▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – ERWINASE® (CRISANTASPASE) POWDER FOR SOLUTION FOR INJECTION/INFUSION

1 NAME OF THE MEDICINE

Crisantaspase

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10,000 IU cristantaspase (L-asparaginase from Erwinia chrysanthemi).

For the full list of excipients, see Section 6.1 List of excipients.

One unit of asparaginase activity is defined as the amount of enzyme that catalyses the hydrolysis of one µmol of L-asparagine per minute at pH 8.6 and 37°C.

3 PHARMACEUTICAL FORM

Powder for solution for injection/infusion.

White, lyophilised powder in a vial.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ERWINASE 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 pegylated asparaginase obtained from E. coli.

4.2 DOSE AND METHOD OF ADMINISTRATION

Administer ERWINASE in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis.

Dosage

The same dosage recommendations apply to paediatric and adult patients.

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.

Monitoring

As wide differences in asparaginase activity have been seen in children, it is possible that the optimal dose of ERWINASE varies between patients. Nadir (pre-dose) serum asparaginase activity level (NSAA) should be routinely monitored and subsequent doses should be

individually adapted as needed to achieve desired NSAA levels (see 5.2 Pharmacokinetic Properties).

Route of administration

If the desired NSAA is not achieved with intravenous administration, changing to intramuscular administration should be considered.

Changing to intramuscular administration may also be considered if the patient experiences severe nausea and vomiting with intravenous administration.

Method of Administration

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

- For intramuscular use, limit the volume of reconstituted ERWINASE 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 ERWINASE in 100 mL of normal saline over 1 to 2 hours. Do not infuse other intravenous drugs through the same intravenous line while infusing ERWINASE.

Instructions for handling

- Visually inspect the ERWINASE 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, ERWINASE should be a clear, colorless solution. Inspect the solution after reconstitution and discard if any visible particles or protein aggregates are present.
- 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 ERWINASE 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

4.3 CONTRAINDICATIONS

ERWINASE is contraindicated in patients with a history of:

- Serious hypersensitivity reactions to ERWINASE, including anaphylaxis or to any of the excipients listed in section 6.1.
- Serious pancreatitis with prior L-asparaginase therapy
- Current pancreatitis not associated with L-asparaginase therapy
- Serious thrombosis with prior L-asparaginase therapy
- Serious haemorrhagic events with prior L-asparaginase therapy

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

ERWINASE treatment should be prescribed by physicians and administered by health care personnel experienced in the use of antineoplastic products and in the treatment of haematological malignancies.

To enable linking of exposed patients to batch numbers, the tradename and batch number of the administered product should be clearly recorded in the patient file.

Hypersensitivity reactions including anaphylaxis

Hypersensitivity reactions including life-threatening anaphylaxis, have been observed with ERWINASE. Reactions may range from non-serious local reactions which resolve spontaneously or after treatment with antihistamines to severe life-threatening systemic reactions.

Because of the risk of severe reactions, ERWINASE should only be administered in a clinical setting with resuscitation equipment and other agents necessary to treat anaphylaxis. Patients should be closely monitored and carefully observed for any adverse reactions throughout the administration period. As a routine precautionary measure, patients should be monitored for one hour after administration. Careful observation is required on re-exposure to ERWINASE after any time interval.

ERWINASE should be permanently discontinued in case of serious hypersensitivity.

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 intramuscular administration of ERWINASE.
Once a patient has received treatment with a particular L-asparaginase as part of a treatment regimen, retreatment with the same L-asparaginase at a later time (e.g., use during a later consolidation phase) is associated with an increased risk of hypersensitivity and anaphylactic reactions.

Allergic reactions to Erwinia asparaginase in patients who have previously developed a hypersensitivity to E. coli have been reported in 3-34% of acute lymphoblastic leukaemia (ALL) patients.

Pancreatitis

Treatment with L-asparaginase, including ERWINASE, can cause pancreatitis. L-asparaginase induced pancreatitis can be limited to biochemical and/or radiological

manifestations, progress to pancreatitis with clinical symptoms and can be severe (see section 4.8). Haemorrhagic or necrotising pancreatitis with fatal outcomes has been reported.

Patients should be informed of the signs and symptoms of pancreatitis 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 L-asparaginase, increases of serum amylase and lipase may be delayed, mild or absent.

Discontinue ERWINASE for severe 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 ERWINASE until the signs and symptoms subside and amylase levels return to normal. After resolution, treatment with ERWINASE may be resumed.

There have been isolated reports of first onset of clinical pancreatitis and detection of pancreatic pseudocyst formation a few 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.

Hyperglycaemia
Treatment with L-asparaginase, including ERWINASE, can cause glucose intolerance and potentially severe hyperglycaemia. In some cases, ketoacidosis has been reported and glucose intolerance has been irreversible.
Patients must be monitored for development of hyperglycaemia and potential complications. Monitor glucose levels in patients at baseline and periodically during treatment. Administer insulin therapy as necessary in patients with hyperglycaemia. Treatment with L-asparaginase may need to be stopped.

Coagulation disorders
Coagulation disorders as a result of a reduction in the number of coagulation factors and coagulation inhibitors (such as antithrombin III, proteins C and S), hypofibrinogenaemia, increased prothrombin time, increased partial thromboplastin time and a decrease in the plasminogen level can result in thromboembolic and haemorrhagic complications. Thrombosis of peripheral, pulmonary or central nervous system blood vessels has been reported, potentially fatal or with residual delayed affects dependent upon the location of the occlusion (section 4.8).

Patients may be evaluated against the baseline on routine coagulation parameters, including prothrombin time, partial thromboplastin time, fibrinogen concentration and antithrombin III concentrations and should be regularly monitored during treatment.

Preventive measures should be considered. If significant symptomatic coagulopathy occurs, in addition to other clinically indicated interventions, ERWINASE treatment should be

withheld until this is resolved. Treatment may then be recommenced according to the local protocol if the benefit of continued administration outweighs the risk from re-exposure.

Hepatotoxicity
Treatment with L-asparaginase, including ERWINASE, can cause or worsen hepatic injury/dysfunction (including increase in transaminases and bilirubin, hepatic steatosis, hepatic failure and fatal outcome). In addition, L-asparaginase reduces hepatic protein synthesis, leading to e.g. hypoalbuminaemia, hypofibrinogenaemia (see also Coagulation disorders and section 4.8).

Caution is required when ERWINASE is given in combination with other hepatotoxic products (see also Section 4.5).

Hepatic function should be monitored regularly during therapy.

In case of severe hepatic adverse reactions, discontinuation of ERWINASE should be considered until complete or near-complete recovery. Treatment should be re-instituted only under very close monitoring.

Neurological Toxicities (including posterior reversible encephalopathy syndrome)
CNS toxicity, including encephalopathy, seizures and CNS depression as well as posterior reversible encephalopathy syndrome (PRES) may occur rarely during treatment with any asparaginase including ERWINASE (see section 4.8).

PRES is characterised in MRI by reversible (from a few days to months) lesions/oedema, primarily in the posterior region of the brain. Symptoms of PRES essentially include elevated blood pressure, seizures, headaches, changes in mental state and acute visual impairment (primarily cortical blindness or homonymous hemianopsia). It is unclear whether the PRES is caused by asparaginase, concomitant treatment or the underlying diseases. PRES is treated symptomatically, including measures to treat any seizures. Discontinuation or dose reduction of concomitantly administered immunosuppressive medicinal products may be necessary. Expert advice should be sought.

Fatal outcome of L-asparaginase-induced CNS toxicity has been reported.

Hyperammonaemia
Asparaginase facilitates the rapid conversion of asparagine and glutamine to aspartic acid and glutamic acid, with ammonia as a by-product of both reactions. Administration of asparaginase may therefore cause serum levels of ammonia to rise sharply.

The symptoms of hyperammonaemia can include nausea, vomiting, headache, dizziness and confusion. In severe cases, encephalopathy can develop with or without hepatic impairment, especially in older adults, which can be life-threatening or fatal.

If symptoms of hyperammonaemia or CNS toxicity are present, ammonia levels should be monitored closely and treatment initiated as appropriate.

Osteonecrosis with concomitant glucocorticoids
Osteonecrosis has been reported in patients receiving asparaginase and glucocorticoids concomitantly. It may be multifocal, progressive and result in joint destruction with lasting disability. Onset may not occur until after completion of asparaginase treatment. It is more common in patients aged 10 to 20 years and females.
Osteonecrosis may occur through potentiation of glucocorticoid effects. Asparaginase-induced impaired plasma protein synthesis may result in increased tissue exposure by highly plasma protein bound glucocorticoids.

Patients should be informed of the signs and symptoms of osteonecrosis and instructed to promptly report if these occur.

Use in renal impairment
Renal impairment may be caused or aggravated by the chemotherapy regimen.

Immunosuppression, infections
L-asparaginase has been reported to have immunosuppressive activity in animal experiments. As ERWINASE is used concomitantly with other agents that can reduce immune response, this can increase the risk of infections.
Bacterial, viral, fungal and opportunistic infections, some with fatal outcome, have been reported.

The peripheral blood count should be monitored closely. Dose reductions of concurrently administered myelosuppressive agents may need to be considered.

Use in the elderly
The safety and effectiveness of ERWINASE has not been established in geriatric patients.

Paediatric use
Safety and effectiveness have not been established in paediatric patients aged less than one year.
Compared with younger children, the incidence of hepatic and pancreatic toxicities and of venous thromboembolic events may be increased in adolescents and young adults.

Effects on laboratory tests
ERWINASE can affect the interpretation of thyroid function tests due to a significant decrease in the level of thyroxine-binding globulin (TBG) in the serum (see also “Undesirable effects”).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Asparaginase should not be mixed with any other medicinal products prior to administration.

Drugs affecting liver function
Concomitant use of crisantaspase and medicinal products affecting liver function may additionally increase the risk of a change in liver parameters (e.g. increase of AST, ALT and bilirubin).

Methotrexate, cytarabine

Non-clinical data indicate that prior or concurrent administration of L-asparaginase attenuates the effect of methotrexate and cytarabine. Administration of L-asparaginase after methotrexate or cytarabine results in a synergistic effect. The clinical effect of sequence-dependent L-asparaginase administration on the efficacy of methotrexate and cytarabine is unknown.

Glucocorticoids

Concomitant use of L-asparaginase and glucocorticoids may result in an increased tissue exposure to glucocorticoids due to decreased plasma protein binding or altered metabolism.

Concomitant use of ERWINASE with prednisone or dexamethasone may increase the risk of a change in clotting parameters, such as a decrease in fibrinogen and ATIII levels. Concomitant use of ERWINASE and glucocorticoids may increase the risk of developing osteonecrosis.

Vincristine

Administration of ERWINASE concurrently with or immediately before treatment with vincristine may be associated with increased toxicity and increased risk of anaphylaxis.

Imatinib

It has been reported that concomitant use of imatinib with L-asparaginase may be associated with increased liver toxicity. Concomitant use of imatinib therefore requires special precautionary measures.

Oral contraceptives

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.

There may be an increase in risk of thromboembolic events during concomitant use of oral contraceptives and asparaginase.

Pharmacokinetic interactions

The possibility of interactions with medicinal products whose pharmacokinetics are affected by L-asparaginase-induced changes in the liver function or plasma protein levels should be taken into account when administering L-asparaginase, including crisantaspase.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

In a fertility and early embryonic development study in rats, crisantaspase 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 starting 4 weeks before mating in males and 2 weeks before mating to gestation day 6 in females. 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) given every other day for 10 weeks.

Use in pregnancy – Pregnancy Category D

Pregnancy testing is recommended for females of reproductive potential before starting ERWINASE treatment.

ERWINASE can cause embryo-fetal harm when administered to pregnant women [see Use in Pregnancy]. Advise females of reproductive potential to use effective contraception during treatment with ERWINASE and for 3 months after the final dose. Since an indirect interaction between oral contraceptives and ERWINASE cannot be ruled out, a method of contraception other than oral contraceptives should be used in women of childbearing potential.

Based on findings from animal reproduction studies, ERWINASE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, intramuscular administration of crisantaspase 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 Animal Data). There are no available data on ERWINASE 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.

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.

Animal Data

In embryofetal development studies, crisantaspase 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 foetuses, 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).

In a pre- and postnatal development study in rats there were no adverse effects on gestation, parturition, or growth, development or reproductive performance of offspring following intramuscular doses to the dam at 14400 IU/m^2 (approximately 0.6 times the maximum recommended human dose) every other day from gestation day 6 to postnatal day 20.

Use in lactation

There are no data on the presence of crisantaspase 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 ERWINASE, and for 3 months after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No data are available. Potential CNS depression, nausea and vomiting should be taken into account when driving and using machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The two most frequent adverse reactions are:

- Hypersensitivity, including hives, fever, bronchospasms, arthralgia, angioedema, hypotension, other allergic reactions or anaphylactic shock. In case of severe hypersensitivity reaction treatment should be discontinued immediately and not resumed (see section 4.4).
- Coagulation abnormalities, due to protein synthesis impairment, are the second most frequent class of adverse reactions. The following coagulation proteins were decreased in the majority of patients after a 2-week course of ERWINASE by intramuscular administration: fibrinogen, protein C activity, protein S activity, and anti-thrombin III. Other risk factors contributing to coagulation abnormalities include the disease itself, concomitant steroid therapy and central venous catheters (see section 4.4).

The adverse reactions are generally reversible.

Tabulated list of adverse reactions

The data on adverse reactions in Table 1 have been established on the basis of 3 clinical studies (100EUSA12, ALL07P2 and ERWINASE Master Treatment Protocol [EMTP]) with ERWINASE in 1028 patients (primarily paediatric patients), the majority of whom had lymphoblastic leukaemia, as well as post-marketing experiences with ERWINASE and other L-asparaginase preparations when used as part of a multi-agent chemotherapy regimen in paediatric and adult patients.

Frequency definitions: very common (≥ 1/10), common (≥1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be calculated using the available data).

Table 1: Adverse events

System/organ class	Adverse events	Frequency category
Infections and infestations	Infections/sepsis[1,2]	Very common
	Leukopenia (including neutropenia)[3]	Very common
	Thrombocytopenia[3]	Very common
	Anaemia[3]	Very common
	Febrile neutropenia[3]	Very common
	Pancytopenia	Common
	Haemolytic anaemia	Not known
Immune system disorders	Hypersensitivity reactions (not at or near the site of administration)*	Very common
	Anaphylaxis	Uncommon
Metabolism and nutrition disorders	Hyperlipidaemia, including increased cholesterol and hypertriglyceridaemia	Very common
	Weight loss[4]	Very common
	Hyperglycaemia	Very common
	Diabetic ketoacidosis	Uncommon
	Hyperammonaemia	Uncommon
	Secondary hypothyroidism	Not known
	Anorexia	Not known
Nervous system disorders	Encephalopathy[5]	Common
	Aphasia[6]	Common
	Hallucinations[6]	Common
	Confusional state[6]	Common
	Headache[6]	Common
	Lethargy[5]	Uncommon
	Paresis[6]	Uncommon
	Dizziness[6]	Uncommon
	Seizures[5]	Uncommon
	Coma[5]	Uncommon
	Posterior reversible encephalopathy syndrome (PRES)*	Rare
	Somnolence[5]	Not known
	Agitation[6]	Not known

Vascular disorders	Venous and arterial thrombotic, embolic and ischaemic events[2,7]	Common
	Haemorrhage[2]	Common
	Hypotension	Uncommon
	Hypertension	Not known
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
Gastrointestinal disorders	Pancreatitis* [2,8]	Common
	Vomiting	Very common
	Nausea	Very common
	Diarrhoea	Common
	Abdominal pain/discomfort	Common
	Parotitis	Not known
Hepatobiliary disorders	Hepatotoxicity • Hepatic steatosis • Hepatic failure • Cholestatic jaundice • Hepatomegaly	Very common Uncommon Rare Not known Not known
	Hypoproteinaemia	Not known
	Hypoalbuminaemia[9]	Not known
	Increased bromsulphalein retention	Not known
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis[2]	Not known
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[10]	Very common
	Reactive arthritis	Very rare
	Osteonecrosis	Not known
Renal and urinary disorders	Nephrotoxicity	Uncommon
	Proteinuria	Not known
	Acute kidney failure	Not known
	Uric acid nephropathy	Not known
	Renal impairment	Not known
General disorders and administration site conditions	Mucositis	Common
	Pyrexia	Common
	Injection site and local hypersensitivity reactions[11] including late-onset reactions[12]	Common
	Fatigue	Common
Investigations	Decrease of coagulant,	Very common

	anticoagulant, and fibrinolytic proteins[13]	
	Coagulation time abnormal[14]	Very common
	Increased amylase and/or lipase	Very common
	Increased blood bilirubin, transaminases, alkaline phosphatase	Very common
	Decreased thyroxine-binding globulin	Not known

*See "Description of selected adverse reactions"

[1] Including, for example, bacterial, viral, fungal and opportunistic infections
[2] Including fatal outcomes.
[3] Caused by bone marrow depression.
[4] Severe weight loss (>20%) has also been reported.
[5] Possibly secondary to a primary adverse reaction such as hyperglycaemia, hyperammonaemia, encephalopathy, sepsis, cerebral accident, hypersensitivity reactions or effects of other concomitant medication
[6] Neurotoxicity unrelated to an underlying clinical condition has been reported with other L-asparaginase products.
[7] Including peripheral, pulmonary, cerebral (e.g. sinus thrombosis), cardiac (e.g. myocardial infarction), intestinal, renal and hepatic.
[8] Including necrotising, haemorrhagic, and pseudocyst formation
[9] Hyperalbuminaemia can be symptomatic with peripheral oedema.
[10] Including myalgia, arthralgia, pain in extremity.
[11] Including urticaria, skin rash, pruritus, erythema, pain, oedema, swelling, induration at the injection site.
[12] A delayed local skin reaction with blisters has been reported with another L-asparaginase product.
[13] The following have been documented with Crisantaspase Porton Biopharma: antithrombin III lowered, protein C and protein S activity; decreased fibrinogen levels. Lowered plasminogen levels have been reported with E. coli-derived L-asparaginase.
[14] Including prolonged activated partial thromboplastin time.

Description of selected adverse events.

Hypersensitivity

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, 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 (see section 4.4).

Pancreatitis

Pancreatitis has been reported in 4% of patients in clinical trials.

L-asparaginase-induced pancreatitis can be limited to biochemical and/or radiological manifestations, progress to pancreatitis with clinical symptoms and be severe (see section 4.4).

Fatal outcome of pancreatitis due to L-asparaginase products, including ERWINASE, has been reported.

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

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

In a study with ERWINASE treatment by IM administration (Study ALL07P2), 6 of 56 (11%) patients developed antibodies to ERWINASE. 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 developed antibodies to ERWINASE. Of these 4 patients, 3 experienced a hypersensitivity reaction (10%, 3 of 30). None of these 4 patients had neutralising antibodies.

Neutralising antibodies to ERWINASE have been reported in the literature and may cause reduced asparaginase activity without clinical hypersensitivity (“silent inactivation).

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 medication 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.

Other special populations
No special individual populations of patients have been identified in which the safety profile differs from that defined above.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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. An overdose of asparaginase can

cause chronic intoxication, characterised by impaired liver or kidney function. Patients who accidentally receive an overdose of L-asparaginase should be monitored closely and receive any appropriate symptomatic and supportive treatment. In the event of overdose, administration of L-asparaginase should be discontinued immediately.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Crisantaspase catalyzes the deamidation of asparagine to aspartic acid and ammonia, resulting in a reduction in circulating levels of asparagine.
The mechanism of action of ERWINASE 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.

Clinical trials

Study ALL07P2
Study ALL07P2 was an open-label, single-arm, pharmacokinetic, pharmacodynamic and safety study conducted in 58 paediatric patients with ALL who were hypersensitive to pegylated asparaginase (pegaspargase) who received Erwinase in a replacement schedule.

The primary objective of the study was to determine the proportion of patients with a 48-hour trough serum asparaginase activity was ≥0.1 IU/mL. Patients received Erwinase 25,000 IU/m^2 intramuscularly for 6 doses on a 3 times per week regimen.

Study 100EUSA12
Study 100EUSA12 was an open-label, single arm, pharmacokinetic study of intravenous ERWINASE conducted in 30 paediatric and young adult patients with ALL/lymphoblastic lymphoma (LBL) who had developed hypersensitivity to native E. coli asparaginase, pegaspargase, or Calaspargase pegol.

The primary objective of the study was to determine the proportion of patients with 2-day nadir serum asparaginase activity (NSAA) levels (48-hour levels taken after the fifth dose) that were ≥0.1 IU/mL in the first 2 weeks of ERWINASE treatment. Patients received Erwinase 25,000 IU/m^2 intravenously three days per week for up to 30 weeks.

The results of the two studies are presented in Table 2, below.

Table 2. 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 ALL07P2 (IM)[a]	Study 100EUSA12 (IV)[b]	Study ALL07P2 (IM)[a]	Study 100EUSA12 (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 hours
b. Trough sampling time is post-dose 5 at 48 hours and post-dose 6 for 72 hours

In addition to the above, the literature available in the public domain supports the clinical aspects of ERWINASE.

5.2 PHARMACOKINETIC PROPERTIES

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

Following intramuscular administration of ERWINASE 25,000 International Units/m^2 to 48 ALL patients aged ≥ 2 years to ≤ 18 years in Study ALL07P2 on a Monday, Wednesday, and Friday schedule for 6 doses, median asparaginase activity level at 48 hours post-dose was 0.65 IU/ml (range 0.24 to 1.84 IU/ml) and at 72 hours was 0.28 IU/ml (range 0.11 to 0.80 IU/ml). Of the patients who completed Course 1, 100 % 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.

Following intravenous administration of ERWINASE 25,000 International Units/m^2 to 24 evaluable patients (aged ≥ 1 year to ≤ 17 years) in Study 100EUSA12 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. The asparaginase activity levels at 48 hours post dose ranged from 0.01 to 1.16 IU/ml and at 72 hours ranged from 0 to 0.36 IU/ml.

The wide range of observed serum asparaginase activity levels with both intra-muscular and intravenous administration indicate marked inter-individual variability. Nadir (pre-dose)

serum asparaginase activity level (NSAA) should be routinely monitored and subsequent doses should be individually adapted as needed to achieve desired NSAA levels (see 4.2 Dose and Method of Administration).

Genotoxicity
No data available. Genotoxicity of crisantaspase was not investigated, but crisantaspase is not expected to be genotoxic.

Carcinogenicity
No data available. No long-term carcinogenicity studies in animals have been performed with crisantaspase.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Glucose monohydrate, sodium chloride, sodium hydroxide, acetic acid

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products. See section 4.5 Interaction with other medicinal products and other forms of Interaction. Accordingly, other intravenous medicinal products must not be infused through the same intravenous line as when administering ERWINASE.

6.3 SHELF LIFE

Shelf life of the product as packed for sale
In Australia, information on the shelf-life can be found on the public summary of Australian Register of Therapeutic Goods (ARTC). The expiry can be found on the packaging.

Shelf-life following reconstitution for injection
Chemical and physical stability of the reconstituted solution for injection has been demonstrated to be 15 minutes in the original container and 4 hours in a glass or polypropylene syringe, if stored below 25°C.

From a microbiological point of view, the reconstituted solution for injection should be used immediately. If storage is necessary, hold at 2°-8°C for not more than 24 hours.

Stability of the diluted medicinal product for infusion
Chemical and physical stability during use of the diluted medicinal product for infusion has been demonstrated to be 4 hours if stored below 25°C in a polyvinylchloride (PVC) infusion bag. Shelf life has not been studied for other types of infusion bags.

From a microbiological point of view, the diluted solution for infusion should be used immediately. If storage is necessary, hold at 2°-8°C for not more than 24 hours.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (+2°C to +8°C).
For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 NATURE AND CONTENTS OF CONTAINER

Box with 5 vials of 3 ml nominal capacity, made from clear neutral type I glass, closed with 13 mm bromobutyl rubber freeze-drying stoppers and aluminium overseals containing a white lyophilised solid.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Product is for single use in one patient only. Discard any residue.
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Crisantaspase is a biologic compound belonging to the group of L-asparaginases and is derived from the bacteria Erwinia chrysanthemi.

Crisantaspase contains primarily the native L-Asparaginase which is a non-disulfide bonded, tetrameric protein consisting of four identical polypeptide chain subunits with a combined Molecular Weight of 140 kDa. Each individual subunit has a Molecular Weight of 35 kDa.

CAS number

1349 719-22-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

PPD Australia Pty Ltd
Level 5, 412 St Kilda Road
Melbourne, Australia
Email: medinfo@portonbiopharma.com

9 DATE OF FIRST APPROVAL

DD Month YYYY

10 DATE OF REVISION

DD Month YYYY

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
ALL	Initial Product Information Document