Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Erwinase 10 000 U powder for solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 000 U crisantaspase (L-asparaginase from *Erwinia chrysanthemi)*. For the full list of excipients, see section 6.1.

One unit of asparaginase activity is defined as the amount of enzyme that catalyses the hydrolysis of one micromol 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 used in combination with other chemotherapeutic agents to treat patients, principally children, with acute lymphoblastic leukaemia who have developed hypersensitivity (clinical allergy or silent inactivation) to *E. coli* asparaginase or pegylated asparaginase obtained from *E. coli*.

4.2 Posology and method of administration

Posology

The recommended dose is 25 000 U/m^2 IM or IV, three times weekly (Monday, Wednesday, Friday) for two weeks, to replace each dose of pegaspargase or each cycle of the treatment with asparaginase.

The treatment can be further adapted according to the local protocol.

As wide differences in asparaginase activity have been seen in children, it is possible that the optimal dose of crisantaspase varies between patients. It is therefore recommended that the asparaginase level be checked so that the dose can be individually adapted.

Paediatric patients
The same dosage applies to children as to adults.

Method of administration
Erwinase solution can be administered intravenously or by intramuscular injection.

For IV infusion, it is recommended that the reconstituted Erwinase solution be further diluted in 100 ml of normal saline solution and administered over 1 to 2 hours.

For instructions on the reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- History of severe hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severely impaired liver function.
- Current or past severe pancreatitis associated with L-asparaginase therapy.

- Current pancreatitis not associated with L-asparaginase therapy.

4.4 Special warnings and precautions for use

In order to improve the traceability of biological medicinal products, the tradename and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Hypersensitivity reactions
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 (L-asparaginase from *Erwinia chrysanthemi*) and L-asparaginase from *E. coli*.

Reactions include:

- reactions limited to the area at or near the site of IM or IV administration and
- other reactions, including: o reactions with symptoms consistent with an anaphylactic reaction and o 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 intramuscular administration of Erwinase.

Although anaphylaxis is uncommon, facilities should be made available for its management during administration, such as epinephrine, IV glucocorticoids and oxygen. In the event of severe hypersensitivity reactions, treatment with Erwinase should be discontinued (see section 4.3).

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 acute lymphoblastic leukaemia (ALL) patients with percentages from 3-34%.

Pancreatitis
Treatment with L-asparaginase, including crisantaspase, 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). Fatal outcome of pancreatitis due to L-asparaginase products, including crisantaspase, 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 L-asparaginase, increases of serum amylase and lipase may be delayed, mild or absent.

Erwinase should be permanently discontinued in case of severe pancreatitis (see section 4.3).

Hypertriglyceridaemia, 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 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.

Glucose intolerance

Treatment with L-asparaginase, including crisantaspase, can cause glucose intolerance and potentially severe hyperglycaemia. In some patients, ketoacidosis has been reported.

Patients must be monitored for development of hyperglycaemia and potential complications. Hyperglycaemia can be treated with insulin and treatment with L-asparaginase may need to be stopped.

Coagulation disorders
Administration of L-asparaginase, including crisantaspase, 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).

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.

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

Hepatic function should be monitored regularly during therapy. See also section 4.5.

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 disorders
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 crisantaspase (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.
Since hyperammonaemia, if present, may cause or contribute to CNS toxicity, it is advisable to measure serum ammonia in patients with CNS toxicity. In symptomatic patients, initiate treatment as appropriate.

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

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. This should be considered, as Erwinase is used concomitantly with other agents that can reduce immune response and increase the risk of infections.

Special precautions for use
Erwinase should only be administered by doctors who are experts in the treatment of haematological malignancies.

Erwinase contains sodium
This medicine contains less than 1 mmol of sodium (23 mg) per dose, which means that it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed.

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

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 ASAT, ALAT 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. Crisantaspase also functions as a "rescue factor" if it is administered 24 hours after a high dose of methotrexate.

- Prednisone Use of crisantaspase in combination with or immediately before treatment with prednisone may be associated with increased toxicity (may increase the risk of a change in clotting parameters, such as a decrease in fibrinogen and ATIII levels).

- Vincristine Administration of crisantaspase 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.

Pharmacokinetic interactions
Crisantaspase 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").

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.

Administration of allopurinol is recommended in case of urate nephropathy, in order to reduce hyperuricaemia.

4.6 Fertility, pregnancy and lactation

For effects related to the co-administration of a chemotherapy, please refer to the SmPC of the chosen chemotherapy.

Pregnancy:
There are no or limited data available on the use of L-asparaginase in pregnant women. Teratogenicity was found in animal studies (see section 5.3).

Erwinase is not recommended during pregnancy or for women of childbearing age and men who wish to father a child and who are not using contraceptives, unless clearly indicated.

Breastfeeding:
It is not known whether L-asparaginase is excreted in human breast milk. The excretion of L-asparaginase has not been studied in animals. A risk to the breastfed children cannot be excluded, therefore Erwinase should not be used during breastfeeding.

Fertility:
The effects of crisantaspase on fertility are not known.

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 Undesirable effects

a) 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. 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. 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.

b) Tabulated list of adverse reactions

The data on adverse reactions in Table 1 have been established on the basis of 3 clinical studies (100EUSA12, AALL07P2 and Erwinaze Master Treatment Protocol [EMTP]) with crisantaspase in 1028 patients (primarily paediatric patients), the majority of whom had lymphoblastic leukaemia, as well as post-marketing experiences with crisantaspase and other L-asparaginase preparations in paediatric and adult patients.

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).

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) and very rare (< 1/10 000) and not known (cannot be calculated using the available data).

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
	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	Very common
	• Hepatic steatosis	Uncommon
	• Hepatic failure	Rare
	• Cholestatic jaundice	Not known
	• Hepatomegaly	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
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, anticoagulant, and fibrinolytic proteins[13]	Very common
	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: 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.

c) Description of selected adverse reactions.

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
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 crisantaspase, has been reported.

Posterior reversible encephalopathy syndrome
In rare cases, a posterior reversible encephalopathy syndrome (PRES) has been observed during therapy with asparaginase. (see section 4.4).

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

In a study with crisantaspase treatment by IM administration (Study AALL07P2), 6 of 56 (11%) patients treated with crisantaspase 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 crisantaspase treatment by IV administration (Study 100EUSA12), 4 of 30 (13.3%) patients treated with crisantaspase developed antibodies to crisantaspase. Of these 4 patients, 3 experienced a hypersensitivity reaction (10%, 3 of 30). None of these 4 patients had neutralising antibodies.

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.

d) Paediatric 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.

Reporting of suspected adverse reactions
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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

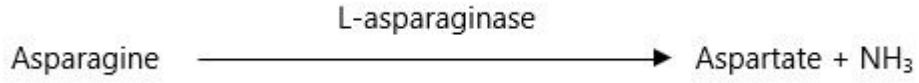
There is no known antidote for asparaginase overdoses. No data are available on the elimination (peritoneal or by haemodialysis) of the product. An overdose of asparaginase can cause chronic intoxication, characterised by impaired liver or kidney function. Patients who accidentally receive an overdose 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

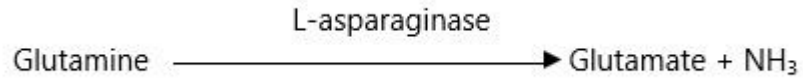
Pharmacotherapeutic category: other antineoplastic agents, ATC code: L01XX02

Mechanism of action
L-asparaginase catalyses the deamination of asparagine to aspartic acid with the release of ammonia. The biochemical reaction may be depicted schematically as follows:



Asparagine is found incorporated into most proteins and protein synthesis is halted in its absence, thereby inhibiting RNA and DNA synthesis with a resulting halt to cellular proliferation.

Since lymphoblastic cells do not demonstrate any synthetase activity, they are dependent on exogenous asparagine. The antitumour activity of L-asparaginase is a result of ongoing depletion of exogenous asparagine.
It has also been noted that L-asparaginase, in addition to its L-asparaginase activity, has significant glutaminase activity. It catalyses the deamination of glutamine in glutamic acid with the release of ammonia as follows:



Glutamine may lead to alternative asparagine synthesis and therefore glutamine depletion may complement asparagine depletion. However, exact potential of this glutaminase activity remains unknown.

5.2 Pharmacokinetic properties

The half-life of crisantaspase after IV infusion is 6.4 ± 0.5 hours.
The half-life of crisantaspase after IM injection is about 16 hours.
L-asparaginase penetrates through to the cerebrospinal fluid to a small degree and is also found in lymph.

It was demonstrated that a minimum serum activity of asparaginase ≥0.1 U/ml was correlated with asparaginase depletion (asparagine < 0.4 microg/ml or 3 microM) and with serum levels which predict efficacy.

IM study:
The serum trough concentrations of crisantaspase were determined in 48 ALL patients aged between 2 and 18 years enrolled in a single-arm, multi-centre, open-label study on safety and clinical pharmacology, AALL07P2. 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 U/ml.

Following intramuscular administration at a dose of 25 000 U/m^2 for the first course, serum asparaginase activity was maintained above 0.1 U/ml at 48 hours post-dose in 92.5% of patients and at least at 0.1 U/ml after 72 hours in 88.5% of patients.

IV study:
The serum trough asparaginase activity was determined in 24 ALL patients aged between 1 and 17 years enrolled in a single-arm, multi-centre, open-label, pharmacokinetic study, 100EUSA12. The primary objective of the study was to determine the proportion of patients with nadir (trough) serum asparaginase activity levels after 2 days (48-hour levels taken after the fifth dose) that were ≥0.1 U/ml in the first 2 weeks of crisantaspase treatment (three times per week IV) in patients with ALL/LBL who had developed hypersensitivity to native *E. coli* asparaginase, pegaspargase or calaspargase pegol.

Following intravenous administration over 1 hour at a dose of 25 000 U/m^2 for the first course, serum asparaginase activity was maintained ≥ 0.1 U/ml at 48 hours post-dose 5 (primary endpoint) in 83% of patients and ≥ 0.1 U/ml 72 hours post dose 6 (secondary endpoint) in 43% of patients.

Neutralising antibodies
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.

Cerebrospinal fluid activity
After IM administration of 25 000 U/m^2 crisantaspase 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.

5.3 Preclinical safety data

Reproduction toxicity:
In reproductive toxicity studies, L-asparaginase was seen to cross the placenta in rabbits. Teratogenic effects have been observed in rabbits, rats and mice at or below the clinically relevant doses. Malformations of the lungs, kidneys and skeleton (spina bifida, abdominal expulsion, no tail) were seen in rabbits. Treatment of pregnant rats and mice produced exencephaly and skeletal anomalies.

Fertility
There are no relevant findings on male and female embryonic developments in rats at doses up to 50% of the recommended human dose when adjusted for the total body surface area, which was the highest dose tested in this study.

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
3 years.

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 unless the reconstitution method precludes the risk of microbiological contamination. If not used immediately, the user is responsible for the storage times and conditions.

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 unless the reconstitution method and dilution preclude the risk of microbiological contamination. If not used immediately, the user is responsible for the storage times and conditions.

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 and other handling

The contents of each vial should be reconstituted in 1 ml or 2 ml of saline solution (0.9%) for injection.

When reconstituted with 1 ml, the resultant concentration is 10 000 U/ml. When reconstituted with 2 ml, the resultant concentration is 5 000 U/ml.

Slowly add the saline solution (0.9%) for injection against the inner vial wall, do not add it directly onto or into the powder. Allow the contents to dissolve by gentle mixing or swirling, maintaining the vial in an upright position. Avoid 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 particles of protein aggregates may be visible if shaking is excessive, resulting in visible foaming. If there are any visible particles or protein aggregates present, the reconstituted solution should be rejected.

The reconstituted 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 an aseptic glass or polypropylene syringe under sterile conditions. The reconstituted solution should then be stored below 25 °C and used within 4 hours.

For IV infusion, it is recommended to further dilute the reconstituted Erwinase solution in 100 ml saline solution (0.9%). To make preparation easier, the reconstituted Erwinase solution can be transferred directly to a bag prefilled with 100 ml saline (0.9%) for infusion.

It is recommended that the diluted solution for infusion should be used immediately after preparation. If not used immediately, the diluted solution for infusion can be stored in the infusion bag (see section 6.3).

Erwinase is not a cytotoxic medicinal product and does not require the special precautions needed for manipulating such agents. Nevertheless, when preparing or administering Erwinase the fact should be taken into account that it can be sensitising.

Inhalation of the powder or the solution should be avoided. In the event of it coming into contact with the skin or mucous membranes, in particular with the eyes, these should be rinsed with plenty of water for at least 15 minutes.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Porton Biopharma Limited
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8 MARKETING AUTHORISATION NUMBER

PA23208/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18th June 2021
Date of last renewal: 7th October 2025

10 DATE OF REVISION OF THE TEXT

May 2025