

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Erwinase 10,000 Units. Powder for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Crisantaspase (Asparaginase from *Erwinia chrysanthemi*; *Erwinia* L-asparaginase), 10,000 Units/vial.

Excipients with known effect:

Glucose monohydrate: 5 mg / vial

Sodium chloride: 0.5 mg / vial

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection.

White solid in a vial.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Erwinase is used in combination with other antineoplastic agents to treat acute lymphoblastic leukaemia.

Patients receiving treatment with L-asparaginase from *Escherichia coli* and who develop hypersensitivity to that enzyme may be able to continue treatment with Erwinase as the enzymes are immunologically distinct.

4.2 Posology and method of administration

Erwinase should be prescribed and administered by physicians and/or health care personnel experienced in the use of antineoplastic products. It should only be given in a hospital setting where appropriate resuscitation equipment is available. Patients should be closely monitored and carefully observed for any adverse reactions throughout the administration period (see section 4.4).

Posology

Reference to current recognised acute lymphoblastic leukaemia protocols should be made for information on dose, route and frequency of treatment.

Method of administration

Erwinase solution can be given by intravenous infusion or intramuscular injection.

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

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

4.3 Contraindications

- History of severe hypersensitivity reaction to crisantaspase 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

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.

Special precautions for use

Erwinase should only be administered by consultant haematologists/oncologists with adequate laboratory facilities for monitoring its use.

Erwinase should preferably be given without interruption. If, however, an interruption cannot be avoided, treatment should be resumed with a low dose, 300 Units/m²/day (10 Units/kg/day), and increased to the full dose over five days if tolerated.

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 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.

Anaphylaxis is uncommon but facilities should be made available for its management during administration. If a severe reaction occurs, Erwinase must be discontinued (see section 4.3).

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

Asparaginase is a bacterial protein and repeated use can therefore, lead to sensitisation reactions.

Pancreatitis

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 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.

Glucose Intolerance

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.

Administration of insulin and possibly discontinuation of L-asparaginase treatment may be necessary to manage hyperglycemia.

Coagulation Disorders

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 regularly 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 be continued according to protocol if the benefit of continued administration is considered to outweigh the risk from re-exposure.

Hepatic Effects

Treatment with L-asparaginase, including Erwinase, 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. hypoalbuminemia (see also Coagulation Disorders and section 4.8).

Hepatic function tests 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 must 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 Erwinase (see section 4.8).

PRES is characterised in magnetic resonance imaging (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 hyperammonemia, if present, may cause or contribute to CNS toxicity, consider measuring 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.

Tumor Lysis Syndrome, Renal Impairment

Tumor cell destruction can result in hyperuricemia, tumor lysis syndrome and urate nephropathy. Renal impairment may be caused or aggravated by the chemotherapy regimen. Renal function tests and serum uric acid levels should be monitored.

Immunosuppression, Infections

L-asparaginase has been reported to have immunosuppressive activity in animal experiments. The possibility that use of Erwinase in man may predispose to infection should be considered, as Erwinase is used concomitantly with other agents that can reduce immune response and increase the risk for infections.

4.5 Interaction with other medicinal products and other forms of interactions

No formal interaction studies have been performed,

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

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, 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 effectiveness of methotrexate and cytarabine is unknown. 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.
- **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.
- **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 (see section 4.6). **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 Erwinase.

4.6 Fertility, pregnancy and lactation

For effects related to the co-administered chemotherapy is referred to the SmPC of the chosen chemotherapy.

Fertility

In animal studies, L-asparaginase decreased sperm counts in male rats (see Section 5.3). It is not known if this finding is relevant for humans.

Pregnancy

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 agents during pregnancy do not provide sufficient data to reach any conclusions. However, based on effects on embryonal/foetal development shown in pre-clinical studies (see section 5.3 Preclinical Safety Data),

Erwinase should not be used during pregnancy unless the benefit justifies the potential risk to the foetus.

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.

Breast-feeding

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 breast-fed children cannot be excluded, therefore Erwinase should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Erwinase may have a minor influence on the ability to drive and use machines. Dizziness, somnolence and other central nervous system effects may occur following administration of Erwinase (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

The two most frequent adverse reactions are hypersensitivity, including urticaria, angioedema, bronchospasm, hypotension or even anaphylactic shock. In case of severe hypersensitivity reaction, treatment should be discontinued immediately and withdrawn see section 4.4.

Coagulation abnormalities (e.g. thrombosis), due to protein synthesis impairment, are the second most frequent class of adverse reactions. Thrombosis of peripheral, pulmonary or central nervous system blood vessels have been reported, potentially fatal or with residual delayed effects 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

Adverse effects reported spontaneously and in the literature, from patients treated with L-asparaginase as part of their chemotherapy regimen, are listed in the table below. Adverse effects are categorised by system organ class and frequency.

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 ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$) and very rare ($<1/10,000$). 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
	Febrile neutropenia ³	Very common
Immune systems disorders	Hypersensitivity reactions (not at or near the site of administration)*	Very common
	Anaphylaxis ⁷	Uncommon
Metabolism and nutrition disorders	Hyperlipidemia, including increased cholesterol, and hypertriglyceridemia	Very common
	Weight loss ⁴	Very common
	Hyperglycemia	Very common
	Diabetic ketoacidosis	Uncommon
	Hyperammonemia	Uncommon
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 ischemic events ^{2,7}	Common
	Hemorrhage 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
	Hypoalbuminemia ⁹	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	Renal impairment	Uncommon
General disorders and administration site conditions	Mucositis	Common
	Pyrexia	Common
	Injection site and local hypersensitivity reactions ¹¹ including late-onset reactions ¹²	Common
	Pain	Common
	Fatigue	Common
Investigations	Increases in blood urea nitrogen, and/or serum creatinine	Very common
	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

*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 Severe weight loss (>20%) has also been reported.

⁵ Possibly secondary to a primary adverse reaction such as hyperglycemia, hyperammonemia, encephalopathy, sepsis, cerebrovascular event, hypersensitivity reactions, or effects of other concurrent drug therapy.

⁶ Neurotoxicity unrelated to an underlying clinical condition has been reported with other L-asparaginase products.

⁷ Including peripheral, venous, pulmonary, cerebral (e.g., sinus thrombosis), cardiac (e.g., myocardial infarction), intestinal, renal, hepatic

⁸ Including necrotising, hemorrhagic, and pseudocyst formation

⁹ Hypoalbuminemia can be symptomatic with peripheral oedema

¹⁰ Including myalgia, arthralgia, pain in extremity

¹¹ Including injection site urticaria, rash, pruritus, erythema, pain, oedema, swelling, induration, hematoma

¹² A delayed local skin reaction with blisters has been reported with another L-asparaginase product.

¹³ The following have been documented with Erwinase: decreased antithrombin III, Protein C and Protein S activity; decreased fibrinogen levels. Decreased plasminogen levels have been reported with E. coli-derived L-asparaginase.

¹⁴ Including prolonged activated partial thromboplastin time, prothrombin time, and INR.

Description of selected adverse reactions

Hypersensitivity

Including reactions consistent with anaphylactic reactions (e.g., hypotension, bronchospasm/wheezing, hypoxia, respiratory distress/dyspnea, 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 (see section 4.4).

Posterior reversible encephalopathy syndrome

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

Immunogenicity

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

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

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.

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. Patients who accidentally receive an overdose of L-asparaginase should be monitored closely and receive any appropriate symptomatic and supportive treatment. L-asparaginase can cause chronic intoxication, characterised by impaired liver or kidney function. The administration of L-asparaginase should be stopped immediately and symptomatic treatment commenced straight away.

5 PHARMACOLOGICAL PROPERTIES

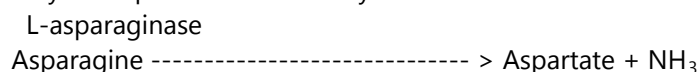
5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents

ATC code: L01XX02

Mechanism of action

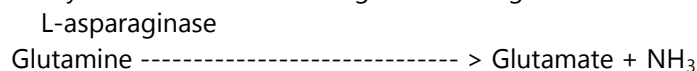
L-asparaginase catalyses the deamination of asparagine to aspartic acid with the release of ammonia. The biochemical reaction may be depicted schematically as follows:



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.

Neoplastic cells associated with Acute Lymphoblastic Leukaemia (ALL) are asparagine-dependent. Reduction of plasma asparagine levels achieved by administration of L-asparaginase produces an anti-neoplastic effect.

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 Erwinase after i.v. infusion is 6.4 ± 0.5 hours.

The half-life of Erwinase after i.m. injection is about 16 hours.

L-asparaginase penetrates through to the cerebrospinal fluid to a small degree and is also found in lymph.

Serum trough asparaginase activity ≥ 0.1 IU/mL has been demonstrated to correlate with asparagine depletion (asparagine < 0.4 mcg/mL or $3 \mu\text{M}$) and to serum levels that predict clinical efficacy.

With repeated use, the drug may be bound by specific antibodies and eliminated.

IM study:

The serum trough concentrations of crisantaspase were determined in 48 ALL patients aged ≥ 2 year to ≤ 18 years enrolled in a single-arm study, multi-centre, open-label, safety and clinical pharmacology trial 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 IU/mL.

Following intramuscular administration at a dose of $25,000 \text{ IU/m}^2$ for the first course, serum asparaginase activity is maintained above 0.1 IU/mL at 48 hours post-dose in 92.5% of patients, and at least at 0.1 IU/mL after 72 hours in 88.5% of patients.

IV Study:

The serum trough asparaginase activity was determined in 24 ALL patients aged ≥ 1 year to ≤ 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 2-day nadir (trough) serum asparaginase activity levels (48-hour levels taken after the fifth dose) that were ≥ 0.1 IU/mL in the first 2 weeks of Erwinase 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 $25,000 \text{ IU/m}^2$ for the first course, serum asparaginase activity was maintained ≥ 0.1 IU/mL at 48 hours post-dose 5 (primary endpoint) in 83% of patients, and ≥ 0.1 IU/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 $25,000 \text{ U/m}^2$ 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

Acute toxicity:

LD₅₀ i.p. in mice: 5×10^5 IU/kg
LD₅₀ i.p. in rabbits: 12,000 IU/kg
LD₅₀ i.p. in rats: 3,200 IU/kg

Subacute and chronic toxicity:

No pathological effects were observed at doses of up to $1,000 \text{ IU/kg/day}$ in rabbits, up to $5,000 \text{ IU/kg/day}$ in dogs and up to $10,000 \text{ IU/kg/day}$ in Rhesus monkeys (for comparison: the recommended daily doses correspond to approximately 200 IU/kg). In rats and mice, subdural bleeding and renal tubuli damage occurred at very high doses.

Reproduction toxicity:

The product has been shown to be able to cross the placenta in rabbits, and embryotoxicity studies with Erwinia L-asparaginase have given evidence of teratogenic potential in rabbits. Animal studies provide evidence of injury to the embryo (malformation, foetal death). In view of asparagine depletion, teratogenic effects are anticipated.

Fertility

In a fertility and early embryonic development study in rats, crisantaspase had no effect on male or female fertility when administered IM at doses of up to $2,000 \text{ IU/kg}$ (approximately 50% of the recommended human dose, when adjusted for total body surface area) every other day for a total of 35 doses. Findings in male rats included a decrease in sperm count by approx. 12 to 15% at doses of 500 to $2,000 \text{ IU/kg}$ (approximately 12 to 50% of the recommended human dose).

Carcinogenicity:

No genotoxicity or carcinogenicity studies have been conducted on *Erwinia* sp. asparaginase.

Asparaginase from *Erwinia chrysanthemi* is an enzyme, for which the structure and well documented activity do not suggest any carcinogenic or mutagenic potential. *In vitro*, no karyotype changes occurred, only a deceleration or arrest of the rate of mitosis (cytostatic effect).

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Sodium Chloride
Glucose Monohydrate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. See section 4.5 Interaction with Other Medicinal Products and Other Forms of Interaction.

6.3 Shelf life**Shelf-life of product as packed for sale**

3 years

Shelf life following reconstitution according to directions: 15 minutes in the original container, 4 hours in a polypropylene syringe.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 4 hours when stored below 25°C unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store between 2°C and 8°C.

For storage conditions of the reconstituted medicinal product, *see section 6.3*.

6.5 Nature and contents of container

Type I clear neutral glass vials of 3 ml nominal capacity, closed with 13 mm bromobutylstoppers and aluminium overseals containing a white lyophilised solid. Pack size of 5 vials.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

The contents of each vial should be reconstituted in 1 ml to 2 ml of sodium chloride (0.9%) solution for injection. Slowly add the reconstitution solution against the inner vial wall, do not squirt directly onto or into the powder. Allow the content to dissolve by gentle mixing or swirling maintaining the vial in an upright position. 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 resulting in visible foaming. If there is any visible particles or protein aggregates present the reconstituted solution should be rejected.

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 polypropylene syringe for the period of the delay. The solution should be used within 4 hours and stored below 25°C.

Erwinase is not a cytotoxic drug (such as vincristine or methotrexate) 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.

It should be handled in the same way as other therapeutic enzymes such as hyaluronidase.

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 in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Jazz Pharmaceuticals France SAS
City One
84 Quai Charles de Gaulle
69006 Lyon
France

8 MARKETING AUTHORISATION NUMBER

PA1020/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 1998

Date of last renewal: 18 September 2013

10 DATE OF REVISION OF THE TEXT

March 2020