25 May 2021

IMPORTANT PRESCRIBING INFORMATION

Subject:	Temporary importation of Erwinase® (crisantaspase) injection, powder, lyophilized, for solution to address a drug shortage in the United States (U.S.)

Dear Healthcare Professional,

In order to alleviate a critical shortage of U.S.-licensed asparaginase erwinia chrysanthemi injection, powder, lyophilized, for solution in the US market, Porton Biopharma Limited (PBL) is coordinating with the U.S. Food and Drug Administration (FDA) to make available in the U.S. the non-FDA licensed Erwinase (crisantaspase) 10,000 IU/vial powder for solution for injection/infusion.

At this time, no other entity except PBL (via its distributor Clinigen Inc.) is authorized by the FDA to import and distribute Erwinase in the U.S. However, this does not represent a formal FDA approval of Erwinase in the U.S.

Effective immediately, PBL (via its distributor Clinigen Inc.) will distribute the following presentation of Erwinase (Batch number: W060172) to address the critical shortage:

Product Name	Pack Size	Description	U.K. Marketing Authorization Number	NDC
Erwinase, 10,000 IU/vial, Powder for solution for injection/infusion.	5 vials	Powder for solution for injection/infusion. White lyophilised powder in a vial.	PL 44403/0002	NDC 81561-413-05*

*This NDC code has been assigned by PBL. The code is presented on the carton. It should be noted that the importer and distributor in the U.S. will be Clinigen Inc. The same NDC code will be used throughout the distribution chain of the product in the U.S.

It is important to note the following:

- **Erwinase is available in the U.S. only by prescription.**

- **There is no barcode on this product for use with U.S. barcode scanning systems.** Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

- **Contraindications to use of Erwinase include:**
  - Serious hypersensitivity reactions to asparaginase erwinia chrysanthemi, including anaphylaxis
  - Serious pancreatitis with any prior asparaginase therapy
  - Serious thrombosis with any prior asparaginase therapy
  - Serious hemorrhagic events with any prior asparaginase therapy

- **There are differences between the U.S.-licensed asparaginase erwinia chrysanthemi Prescribing Information and the Erwinase Summary of Product Characteristics (Appendix 2). Use the recommended dosage for U.S.-licensed asparaginase erwinia chrysanthemi**

  - To substitute for each planned dose of pegaspargase, the recommended dosage of Erwinase is 25,000 International Units/m^2 administered intramuscularly or intravenously three times a week (Monday/Wednesday/Friday) for two consecutive weeks (total six doses).

  - When administering Erwinase intravenously, the desired NSAA levels may not be achieved; consider monitoring nadir (pre-dose) serum asparaginase activity (NSAA)

levels and switching to intramuscular administration if desired NSAA levels are not achieved with intravenous dosing.

- **There are differences between the U.S.-licensed product and Erwinase in the Preparation and Handling Instructions (Appendix 2). Use the recommended handling instruction for U.S.-licensed asparaginase erwinia chrysanthemi.**
    - Do not freeze or refrigerate reconstituted solution and administer within 4 hours or discard.
- **There are differences between the U.S.-licensed product and Erwinase in the format and content of the container and carton labelling.**
    - The Erwinase carton includes an insert providing both the U.K. prescribing information (Summary of Product Characteristics) and information for the patient (package leaflet). See the bullet above regarding the recommended dosage instructions for Erwinase.
    - The vial label will display the text used and approved for marketing the product in U.K. Please see the product comparison tables at the end of this letter (Appendix 1).
    - The packaging of Erwinase does not include serialization information and does not meet the product identifier requirements of section 582(b)(2) of the Federal Food, Drug and Cosmetic Act.

Ensure that your staff and others in your office and/or pharmacy who may be involved in the prescribing and/or dispensing of Erwinase - asparaginase injection, powder, lyophilized, for solution receive a copy of this letter, review the information and instruct patients on the differences between Erwinase and U.S.-licensed asparaginase erwinia chrysanthemi**.**

This letter and the attachments are not intended as a complete description of the benefits and risks related to the use of Erwinase. See the full prescribing information on the UK MHRA website at https://products.mhra.gov.uk/product/?product=ERWINASE%2010%20000%20UNITS%2FVIAL%20%20LYOPHILISATE%20FOR%20SOLUTION%20FOR%20INJECTION

Contact Information:

If you have any questions about the information contained in this letter, any quality related problems, or questions on the use of Erwinase, please contact Porton Biopharma Limited via email medinfo@portonbiopharma.com or contact directly at 1-855-209-2652.

To place an order, contact McKesson Plasma and Biologics (MPB) directly at 1-877-625-2566.

Adverse Events and Product Quality Complaints:

Report adverse events associated with the use of Erwinase to drugsafety@portonbiopharma.com via email or contact Porton Biopharma Limited directly at 1-855-209-2652.

Adverse events, medication errors or quality problems experienced with the use of Erwinase may also be reported to the FDA's MedWatch Adverse Event Reporting Program either online, regular mail, or by fax:

- Complete and submit the report Online: www.fda.gov/medwatch/report.htm
- Regular Mail or Fax: Download form www.fda.gov/medwatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178 (1-800-332-0178).

We remain at your disposal to answer any questions you may have about our product and to provide more information if needed.

Yours sincerely,

DocuSigned by:
Elizabeth Madichie
6C984B87F1014AF...

Dr. Elizabeth Madichie

Director of Regulatory Affairs & Pharmacovigilance
Porton Biopharma Limited, U.K.

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Director of Medical Affairs
Clinigen Group plc, U.K.

Enclosures:
Appendix 1 – Product Label and Product Characteristics Side-by-Side Comparison Table
Appendix 2 – Prescribing Information Side-by-Side Comparison Table

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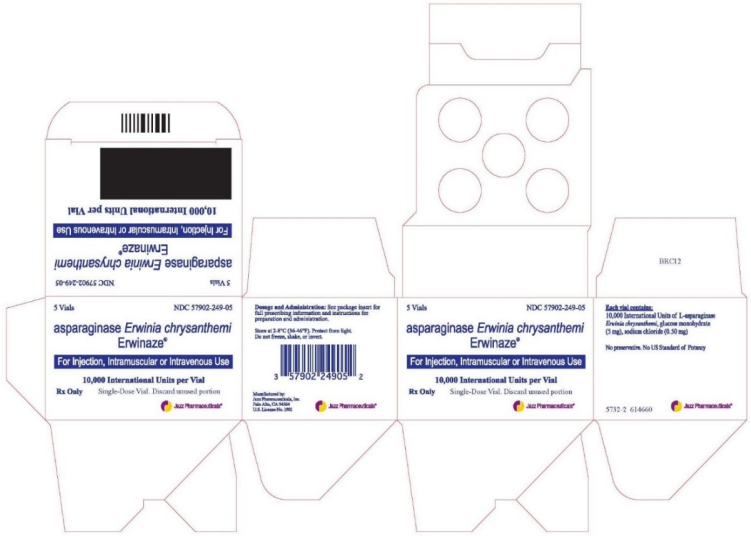
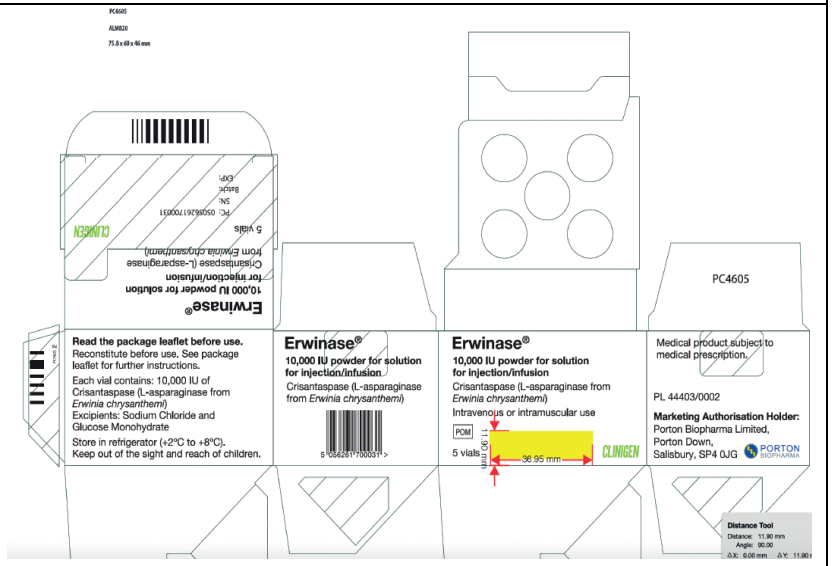
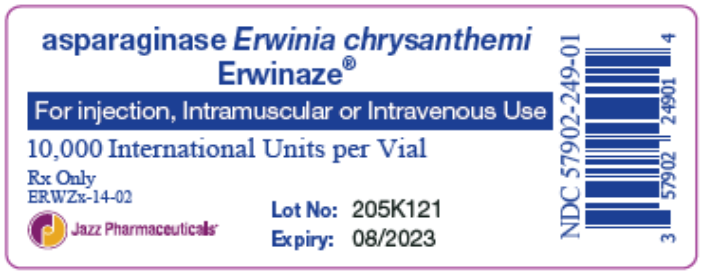
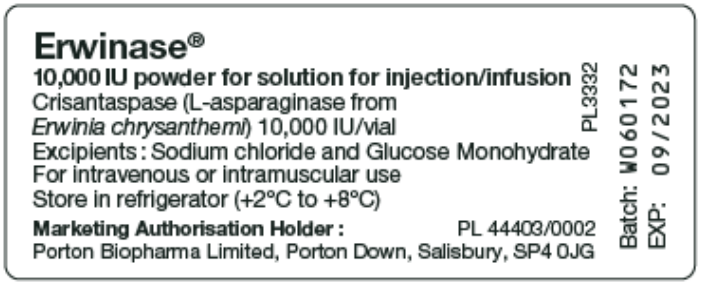
Appendix 1 – Product Label and Product Characteristics Side-by-Side Comparison Table

	U.S. FDA Licensed Product	Imported Product
Product Name	**Erwinaze®- asparaginase injection, powder, lyophilized, for solution**	**Erwinase® 10,000 IU/vial Powder for solution for injection/infusion**
Strength	**10,000 International Units in a single-dose vial**	**10,000 IU/vial**
Carton Label Image		

	U.S. FDA Licensed Product	Imported Product
Product Name	**Erwinaze®- asparaginase injection, powder, lyophilized, for solution**	**Erwinase® 10,000 IU/vial Powder for solution for injection/infusion**
Strength	**10,000 International Units in a single-dose vial**	**10,000 IU/vial**
Vial Label Image		
Route of Administration	Erwinaze can be administered intramuscularly or intravenously.	Erwinase solution can be given by intravenous infusion or intramuscular injection.
Ingredients	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).	Crisantaspase (L-asparaginase from Erwinia chrysanthemi), 10,000 International units/vial. List of excipients Sodium Chloride Glucose Monohydrate
Storage Conditions	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.	Store in a refrigerator (+2°C to +8°C).

Appendix 2 – Prescribing Information Side-by-Side Comparison Table

A side-by-side comparison of the Erwinaze U.S. Prescribing Information (USPI) and Erwinase U.K. Summary of Product Characteristics (SmPC) is provided below. It is important to note that there are no significant differences in the indications, dosage and administration between the two products.

Side-by-Side Comparison Table:

	U.S. FDA Licensed Product	**Imported Product**
Product name	**Erwinaze®- asparaginase injection, powder, lyophilized, for solution**	**Erwinase® 10,000 IU/vial Powder for solution for injection/infusion**
Indication	**1 Indications and Usage** ERWINAZE 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.	**4 Clinical Particulars** **4.1 Therapeutic indications** Erwinase is indicated as a component of a chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukaemia (ALL) who have developed hypersensitivity to *E. coli*-derived asparaginase. Erwinase is indicated in paediatric patients from the age of 4 months and in adults.
Dosage and administration	**2 Dosage and administration** **2.1 Recommended Dosage** 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.	**4.2 Posology and method of administration** <u>Posology</u> The recommended dosage is 20,000 or 25,000 IU/m^2 body surface area administered three times a week (e.g., Monday/Wednesday/Friday). Therapy should be adjusted according to local treatment protocols.

	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** • Visually inspect the ERWINAZE powder for foreign particulate matter and discoloration prior to reconstitution. Discard vial if present. • 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. • 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. • Dissolve contents by gentle mixing or swirling. **Do not shake or invert vial.** • When reconstituted, ERWINAZE should be a clear, colorless solution. Inspect the solution after	**6.6 Special precautions for disposal and other handling** The contents of each vial should be reconstituted in 1 mL to 2 mL of sodium chloride (0.9%) solution for injection. When reconstituted with 1 mL the resultant concentration is 10,000 IU/mL. When reconstituted with 2 mL the resultant concentration is 5,000 IU/mL Slowly add the sodium chloride (0.9%) solution for injection. 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, avoiding

	reconstitution and discard if any visible particles or protein aggregates are present.	contact of the solution with the stopper. 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. Erwinase is not a cytotoxic medicinal product (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.
	• Calculate the dose needed and the volume needed to obtain the calculated dose. • 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. • If partial vial is used, do not save or reuse the unused drug for later administration. Discard unused portions. • Do not freeze or refrigerate reconstituted solution and administer within 4 hours or discard *[see How Supplied/Storage and Handling (16)]*.	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. Any unused product or waste material should be disposed of in accordance with local requirements. The solution should be used within 8 hours.
	2.3 Administration Instructions Administer ERWINAZE in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis.	Method of administration

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	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 to 2 hours. Do not infuse other intravenous drugs through the same intravenous line while infusing ERWINAZE.	Erwinase solution can be given by intravenous infusion or intramuscular injection. For IM injection the volume of reconstituted solution administered at a single injection site should not exceed 2 mL. Multiple injection sites should be used if this volume is exceeded. For IV infusion, the reconstituted solution should be further diluted in 100 mL of normal saline and administered over 1 to 2 hours. For further instructions on reconstitution of the medicinal product before administration, see section 6.6.
Description	**3 DOSAGE FORMS AND STRENGTHS** For injection: 10,000 International Units as a lyophilized powder in a single-dose vial for reconstitution **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).	**2 QUALITATIVE AND QUANTITATIVE COMPOSITION** Crisantaspase (L-asparaginase from *Erwinia chrysanthemi*), 10,000 International units/vial. For a full list of excipients, see section 6.1. **3. PHARMACEUTICAL FORM** Powder for solution for injection/infusion. White lyophilised powder in a vial. **6.1 List of excipients** Sodium Chloride (0.5 mg) Glucose Monohydrate (5.0 mg)

Contraindications	**4 CONTRAINDICATIONS** ERWINAZE is contraindicated in patients with a history of: • Serious hypersensitivity reactions to ERWINAZE, including anaphylaxis • Serious pancreatitis with prior L-asparaginase therapy • Serious thrombosis with prior L-asparaginase therapy • Serious hemorrhagic events with prior L-asparaginase therapy	**4.3 Contraindications** • History of severe hypersensitivity to the active substance or to any of the excipients listed in section 6.1 • Current or past severe pancreatitis associated with L-asparaginase therapy • Current pancreatitis not associated with L-asparaginase therapy

Precautions	**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)]*.
		4.4 Special warnings and precautions for use
		In order to improve traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded (or stated) in the patient file.
		
		<u>Hypersensitivity reactions</u>
		Administration of Erwinase can cause hypersensitivity reactions (infusion/injection reactions), including reactions presenting as anaphylaxis.
		Severe reactions are common.
		Reactions have occurred following the first or subsequent administrations.
		There is little or no cross-reactivity between crisantaspase and E. coli-derived L-asparaginase.
		Reactions include
		• reactions limited to the area at or near the site of IM or IV administration, and
		• other reactions, including
		  ○ reactions with symptoms consistent with an anaphylactic reaction, and
		  ○ reactions accompanied by fever (see section 4.8).

		Reactions can begin during or immediately following administration. In the majority of patients, local and non-local reactions occur within the first 24 hours. Later onset of reactions has been reported two days or later after IM administration.
	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.	Facilities should be made available for management of an anaphylactic reaction, should it occur, during administration. If a severe reaction occurs, Erwinase must be discontinued (see section 4.3). 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 and hypersensitivity reactions occurring.
	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.	<u>Pancreatitis</u> Treatment with L-asparaginase, including Erwinase, can cause pancreatitis. L-asparaginase-induced pancreatitis can be limited to biochemical and/or radiologic manifestations, progress to pancreatitis with clinical symptoms, and be severe (see section 4.8). Fatal outcome of pancreatitis due to L-asparaginase products, including Erwinase, has been reported. Patients must be closely monitored for signs and symptoms of pancreatic toxicity and instructed to promptly report potential symptoms of pancreatitis. If pancreatitis is suspected based on clinical symptoms, serum amylase and lipase should be determined. In patients treated with

	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.	L-asparaginase, increases of serum amylase and lipase may be delayed, mild or absent. Erwinase must be permanently discontinued in case of severe pancreatitis (see section 4.3). Hypertriglyceridemia, if marked, can contribute to the development of pancreatitis (see section 4.8). There have been isolated reports of first onset of clinical pancreatitis and detection of pancreatic pseudocyst formation several months after the last administration of L-asparaginase. Patients must be monitored for late-occurring signs of pancreatitis. Development of chronic pancreatitis as well as persistent pancreatic insufficiency (exocrine insufficiency with, e.g., malabsorption; persistent glucose intolerance/diabetes mellitus) has been reported with L- asparaginase treatment. <u>Glucose Intolerance</u> Treatment with L-asparaginase, including Erwinase, can cause glucose intolerance and potentially severe hyperglycemia. In some patients, ketoacidosis has been reported. Patients must be monitored for developing hyperglycemia and potential complications.

	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.	Administration of insulin and possibly discontinuation of L-asparaginase treatment may be necessary to manage hyperglycemia. <u>Coagulation Disorders</u> Administration of L-asparaginase, including Erwinase, leads to decreased synthesis of coagulant, anticoagulant, and fibrinolytic proteins, abnormal coagulation times, and clinical coagulation abnormalities that can cause serious thromboembolic and bleeding events (see section 4.8). Routine clotting screening should be performed before treatment initiation and monitored during treatment. Preventive measures must be considered. If significant symptomatic coagulopathy occurs in addition to other clinically indicated interventions withhold Erwinase treatment until resolved. Treatment may then continue according to protocol, if the benefit of continued administration is considered to outweigh the risk from re-exposure.

Adverse reactions	**6 ADVERSE REACTIONS** The following clinically significant 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)]* **6.1 Clinical Trials Experience** 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	**4.8 Undesirable effects** a. Summary of the safety profile The two most frequent adverse reactions are: • Hypersensitivity, including urticaria, fever, arthralgia angioedema, bronchospasm, hypotension or even anaphylactic shock. In case of severe 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. Undesirable effects are generally reversible. b. Tabulated list of adverse reactions The adverse reaction data presented in Table 1 have been identified from 3 clinical studies (100EUSA12, ALL07P2, and Erwinase Master Treatment Protocol [EMTP]) with Erwinase in 1028 patients (primarily pediatric patients), the majority having acute lymphoblastic leukemia, as well as post-marketing experience with Erwinase and other L-asparaginase preparations in pediatric and adult patients.

(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

Some of the adverse reactions listed below are known to be associated with multi-agent chemotherapeutic regimens (e.g., reactions resulting from bone marrow depression, and infections), and the contributory role of Erwinase is not clear. In individual cases of other adverse reactions, other medicinal products of the regimen may have contributed.

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".

Table 1.: Adverse Reactions

System organ class	Adverse Reactions	Frequency Category
Infections and infestations	Infections/ sepsis[1,2]	Very common
Blood and lymphatic system disorders	Leukopenia (including neutropenia)[3]	Very common
	Thrombocytopenia[3]	Very common
	Anemia[3]	Very common
	Decrease of coagulant, anticoagulant, and fibrinolytic proteins[4]	Very common
	Coagulation time abnormal[5]	Very common
	Febrile neutropenia[3]	Very common
Immune system disorders	Hypersensitivity reactions (not at or near the site of administration)[6]	Very common
	Anaphylaxis[7]	Uncommon
Metabolism and nutrition disorders	Hyperlipidemia, including Increased cholesterol, and hypertriglyceridemia	Very common

allergy to native *E. coli* asparaginase or pegaspargase. Patients received ERWINAZE 25,000 International Unit/m /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

	Increased amylase and/or lipase	Very common
	Weight loss[8]	Very common
	Hyperglycemia	Very common
	Diabetic ketoacidosis	Uncommon
	Hyperammonemia	Uncommon
Nervous system disorders	Central nervous system (CNS) depression or toxicity[9]	Common
	• Convulsions (grand mal, partial seizures)[10] • Encephalopathy[11] • Posterior reversible encephalopathy syndrome*	Uncommon Common Rare
	Headache	Common
Vascular disorders	Venous and arterial thrombotic, embolic and ischemic events[2,12]	Common
	Haemorrhage[2]	Common
	Hypotension	Uncommon
	Hypertension	Not Known
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
Gastrointestinal disorders	Pancreatitis[2,13]	Common
	Vomiting	Very common
	Diarrhoea	Common
	Abdominal pain/discomfort	Common
	Nausea	Very common
	Parotitis	Not known
Hepatobiliary disorders	Increased blood bilirubin, transaminases, alkaline phosphatase	Very common
	Hepatotoxicity • Hepatic steatosis • Hepatic failure	Very common Uncommon Not known

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 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.

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.

	• Cholestatic jaundice • Hepatomegaly	Not known Not known
	Hypoalbuminemia[14]	Not known
	Increased BSP retention	Not known
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis[2]	Not known
Musculoskeletal and connective tissue disorders	Musculoskeletal pain15	Very common
	Reactive arthritis	Not known
Renal and urinary disorders	Renal impairment	Uncommon
General disorders and administration site conditions	Mucositis	Common
	Pyrexia	Common
	Injection site and local hypersensitivity reactions[16] including late-onset reactions[17]	Common
	Fatigue	Common
Investigations	Increases in blood urea nitrogen, and/or serum creatinine[18]	Very common

* See “Description of selected adverse reactions”

[1] Including, for example, bacterial, viral, fungal, and opportunistic infections.
[2] Including fatal outcomes
[3] Resulting from bone marrow depression.
[4] The following have been documented with Erwinase: decreased antithrombin III, Protein C and Protein S activity; decreased fibrinogen levels (As a consequence of inhibition protein synthesis) Decreased plasminogen levels have been reported with E. coli-derived L-asparaginase.

[9] CNS depression (e.g., coma, somnolence, lethargy), and other manifestations of neurotoxicity including paresis, aphasia, hallucinations, confusion, agitation, dizziness, headache, possibly secondary to a primary adverse reaction such as hyperglycemia, hyperammonemia, encephalopathy, sepsis, cerebrovascular event, hypersensitivity reactions, or effects of other concurrent drug therapy. Neurotoxicity (e.g., somnolence, lethargy, confusion, dizziness, headache) unrelated to an underlying clinical condition has

PORTON BIOPHARMA

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.

[5] Including prolonged activated partial thromboplastin time, prothrombin time, and INR.
[6] Including reactions consistent with anaphylactic reactions (e.g., hypotension, bronchospasm/wheezing, hypoxia, respiratory distress/dyspnoea, dysphagia, rhinitis, angioedema, urticaria, rash, pruritus, erythema, pallor, and/or malaise); febrile reactions, e.g., with chills, flushing, hypertension, tachycardia, vomiting, nausea, and/or headache; and reactions e.g., with musculoskeletal symptoms such as arthralgia and skin manifestations, such as purpura/petechiae
[7] Severe and immediate systemic reaction.
[8] Severe weight loss (>20%) has also been reported.

been reported with other L-asparaginase products.
[10] Seizures can be associated with a cerebrovascular event or metabolic encephalopathy.
[11] Encephalopathy can be a consequence of hyperammonemia.
[12] Including peripheral, pulmonary, cerebral (e.g., sinus thrombosis), cardiac (e.g., myocardial infarction), intestinal, renal, hepatic
[13] Including acute, necrotizing, hemorrhagic, and pseudocyst formation
[14] Hypoalbuminemia can be symptomatic with peripheral edema
[15] Including myalgia, arthralgia, pain in extremity
[16] Including injection site urticaria, rash, pruritus, erythema, pain, edema, swelling, induration, hematoma
[17] A delayed local skin reaction with blisters has been reported with another L-asparaginase product.
[18] Including increases within the laboratory normal range

c. Description of selected adverse reactions

Posterior reversible encephalopathy syndrome

In rare cases, a posterior reversible encephalopathy syndrome (PRES) has been observed during therapy with asparaginase-containing regimens.

PORTON BIOPHARMA

	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%)
-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 all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in other studies or to other asparaginase *Erwinia chrysanthemi* products may be misleading.

In a study with ERWINAZE treatment by intramuscular administration (Study 1), 6 of 56 (11%) patients treated

Immunogenicity

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

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 crisantaspase with the incidence of antibodies to other products may be misleading.

In a study with Erwinase treatment by IM administration (Study ALL07P2), 6 of 56 (11%) patients treated with

	with ERWINAZE developed antibodies to ERWINAZE. Of these 6 anti-drug antibody (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.	Erwinase developed antibodies to crisantaspase. Of these 6 ADA positive patients, one experienced a hypersensitivity reaction (2%, 1 of 56). None of these 6 patients had neutralising antibodies. In a study with Erwinase treatment by IV administration (Study 100EUSA12), 4 of 30 (13.3%) patients treated with Erwinase developed anti-crisantaspase antibodies. Of these 4 patients, 3 experienced hypersensitivity reactions (10%, 3 of 30). None of these 4 patients had neutralising antibodies <u>Neutralising antibodies</u> As with other L-asparaginase preparations, development of specific neutralising antibodies has been reported with repeated dosing and is associated with reduced L-asparaginase activity. <u>Reporting of suspected adverse reactions</u> Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Drug interactions	*Note: The following information is provided in the USPI under section 12.3 Pharmacokinetics* <u>Drug Interaction Studies</u> No formal drug interaction studies between ERWINAZE and other drugs have been performed	**4.5 Interaction with other medicinal products and other forms of interaction** No formal medicinal product interaction studies have been performed. Asparaginase must not be mixed with any other medicinal products prior to administration. In addition concomitant use of L-asparaginase and medicinal products affecting liver function may increase the risk of a change in liver parameters (e.g. increase of ASAT, ALAT, bilirubin). Since an indirect interaction between components of the oral contraception and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. Another method than oral contraception should be used in women of childbearing potential (see section 4.6). • Methotrexate, cytarabine L-asparaginase may diminish or abolish methotrexate's and cytarabine's effect on malignant cells; this effect persists as long as plasma asparagine levels are suppressed. Accordingly, do not use methotrexate or cytarabine with, or following L-asparaginase, while asparagine levels are below normal. Alternatively, administration of L-asparaginase after methotrexate or cytarabine results in a synergistic effect.

		The extent to which these affect the overall effectiveness of established treatment protocols is not known. • Prednisone 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). • Vincristine Administration of vincristine concurrently with or immediately before treatment with L-asparaginase may be associated with increased toxicity and increased risk of anaphylaxis.
Special populations	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** <u>Risk Summary</u> Based on findings from animal reproduction studies, ERWINAZE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, intramuscular administration of asparaginase *Erwinia chrysanthemi* to pregnant rats and rabbits during organogenesis at doses approximately 0.005-0.5 times the maximum recommended human dose resulted in structural abnormalities and embryo-fetal mortality *(see Data).* There are no available data on ERWINAZE use in pregnant women to evaluate the drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Advise pregnant women of the potential risk to the fetus.	**4.6 Fertility, pregnancy and lactation** <u>Pregnancy</u> 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 the potential benefit justifies the potential risk to the fetus.

	The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2 to 4% and 15 to 20%, respectively. <u>Data</u> *Animal Data* In embryofetal development studies, asparaginase *Erwinia chrysanthemi* was administered intramuscularly every other day during the period of organogenesis to pregnant rats (at 3000, 6000, or 12000 IU/m^2) and rabbits (at 120, 300, or 480 IU/m^2). In rats given 12000 IU/m^2 (approximately 0.5 times the maximum recommended human dose), 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 480 IU/m^2 (approximately 0.02 times the maximum recommended human dose). 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 ≥120 IU/m^2 (approximately 0.005 times the maximum recommended human dose).	<u>Fertility</u> There are no human data on the effect of crisantaspase on fertility. In rats, crisantaspase did not affect male and female fertility. However, a decrease in sperm count was observed in male rats (see section 5.3). The relevance of this finding to humans is not known.

	8.2 Lactation Risk Summary There are no data on the presence of asparaginase *Erwinia chrysanthemi* in human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with ERWINAZE, and for 3 months after the last dose. **8.3 Females and Males of Reproductive Potential** Pregnancy Testing Pregnancy testing is recommended for females of reproductive potential before starting ERWINAZE treatment. Contraception *Females* ERWINAZE can cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ERWINAZE and for 3 months after the final dose. Since an indirect interaction between oral contraceptives and ERWINAZE cannot be ruled out, a method of contraception other than oral contraceptives should be used in women of childbearing potential.	Breast feeding It is not known whether crisantaspase (*Erwinia* L-asparaginase) is excreted in human breast milk. Potential serious adverse reactions may occur in nursing infants, therefore Erwinase should be discontinued during breast-feeding. Women of childbearing potential/Contraception in males and females Women of childbearing potential should use effective contraception and avoid becoming pregnant while being treated with asparaginase-containing chemotherapy. Since an indirect interaction between components of the oral contraception and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. A method other than oral contraceptives should be used in women of childbearing potential. Men should use effective contraceptive measures and be advised to not father a child while receiving asparaginase. The time period following treatment with asparaginase when it is safe to become pregnant or father a child is unknown. As a precautionary measure it is recommended to wait for three months after completion of treatment. However, treatment with other chemotherapeutic agents should also be taken into consideration.

	8.4 Pediatric Use The safety and effectiveness of ERWINAZE have been established in pediatric patients ages1 year and older 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 and the information on this use is discussed throughout the labeling. **8.5 Geriatric Use** Clinical studies of ERWINAZE did not include geriatric patients.	d. Pediatric population Compared with children, the incidence of hepatic and pancreatic toxicities and of venous thromboembolic events may be increased in adolescents and young adults. e. Other special populations No special individual populations of patients have been identified in which the safety profile differs from that defined above.
Overdosage	**There are no corresponding clinical data for Erwinaze USPI**	**4.9 Overdose** There is no known antidote for asparaginase overdoses. No data are available on the elimination (peritoneal or by haemodialysis) of the product. Patients who accidentally receive an overdose of L-asparaginase should be monitored closely and receive any appropriate symptomatic and supportive treatment.
	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	**5. PHARMACOLOGICAL PROPERTIES** **5.1 Pharmacodynamic properties** Pharmacotherapeutic group: other antineoplastic agents ATC code: L01XX02 <u>Mechanism of action</u> L-asparaginase catalyses the deamination of asparagine to aspartic acid with the release of ammonia. Asparagine is an amino acid found incorporated into most proteins, and protein synthesis is halted in its absence,

	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.	thereby inhibiting RNA and DNA synthesis with a resulting halt to cellular proliferation. As lymphoblastic cells are lacking asparagine synthetase activity they are dependent upon exogenous asparagine. The anti-tumour activity of L-asparaginase is a result of the sustained depletion of exogenous asparagine. 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. Glutamine may lead to alternative asparagine synthesis and therefore glutamine depletion may complement asparagine depletion. However, exact potential of this glutaminase activity remains unknown.
	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,	**5.2 Pharmacokinetic properties** Based on a population PK model, the mean (%CV) half-life of crisantaspase is 7.5 (24%) hours after intravenous infusion in contrast to 15.6 (20%) hours after intramuscular injection. L-asparaginase penetrates through to the cerebrospinal fluid to a small degree and is also found in lymph. Serum trough asparaginase activity ≥ 0.1 U/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.

	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)]*. <u>Drug Interaction Studies</u> No formal drug interaction studies between ERWINAZE and other drugs have been performed	<u>Clinical trials</u> Study 1 (AALL07P2) was a single-arm, multicentre, open-label, safety and clinical pharmacology trial, which enrolled ALL patients who were unable to continue to receive pegaspargase due to hypersensitivity reactions. The main outcome measure was the proportion of patients who achieved a serum trough asparaginase level ≥ 0.1 IU/mL, which correlates with asparagine depletion and predicts clinical efficacy. Patients received Erwinase 25,000 IU/m^2 intramuscularly for two weeks (total 6 doses) as a replacement for each scheduled dose of pegaspargase. Out of 58 patients enrolled, 48 were evaluable for the main outcome measure in the first treatment course. The median age was 11 years (2 to 18 years) and 59% were male. Study 2 (100EUSA12) was a single-arm, multicentre pharmacokinetic study in patients with ALL/LBL who had developed hypersensitivity to native E. coli asparaginase, pegaspargase, or calaspargase pegol. Patients received Erwinase 25,000 IU/m^2 intravenously 3 days per week for up to 30 weeks. The main outcome measure was the proportion of patients with 2-day nadir serum asparaginase activity (NSAA) levels after the fifth dose ≥ 0.1 IU/mL. Out of 30 patients enrolled, 24 were evaluable for the main outcome measure in the first treatment course. The median age was 7 years (1-17 years) and 63% were male.

<table>
<tr>
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<td>The results of the two studies are presented in the table below.
Proportion of patients with sustained asparaginase activity
<table>
<tr><td rowspan="2">Trough sampling time</td><td colspan="2">Proportion (n/N) and 95% CI with asparaginase activity ≥ 0.1 IU/mL</td><td colspan="2">Proportion (n/N) and 95% CI with asparaginase activity ≥ 0.4 IU/mL</td></tr>
<tr><td>Study 1 (IM)[a]</td><td>Study 2(IV)[b]</td><td>Study 1 (IM)[a]</td><td>Study 2(IV)[b]</td></tr>
<tr><td>48-hour</td><td>100% (35/35)
[90 , 100]</td><td>83% (20/24)
[63 , 95]</td><td>80% (28/35)
[64 , 90]</td><td>29% (7/24)
[13 , 51]</td></tr>
<tr><td>72-hour</td><td>100% (13/13)
[77 , 100]</td><td>43% (9/21)
[22 , 66]</td><td>38% (5/13)
[18 , 65]</td><td>0% (0/21)
[0 , 16]</td></tr>
</table>
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

<u>Neutralising antibodies</u>
As with other L-asparaginase preparations, development of specific neutralising antibodies has been reported with repeated dosing and is associated with reduced L-asparaginase activity.

<u>Cerebrospinal fluid activity</u>
After IM administration of 25,000 IU/m^2 Erwinase per week for 16 weeks, CSF L-asparagine levels were undetectable 3 days after last administration in 5 of 8 children (62.5%), and in 2 of 8 children (25%) after both the 5th and 6th administration during reinforced re-induction therapy.</td>
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<tr>
<td>Carcinogenesis, Mutagenesis, Impairment of Fertility</td>
<td>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</td>
<td>5.3 Preclinical safety data
Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:</td>
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	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 12000 IU/m^2 (approximately 0.50 times the maximum recommended human dose) every other day for a total of 35 doses. Findings in males included decreased sperm count at doses of more than 3000 IU/m^2 (approximately 0.12 times the maximum recommended human dose).	<u>Reproduction and development toxicity</u> 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. In a fertility and early embryonic development study in rats, IM administration of crisantaspase had no effect on male and female fertility at doses approximately 50% of the recommended human dose (based on body surface area). However, a 12 to 15% decrease in sperm count was observed at doses approximately 12 to 50% of the recommended human dose. <u>Carcinogenicity</u> Non-clinical studies have not been conducted to evaluate the carcinogenic or mutagenic potential of crisantaspase. Crisantaspase is an enzyme for which the structure and well documented activity do not suggest any carcinogenic or mutagenic potential.
Clinical data	**14 CLINICAL STUDIES** The efficacy of ERWINAZE for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to *E. Coli*-derived asparaginase as a component of a multi-agent chemotherapeutic regimen 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)-	**5.2 Pharmacokinetic properties** Based on a population PK model, the mean (%CV) half-life of crisantaspase is 7.5 (24%) hours after intravenous infusion in contrast to 15.6 (20%) hours after intramuscular injection. L-asparaginase penetrates through to the cerebrospinal fluid to a small degree and is also found in lymph. Serum trough asparaginase activity ≥ 0.1 U/mL has been demonstrated to correlate with asparagine depletion

	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)]*.	(asparagine < 0.4 mcg/mL or 3 µM) and to serum levels that predict clinical efficacy. <u>Clinical trials</u> Study 1 (AALL07P2) was a single-arm, multicentre, open-label, safety and clinical pharmacology trial, which enrolled ALL patients who were unable to continue to receive pegaspargase due to hypersensitivity reactions. The main outcome measure was the proportion of patients who achieved a serum trough asparaginase level ≥ 0.1 IU/mL, which correlates with asparagine depletion and predicts clinical efficacy. Patients received Erwinase 25,000 IU/m^2 intramuscularly for two weeks (total 6 doses) as a replacement for each scheduled dose of pegaspargase. Out of 58 patients enrolled, 48 were evaluable for the main outcome measure in the first treatment course. The median age was 11 years (2 to 18 years) and 59% were male. Study 2 (100EUSA12) was a single-arm, multicentre pharmacokinetic study in patients with ALL/LBL who had developed hypersensitivity to native E. coli asparaginase, pegaspargase, or calaspargase pegol. Patients received Erwinase 25,000 IU/m^2 intravenously 3 days per week for up to 30 weeks. The main outcome measure was the proportion of patients with 2-day nadir serum asparaginase activity (NSAA) levels after the fifth dose ≥ 0.1 IU/mL.

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 Unit/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 Unit/mL post-dose 1 and 12.11 ± 3.11 International Unit/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 Unit/mL

Out of 30 patients enrolled, 24 were evaluable for the main outcome measure in the first treatment course. The median age was 7 years (1-17 years) and 63% were male.

The results of the two studies are presented in the table below.

Proportion of patients with sustained asparaginase activity

Trough sampling time	Proportion (n/N) and 95% CI with asparaginase activity ≥ 0.1 IU/mL		Proportion (n/N) and 95% CI with asparaginase activity ≥ 0.4 IU/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

Cerebrospinal fluid activity

After IM administration of 25,000 IU/m^2 Erwinase per week for 16 weeks, CSF L-asparagine levels were undetectable 3 days after last administration in 5 of 8 children (62.5%), and in 2 of 8 children (25%) after both the 5th and 6th administration during reinforced re-induction therapy.

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

6.4 Special precautions for storage
Store in a refrigerator (+2°C to +8°C).

For storage conditions of the reconstituted medicinal product, see section 6.3.</td>
</tr>
<tr>
<td></td>
<td>17 PATIENT COUNSELING INFORMATION
<u>Hypersensitivity</u>
Inform patients of the risk of allergic reactions, including anaphylaxis. Instruct patients on the symptoms of allergic reactions and to seek medical advice immediately if they experience such symptoms [see Warnings and Precautions (5.1)].</td>
<td>There is no corresponding section for Erwinase SmPC</td>
</tr>
</table>

	<u>Pancreatitis</u> Instruct patients on the risk of pancreatitis and to seek medical advice immediately if they experience abdominal pain *[see Warnings and Precautions (5.2)]*. <u>Glucose Intolerance</u> 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 *[see Warnings and Precautions (5.3)]*. <u>Thrombosis</u> 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 *[see Warnings and Precautions (5.4)]*. <u>Pregnancy and Lactation</u> Advise female patients of reproductive potential to use effective contraceptive methods while receiving ERWINAZE and for at least 3 months after the last dose. Advise patients to notify their healthcare provider immediately in the event of a pregnancy or if pregnancy is suspected during ERWINAZE treatment *[see Use in Specific Populations (8.3)]*. Advise lactating women not to breastfeed during treatment with ERWINAZE and for at least 3 months after the last dose *[see Use in Specific Populations (8.2)]*.	

Company information	Manufactured by: Jazz Pharmaceuticals, Inc. 3170 Porter Drive, Palo Alto, CA 94304 U.S. License No. 1901 Erwinaze® is a registered trademark of Porton Biopharma Limited used under license by Jazz Pharmaceuticals. **PRINCIPAL DISPLAY PANEL** **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 Dose Vial. Discard unused portion.**	**7. MARKETING AUTHORISATION HOLDER** Porton Biopharma Limited Manor Farm Road Porton Down, Salisbury, SP4 0JG United Kingdom **8. MARKETING AUTHORISATION NUMBER(S)** PL 44403/0002 **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 TEXT** 06/2020