arm, multi-center, open-label, pharmacokinetic (PK) study trial of intravenous administration of ERWINAZE.

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 11 years (2 to 18 years); 59% were male, 78% were White, 10% were Black/African American, 5% were Asian, and 7% were other or unknown. A total of 35% were Hispanic or Latino. In Study 1, the number of ERWINAZE courses ranged from 1 to 9. In this study, 76% (44 of 58) completed all planned therapy. Fourteen (24%) patients stopped therapy prior to completion; seven due to allergic reactions, five due to physician or patient choice, one due to disease progression, and one due to discontinuation during frontline protocol. All other chemotherapy was continued according to the patient's prescribed treatment regimen [*see Clinical Studies (14)*].

Study 2 enrolled 30 patients [29 were being treated for ALL and one for lymphoblastic lymphoma (LBL)] following allergy to native *E. coli* asparaginase or pegaspargase. Patients received ERWINAZE 25,000 International Units/m^2/dose, administered by intravenous infusion on a Monday, Wednesday, and Friday schedule (6 doses) as a replacement for doses remaining on their original treatment plan. The Study 2 population included patients with a median age of 7 years (1 to 17 years); 63% were male, 27% were Hispanic or Latino, 83% were White, 3% were Black/African American, 7% were Asian, and 7% were other (American Indian, Alaska Native or Indian) [*see Clinical Studies (14)*].

The EMTP trial enrolled 1368 patients with ALL or lymphoblastic lymphoma who received ERWINAZE after developing systemic hypersensitivity to an *E. coli*-derived asparaginase. Of these 1368 patients, safety data were received for 940 patients with a median age of 9 years (0 to 76 years), 63% were male, 91% with leukemia, 3% with lymphoma, and 6% with unknown disease information. 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. The route of administration was intramuscular n=852, intravenous n=29, other or unknown n= 59. In the EMTP trial, the planned number of doses of ERWINAZE ranged from 3 to 48 doses. Seventy-eight percent of patients (693 of 893) were able to receive all planned doses to complete their prescribed treatment regimen.

In Study 1 and Study 2, safety information was prospectively and systematically collected. In Study 1, all Grades of adverse events were reported for 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, and cerebral venous thrombosis) and only Grade 3 and 4 events were reported for other adverse events. In Study 2 all adverse events of all Grades were prospectively collected. In the EMTP trial, 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 incidence of non-hematologic, non-infectious, adverse events (all Grades) in Study 1, Study 2, and the EMTP trial is provided in Table 1.

Table 1: Per Patient Incidence of Non-Hematologic and Non-Infectious* Adverse Events**				
Type of Event	**Description of Event (Collated Term)**	**Study 1 (IM) N=58**	**Study 2 (IV) N=30**	**EMTP (IM&IV) N=940**
Allergic Reactions	*Total*	8 (14%)	11 (37%)	149 (16%)
	Hypersensitivity (systemic)	8 (14%)	11 (37%)	128 (14%)
	Local Reactions	0	0	31 (3%)
Liver Abnormalities	*Total*	7 (12%)	4 (13%)	42 (4%)
	Elevated transaminase	6 (10%)	4 (13%)	33 (4%)
	Hyperbilirubinemia	6 (10%)	0	8 (<1%)
	Hyperammonemia	0	0	7 (<1%)
Hyperglycemia	Hyperglycemia	7 (12%)	5 (17%)	35 (4%)
Gastrointestinal Symptoms Not Associated with Pancreatitis	*Total*	3 (5%)	6 (20%)	39 (4%)
	Nausea	2 (3%)	6 (20%)	23 (2%)
	Vomiting	3 (5%)	5 (17%)	28 (3%)
	Abdominal Pain/Discomfort	1 (2%)	0	13 (1%)
Pancreatitis	Pancreatitis	1 (2%)	2 (7%)	37 (4%)
Fever	Fever	2 (3%)	3 (10%)	36 (4%)
Clinical Coagulation Abnormalities	*Total*	1 (2%)	2 (7%)	27 (3%)
	Thrombosis***	1 (2%)	2 (7%)	20 (2%)
	Hemorrhagic Disorder	0	0	9 (1%)
Mucositis	Mucositis	0	2 (7%)	11 (1%)
Diarrhea	Diarrhea	0	1 (3%)	10 (1%)

*Hematologic and infectious adverse events observed in these studies are not included in this table. Patients were enrolled in uncontrolled trials and were receiving multi-agent myelosuppressive chemotherapy making causality unclear.

** Type of Event reported in more than 1% in EMTP trial

***Including pulmonary embolism and cerebrovascular accident

The incidence of Grade 3 or greater non-hematologic, non-infectious adverse reactions occurring with ERWINAZE in Study 1, Study 2 and EMTP trial is provided in Table 2.

Table 2: Incidence of Non-Hematologic, Non-Infectious, Grade 3 and 4 Adverse Reactions			
Description of Event -Collated Term	**Study 1 (IM) N=58**	**Study 2 (IV) N=30**	**EMTP (IM&IV) N=940**
Allergic Reactions	5 (9%)	1 (3%)	42 (4%)
-Hypersensitivity (systemic, Grade 3)	5 (9%)	1 (3%)	34 (4%)
-Anaphylactic Reaction (Grade 4)	0	0	8 (<1%)
Hyperglycemia	1 (2%)	1 (3%)	33 (4%)
Liver Abnormalities	3 (5%)	0	7 (<1%)
-Transaminases Abnormal	3 (5%)	0	6 (<1%)
-Hyperbilirubinemia	0	0	1 (<1%)
Pancreatitis	0	2 (7%)	8 (<1%)
Clinical Coagulation Abnormalities	0	0	9 (<1%)
-Thrombosis*	0	0	8 (<1%)

Table 2: Incidence of Non-Hematologic, Non-Infectious, Grade 3 and 4 Adverse Reactions			
Description of Event -Collated Term	**Study 1 (IM) N=58**	**Study 2 (IV) N=30**	**EMTP (IM&IV) N=940**
-Hemorrhagic Disorder	0	0	1 (<1%)
Gastrointestinal Symptoms Not Associated with Pancreatitis	1 (2%)	2 (7%)	6 (<1%)
-Abdominal Pain/Discomfort	1 (2%)	1 (3%)	3 (<1%)
-Nausea	1 (2%)	1 (3%)	3 (<1%)
-Vomiting	1 (2%)	1 (3%)	3 (<1%)

*Including pulmonary embolism and cerebrovascular accident

6.2 Immunogenicity

As with most therapeutic proteins, patients may develop anti-drug antibodies (ADA) to ERWINAZE.

In a study with Erwinaze treatment by intramuscular administration (Study 1), 6 of 56 (11%) patients treated with ERWINAZE developed antibodies to ERWINAZE. Of these 6 ADA positive patients, one experienced a hypersensitivity reaction during Study 1 (2%, 1 of 56). None of these 6 patients had neutralizing antibodies.

In a study with ERWINAZE treatment by intravenous administration (Study 2), 4 of 30 (13.3%) patients treated with ERWINAZE developed anti-ERWINAZE antibodies. Of these 4 patients who developed anti-ERWINAZE antibodies, 3 experienced hypersensitivity reactions (10%, 3 of 30) during the study. None of these 4 patients had neutralizing antibodies.

The presence of ADA to ERWINAZE is associated with a higher risk of hypersensitivity reactions in patients who received ERWINAZE through intravenous infusion compared to intramuscular administration of ERWINAZE.

Immunogenicity assays are highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ERWINAZE with the incidence of antibodies to other products may be misleading.

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

Risk Summary

There are no adequate and well-controlled studies of ERWINAZE in pregnant women. In embryofetal development studies in rats and rabbits, asparaginase *Erwinia chrysanthemi* produced embryofetal toxicities and fetal abnormalities. ERWINAZE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

In embryofetal development studies, asparaginase *Erwinia chrysanthemi* was administered intramuscularly every other day during the period of organogenesis to pregnant rats (at 500, 1000, or 2000 IU/kg) and rabbits (at 10, 25, and 40 IU/kg). In rats given 2000 IU/kg (approximately 50% of the recommended human dose, adjusted for body surface area), maternal toxicity of decreased body weight gain was observed, as well as a fetal finding of increased incidence of partially undescended thymic tissue.

In rabbits, maternal toxicity consisting of decreased body weight was observed at 40 IU/kg (approximately 2% of the recommended human dose, adjusted for body surface area). Increased post-implantation loss, a decrease in the number of live fetuses, and gross abnormalities (e.g., absent kidney, absent accessory lung lobe, additional subclavian artery, and delayed ossification) were observed at doses of ≥10 IU/kg (approximately 0.5% of the recommended human dose, adjusted for body surface area).

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 asparagine 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 following inactive ingredients: glucose monohydrate (5.0 mg), 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 amino acid asparagine for their protein metabolism and survival.

12.3 Pharmacokinetics

Based on a population PK model, the mean (%CV) half-life of intravenous Erwinaze was 7.51 (23.9%) hours in contrast to a mean (%CV) half-life of 15.6 (20%) hours reported for intramuscular Erwinaze. These differences in PK between intravenous and intramuscular Erwinaze are reflected in the proportion of patients with 2-day and 3-day nadir serum asparaginase activity (NSAA) levels of asparaginase *Erwinia chrysanthemi* ≥ 0.1 or 0.4 IU/mL [*see Clinical Studies (14)*].

Following administration of ERWINAZE 25,000 International Units/m^2 intramuscularly to 48 ALL patients aged ≥ 2 years to ≤ 18 years in Study 1 on a Monday, Wednesday, and Friday schedule for 6 doses, 100% of patients who completed course 1 achieved NSAA levels ≥ 0.1 International Units/mL at either 48 hours (n=35) or 72 hours (n=13) post dose 3. Eighty percent (28/35) of those evaluated at 48 hours and 38% (5/13) evaluated at 72 hours had nadir serum asparaginase activity levels ≥ 0.4 International Units/mL [*see Clinical Studies (14)]*.

Following intravenous administration of ERWINAZE 25,000 International Units/m^2 to 24 evaluable patients (aged ≥ 1 year to ≤ 17 years) in Study 2 on a Monday, Wednesday, and Friday schedule, 83% (20/24) and 43% (9/21) of patients who completed Course 1 achieved NSAA levels ≥ 0.1 International Units/mL at 48 hours post-dose 5 and 72 hours post dose 6, respectively. Twenty-nine percent (7/24) of those evaluated at 48 hours and no patients (0/21) evaluated at 72 hours had nadir 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.

In a fertility and early embryonic development study in rats, asparaginase *Erwinia chrysanthemi* had no effect on male or female fertility when administered intramuscularly at doses of up to 2000 IU/kg (approximately 50% of the recommended human dose, when adjusted for total body surface area) every other day for a total of 35 doses. Findings in males included decreased sperm count at doses of more than 500 IU/kg (approximately 12% of the recommended human dose).

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 were 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 11 years (2 to 18 years); 59% were male, 78% were White, 10% were Black/African American, 5% were Asian, and 7% were other or unknown. A total of 35% 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)*].

The safety and efficacy of intravenous administration were determined in Study 2 by characterizing the PK of a 25,000 International Units/m^2 ERWINAZE dose given 3 days per week on a Monday, Wednesday, and Friday schedule for up to 30 weeks. This open-label, single-arm, multicenter PK study enrolled 30 patients. The main outcome measure was determination of the proportion of patients with 2-day NSAA levels (48-hour levels taken after the fifth dose) ≥ 0.1 International Units/mL in the first 2 weeks of ERWINAZE treatment.

Of the thirty patients enrolled, 24 were evaluable for the main outcome measure based on the pharmacokinetic samples in Course 1. The median age was 7 years (1-17 years), 63% were male, 27% were Hispanic or Latino, 83% were White, 3% were Black/African American, 7% were Asian, and 7% were other (American Indian, Alaska Native, or Indian).

In Study 2, serum asparaginase activity of asparaginase *Erwinia chrysanthemi* was determined in 24 evaluable patients (aged ≥ 1 year to ≤ 17 years) following intravenous administration of ERWINAZE 25,000 International Units/m^2. Five minutes after the 60-minute infusion in Course 1, the mean asparaginase activity level was 12.65 ± 3.16 International Units/mL post dose 1 and 12.11 ± 3.11 International Units/mL post dose 4. The main study objective was met with an asparaginase activity level of ≥ 0.1 International Units/mL 48 hours after the fifth dose observed in 83% of patients. The 72-hour post dose 6 asparaginase activity level of ≥ 0.1 International Units/mL was the secondary endpoint, with 43% of patients achieving this endpoint. Results are presented in Table 3 [*see Clinical Pharmacology (12.3)*].

Table 3: Proportion of Patients with Sustained Asparaginase Activity in Study 1 (IM) and Study 2 (IV)

Trough sampling time	Proportion (n/N) and 95% CI with asparaginase activity ≥ 0.1 International Units/mL		Proportion (n/N) and 95% CI with asparaginase activity ≥ 0.4 International Units/mL	
	Study 1 (IM) [a]	Study 2 (IV) [b]	Study 1 (IM) [a]	Study 2 (IV) [b]
48-hour	100% (35/35) [90 , 100]	83% (20/24) [63 , 95]	80% (28/35) [64 , 90]	29% (7/24) [13 , 51]
72-hour	100% (13/13) [77 , 100]	43% (9/21) [22 , 66]	38% (5/13) [18 , 65]	0% (0/21) [0 , 16]

a. Trough sampling time is post-dose 3 at 48 and 72
b. Trough sampling time is post-dose 5 at 48 hours and post dose 6 for 72 hours

16 HOW SUPPLIED / STORAGE AND HANDLING

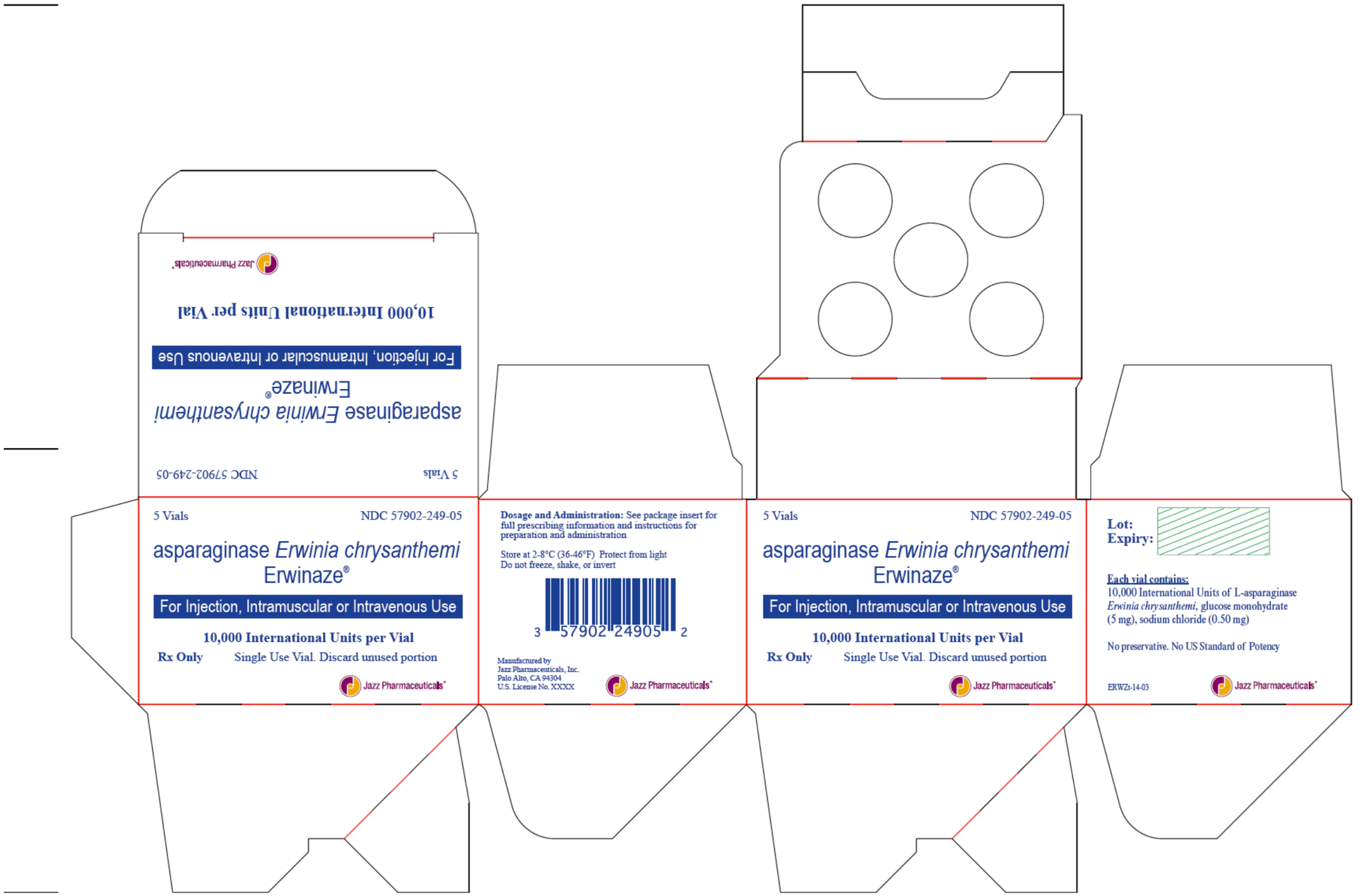
ERWINAZE is a sterile, white lyophilized powder supplied in a clear 3 mL glass vial. Each carton of ERWINAZE (NDC 57902-249-05) contains 5 vials. Each single vial (NDC 57902-249-01) contains 10,000 International Units asparaginase *Erwinia chrysanthemi.*

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:
Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304
U.S. License No. 1901


Jazz Pharmaceuticals
10,000 International Units per Vial
For Injection, Intramuscular or Intravenous Use
asparaginase Erwinia chrysanthemi
Erwinaze®
5 Vials
NDC 57902-249-05
5 Vials
NDC 57902-249-05
asparaginase Erwinia chrysanthemi
Erwinaze®
For Injection, Intramuscular or Intravenous Use
10,000 International Units per Vial
Rx Only
Single Use Vial. Discard unused portion
Jazz Pharmaceuticals
Dosage and Administration: See package insert for full prescribing information and instructions for preparation and administration
Store at 2-8°C (36-46°F) Protect from light
Do not freeze, shake, or invert
3 57902 24905 2
Manufactured by
Jazz Pharmaceuticals, Inc.
Palo Alto, CA 94304
U.S. License No. XXXX
Jazz Pharmaceuticals
5 Vials
NDC 57902-249-05
asparaginase Erwinia chrysanthemi
Erwinaze®
For Injection, Intramuscular or Intravenous Use
10,000 International Units per Vial
Rx Only
Single Use Vial. Discard unused portion
Jazz Pharmaceuticals
Lot:
Expiry:
Each vial contains:
10,000 International Units of L-asparaginase Erwinia chrysanthemi, glucose monohydrate (5 mg), sodium chloride (0.50 mg)
No preservative. No US Standard of Potency
ERWZt-14-03
Jazz Pharmaceuticals

(b) (4)


asparaginase *Erwinia chrysanthemi*
Erwinaze®
For Injection, Intramuscular or Intravenous Use
10,000 International Units per Vial
Rx Only
Jazz Pharmaceuticals
Lot No:
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/s/

ANN T FARRELL
12/19/2014