STERIMAX
2770 Portland Drive, Oakville, Ontario, Canada L6H 6R4
Tél.: 905-890-0661, 1-800-881-3550 ● Fax: 905-890-0508, 1-877-546-7667 ● Web: www.sterimaxinc.com

Importation d'ERWINASE® pour injection, sous étiquette britannique, pour permettre aux patients un accès continu à ERWINASE® pour injection

Date : 2021/04/27

Destinataires

Professionnels de la santé (oncologues médicaux, hématologues, infirmières en oncologie, pharmaciens), chefs des services de médecine dans les hôpitaux, chefs des services de pharmacie dans les hôpitaux, cliniques d'oncologie.

Messages clés

- Afin de maintenir l'accès des patients à ERWINASE, ERWINASE sous étiquette britannique est maintenant disponible.

- ERWINASE (Erwinia L-asparaginase) pour injection est indiquée dans le traitement des patients atteints de leucémie lymphoblastique aiguë (LLA) où on l'emploie principalement en association avec d'autres agents antinéoplasiques pour induire une rémission chez les enfants et les adultes atteints de cette maladie. On peut également l'utiliser pour traiter les patients ayant acquis une hypersensibilité (mais non une anaphylaxie) à la L-asparaginase issue de *E. coli*. Erwinase pour injection ne doit pas être utilisée comme seul agent d'induction, à moins qu'un traitement d'association ne soit jugé inapproprié.

- Santé Canada a autorisé l'importation et la distribution exceptionnelles des flacons d'ERWINASE pour injection, étiquetés au Royaume-Uni, pour des lots limités.

- La concentration de l'ERWINASE, étiquetée au Royaume-Uni, est la même que celle de l'ERWINASE pour injection précédemment autorisée au Canada.

- Les professionnels de la santé sont informés que l'ERWINASE pour injection, étiquetée au Royaume-Uni, ne comporte pas d'étiquetage en français.

- On rappelle aux professionnels de la santé qu'il existe certaines différences entre l'étiquetage canadien et britannique précédemment autorisé (voir les tableaux 1 et 2). Les professionnels de la santé doivent consulter la monographie d'ERWINASE pour prendre connaissance des renseignements thérapeutiques du produit.

Quel est le problème ?

Étant donné que le numéro DIN d'Erwinase est annulé et que Porton Biopharma Ltée est en train d'obtenir une nouvelle licence et une autorisation pour Erwinase au Canada, l'Erwinase sous étiquette britannique sera fournie au Canada en vertu d'une importation exceptionnelle.

Produits concernés

ERWINASE® (produit étiqueté au Royaume-Uni)
10 000 UI poudre pour solution pour injection / perfusion. PL 44403/0002

Numéros de lot : W060172 (lot PBL 206) et lots PBL 208, 209 et 210.
Fabricant : Porton Biopharma Ltée, Porton Down, Salisbury, SP4 0JG, Royaume-Uni
Distributeur au Canada : SteriMax Inc., 2770 Portland Drive, Oakville, Ontario L6H 6R4.

Informations générales
ERWINASE pour injection (Erwinia L-asparaginase) est indiquée dans le traitement des patients atteints de leucémie lymphoblastique aiguë (LLA) où on l'emploie principalement en association à d'autres agents antinéoplasiques pour induire une rémission chez les enfants et les adultes atteints de cette maladie. On peut également l'utiliser pour traiter les patients ayant acquis une hypersensibilité (mais non une anaphylaxie) à la L-asparaginase issue de *E. coli* (8, 9, 11). Erwinase pour injection ne doit pas être utilisée comme seul agent d'induction, à moins qu'un traitement d'association ne soit jugé inapproprié.

Jazz Pharmaceuticals a annoncé l'arrêt de la distribution du produit ERWINASE à partir d'avril 2021.

À l'heure actuelle, Sterimax Inc. ne commercialise pas ERWINASE pour injection au Canada.

Informations destinées aux professionnels de la santé
Le produit ERWINASE, étiqueté au Royaume-Uni, provient de lots mondiaux et est le même que le produit canadien précédemment disponible quant à sa composition.

Il convient de noter les différences suivantes entre l'étiquetage canadien et britannique actuellement approuvé. Il convient également de noter que l'étiquetage du Royaume-Uni ne comporte pas d'information en français. Se reporter à l'annexe 1 pour l'étiquette intérieure d'ERWINASE, l'étiquette extérieure et le Résume des caractéristiques du produit de l'Union européenne approuvé au Royaume-Uni.

TABLEAU 1 : ÉTIQUETTE DU FLACON D'ERWINASE

Section de l'étiquette	Royaume-Uni	Canada
Nom du produit	*(English only / En anglais seulement)* Erwinase® 10,000 IU **powder for solution for injection/infusion** 10,000 IU /vial	Erwinase® 10 000 U. **Poudre lyophilisée stérile**
	Crisantaspase (L-asparaginase from *Erwinia chrysanthemi*)	***Erwinia* L-asparaginase**
Reconstitution	*Not reported on the vial label*	Dissoudre dans 1 ou 2 mL de chlorure de sodium injectable, USP.
Détenteur de l'autorisation de mise en marché	Porton Biopharma Limited Porton Down Salisbury SP4 0JG	Jazz Pharmaceuticals France SAS
Excipients	Sodium Chloride, Glucose Monohydrate	*Non-identifiés sur l'étiquette du flacon*
Distributeur / Représentant local	*Not reported on the vial label*	CGF Pharmatech Inc. Montréal, Canada
Numéro d'AMM	PL44403/0002	DIN 02237815 Remarque : Le DIN est annulé au Canada par le titulaire du numéro d'AMM.
Autre	For intravenous or intramuscular use Store in refrigerator (+2°C to +8°C)	Consulter la notice ci-incluse

TABLE 2 : ÉTIQUETTE DE LA BOÎTE		
Section de l'étiquette	**Royaume-Uni**	**Canada**
Toutes les sections	*English only / En anglais seulement*	*Portion en français*
Nom du produit	Erwinase® 10,000 IU **powder for solution for injection/infusion**	Erwinase® 10 000 unités **Poudre lyophylisée stérile** antileucémique
	Crisantaspase (L-asparaginase from *Erwinia chrysanthemi*)	***Erwinia* L-asparaginase pour injection**
	Each vial contains: 10,000 IU of Crisantaspase (L-asparaginase from *Erwinia chrysanthemi*)	Chaque flacon contient : *Erwinia* L-asparaginase 10 000 unités
Détenteur de l'autorisation de mise en marché	Porton Biopharma Limited Porton Down Salisbury SP4 0JG	Jazz Pharmaceuticals France SAS Lyon, France 69006
Excipients	Sodium Chloride, Glucose Monohydrate	Glucose **5 mg;** Chlorure de sodium **0.5 mg**
Forme et contenu pharmaceutiques	Powder for solution for injection/infusion 5 vials	Poudre lyophylisée stérile pour injection
Reconstitution	Reconstitute before use. See package leaflet for further instructions.	Dissoudre dans 1 ou 2 mL de chlorure de sodium injectable, USP. Agiter doucement pour dissoudre la poudre. Utiliser seulement si la solution est limpide.
Distributeur / Représentant local	*Not reported on the vial label*	CGF Pharmatech Inc. Montréal, Québec H4T 1A7
Numéro d'AMM	PL44403/0002	DIN 02237815
Autre	For intravenous or intramuscular use Read the package leaflet before use. Medical product subject to medical prescription. Store in refrigerator (+2°C to +8°C). Keep out of the sight and reach of children.	Ne contient pas d'agents de conservation. Pour la posologie et le mode d'emploi, consulter la notice du produit.

Pour obtenir les renseignements thérapeutiques complets, y compris la posologie et le mode d'administration, veuillez consulter la notice d'ERWINASE sous étiquette britannique jointe à la boîte et à la présente lettre.

ERWINASE sous étiquette britannique doit être reconstituée dans 1 à 2 mL de solution de chlorure de sodium (0,9 %) pour injection. Veuillez vous référer à la notice britannique fournie pour obtenir des renseignements supplémentaires sur la description, la teneur et la stabilité de la solution après sa reconstitution. Veuillez prendre note que la notice du Royaume-Uni est en anglais et n'est pas disponible en français.

Suite à la reconstitution, inspectez soigneusement le produit reconstitué. La solution doit être limpide et sans particules visibles. De fins agrégats de protéines cristallins ou filiformes peuvent être visibles si l'agitation est excessive. Si des particules ou des agrégats protéiques sont visibles, la solution reconstituée doit être rejetée.

En cas de problème lié au produit ou à la sécurité, veuillez en informer SteriMax OU Porton Biopharma. Reportez-vous à la section « Signaler un problème de santé ou de sécurité » pour obtenir les coordonnées des personnes à contacter.

Signaler un problème de santé ou de sécurité
La prise en charge des effets secondaires liés aux produits de santé dépend des professionnels de la santé et des consommateurs qui les signalent. Tout cas d'effet secondaire grave ou inattendu chez les patients recevant ERWINASE doit être signalé à SteriMax Inc. ou à Santé Canada.

SteriMax Inc.,
2770, Portland Drive
Oakville, Ontario L6H 6R4
Téléphone : +1-800-881-3550
Télécopieur : +1 -877-546-7667
Courriel : pv@sterimaxinc.com OU drugsafety@portonbiopharma.com.

Contactez medinfo@sterimaxin.com OU medinfo@portonbiopharma.com pour obtenir de l'information médicale sur ERWINASE.

Pour corriger votre adresse postale ou votre numéro de télécopieur, contactez Sterimax Inc.

Vous pouvez signaler les effets indésirables soupçonnés d'être associés à l'utilisation de produits de santé de Santé Canada :

- En composant le numéro sans frais 1-866-234-2345; ou
- En consultant la page Web de MedEffect^{MC} Canada sur la déclaration des effets secondaires (https://www.canada.ca/fr/sante-canada/services/medicaments-produits-sante/medeffet-canada/declaration-effets-indesirables.html) pour vous renseigner sur la marche à suivre pour signaler un effet secondaire en ligne, par la poste ou par télécopieur.

Copie originale signée par

Ritesh Acharya, M. Pharm.
Vice-Président exécutif, Affaires scientifiques
SteriMax Inc., Oakville, Ontario

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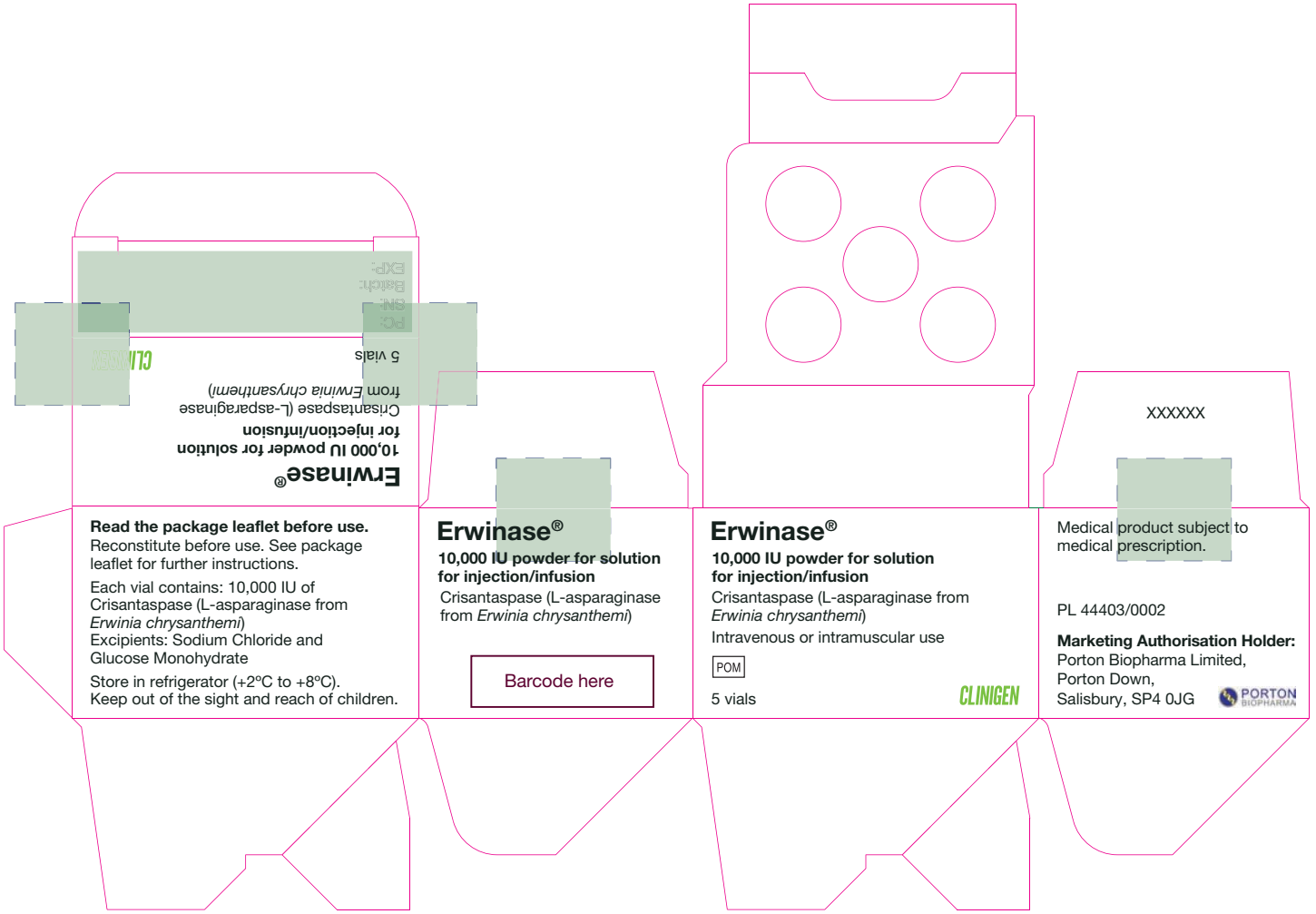
Annex 1: ERWINASE UK inner label, outer label and the EU SmPC



Erwinase®
10,000 IU powder for solution for injection/infusion
Crisantaspase (L-asparaginase from *Erwinia chrysanthemi*) 10,000 IU/vial
Excipients : Sodium chloride and Glucose Monohydrate
For intravenous or intramuscular use
Store in refrigerator (+2°C to +8°C)
Marketing Authorisation Holder : PL 44403/0002
Porton Biopharma Limited, Porton Down, Salisbury, SP4 0JG
xXXXXXXX
Batch :
EXP :

Erwinase®

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Erwinase, 10,000 IU/vial, Powder for solution for injection/infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Crisantaspase (L-asparaginase from *Erwinia chrysanthemi*), 10,000 International units/vial.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.
White lyophilised powder in a vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Erwinase is indicated as a component of a chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukaemia (ALL) who have developed hypersensitivity to *E. coli*-derived asparaginase.
Erwinase is indicated in paediatric patients from the age of 4 months and in adults.

4.2 Posology and method of administration

Posology
The recommended dosage is 20,000 or 25,000 IU/m^2 body surface area administered three times a week (e.g., Monday/Wednesday/Friday).
Therapy should be adjusted according to local treatment protocols.

Method of administration
Erwinase solution can be given by intravenous infusion or intramuscular injection.
For IV infusion, the reconstituted solution should be further diluted in 100 mL of normal saline and administered over 1 to 2 hours.
For IM injection the volume of reconstituted solution administered at a single injection site should not exceed 2 mL. Multiple injection sites should be used if this volume is exceeded.
For further instructions on reconstitution 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
- 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.

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.
Facilities should be made available for management of an anaphylactic reaction, should it occur, during administration. If a severe reaction occurs, Erwinase must be discontinued (see section 4.3).
Careful observation is required on re-exposure to L-asparaginase after any time interval (e.g. between induction and consolidation), which may increase the risk of anaphylactic and hypersensitivity reactions occurring.

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 during treatment. Preventive measures must be considered.
If significant symptomatic coagulopathy occurs in addition to other clinically indicated interventions withhold Erwinase treatment until resolved. Treatment may then continue according to protocol, if the benefit of continued administration is considered to outweigh the risk from re-exposure.

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 section 4.5).
In case of severe hepatic adverse reactions, discontinuation of Erwinase should be considered until complete or near-complete (CTCAE Grade 1) 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.

Renal Impairment
Renal impairment may be caused or aggravated by the chemotherapy regimen. Renal function and serum uric acid levels should be monitored.

Immunosuppression: Infections
L-asparaginase has been reported to have immunosuppressive activity in animal experiments.
This should be considered because 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 interaction

No formal medicinal product interaction studies have been performed.
Asparaginase must not be mixed with any other medicinal products prior to administration.
In addition concomitant use of L-asparaginase and medicinal products affecting liver function may increase the risk of a change in liver parameters (e.g. increase of ASAT, ALAT, bilirubin).
Since an indirect interaction between components of the oral contraception and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. Another method than oral contraception should be used in women of childbearing potential (see section 4.6).

- Methotrexate, cytarabine

L-asparaginase may diminish or abolish methotrexate's and cytarabine's effect on malignant cells; this effect persists as long as plasma asparagine levels are suppressed. Accordingly, do not use methotrexate or cytarabine with, or following L-asparaginase, while asparagine levels are below normal.
Alternatively, administration of L-asparaginase after methotrexate or cytarabine results in a synergistic effect. The extent to which these affect the overall effectiveness of established treatment protocols is not known.

- Prednisone

Concomitant use of prednisone and L-asparaginase may increase the risk of a change in clotting parameters (e.g. a decrease in fibrinogen and ATIII levels).

- Vincristine

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

4.6 Fertility, pregnancy and lactation

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 during pregnancy did not provide sufficient data to conclude. However, based on effects on embryonal/foetal development shown in pre-clinical studies (see section 5.3),
Erwinase should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

Women of childbearing potential/Contraception in males and females
Women of childbearing potential should use effective contraception and avoid becoming pregnant while being treated with asparaginase-containing chemotherapy.
Since an indirect interaction between components of the oral contraception and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe in such clinical situation. A method other than oral contraceptives should be used in women of childbearing potential.
Men should use effective contraceptive measures and be advised to not father a child while receiving asparaginase.
The time period following treatment with asparaginase when it is safe to become pregnant or father a child is unknown. As a precautionary measure it is recommended to wait for three months after completion of treatment. However, treatment with other chemotherapeutic agents should also be taken into consideration.

Breast feeding
It is not known whether crisantaspase (*Erwinia* L-asparaginase) is excreted in human breast milk. Potential serious adverse reactions may occur in nursing infants, therefore Erwinase should be discontinued during breast-feeding.

Fertility
There are no human data on the effect of crisantaspase on fertility. In rats, crisantaspase did not affect male and female fertility. However, a decrease in sperm count was observed in male rats (see section 5.3). The relevance of this finding to humans is not known.

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, fever, arthralgia angioedema, bronchospasm, hypotension or even anaphylactic shock. In case of severe systemic hypersensitivity reaction, treatment should be discontinued immediately and withdrawn.
- Coagulation abnormalities (e.g. thromboses), due to protein synthesis impairment, are the second most frequent class of adverse reactions. Thromboses of peripheral, pulmonary or central nervous system blood vessels have been reported, potentially fatal or with residual delayed affects dependent upon the location of the occlusion. Other risk factors contributing to coagulation abnormalities include the disease itself, concomitant steroid therapy and central venous catheters.

Undesirable effects are generally reversible.

b. Tabulated list of adverse reactions
The adverse reaction data presented in Table 1 have been identified from 3 clinical studies (100EUSA12, ALL07P2, and Erwinase Master Treatment Protocol [EMTP]) with Erwinase in 1028 patients (primarily pediatric patients), the majority having acute lymphoblastic leukemia, as well as post-marketing experience with Erwinase and other L-asparaginase preparations in pediatric and adult patients.
Some of the adverse reactions listed below are known to be associated with multi-agent chemotherapeutic regimens (e.g., reactions resulting from bone marrow depression, and infections), and the contributory role of Erwinase is not clear. In individual cases of other adverse reactions, other medicinal products of the regimen may have contributed.
Frequency definitions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10000 to <1/1000) and very rare (<1/10000).When no valid estimate of the incidence rate for an adverse event from available data can be calculated, the frequency of such ADR has been classified as "Not known".

Table 1. : Adverse Reactions

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

DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Erwinase®

Package leaflet: Information for the patient **10,000 IU**

Powder for solution for injection/infusion Crisantaspase (L-asparaginase from *Erwinia chrysanthemi*)

Read all of this leaflet carefully before you start receiving this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Erwinase is and what it is used for

How does Erwinase work
Erwinase is an anti-blood-cell-cancer treatment from the pharmacotherapeutic group: Antineoplastic and immunomodulating agents. It works by lowering the levels of asparagine in your body, a substance the cancer cells need to survive.

What this medicine is used for
Erwinase is used for the treatment of a cancer of the white blood cells called Acute Lymphoblastic Leukaemia, in patients aged 4 months and above, who have developed allergic reactions to *E.coli*-derived asparaginase.

Erwinase may be used alone or with other treatments.

2. What you need to know before you are given Erwinase

You should not be given Erwinase if :
- you have previously had a severe allergic reaction to the active substance (Crisantaspase-L-asparaginase from *Erwinia chrysanthemi*) or are allergic to any of the other ingredients of this medicine (see section 6).
- You have, or have previously, had serious problems with your pancreas (severe pancreatitis) from using a medicine containing L-asparaginase
- You have serious problems with your pancreas (severe pancreatitis)

Warnings and precautions
Talk to your doctor or pharmacist or nurse before taking Erwinase.
The following complications may arise during treatment with Erwinase:
- Serious life threatening allergic reactions. The hospital will have the necessary precautions in place to deal with such situations.
- Inflammation of the pancreas. If you experience abdominal pain this may be a sign of pancreatitis and should be reported to your doctor immediately. Fatal outcomes associated with pancreatitis have occurred.
- Increases in your blood sugar levels (Hyperglycemia). This can be controlled by receiving insulin sometimes even to fatal amounts (Hyperglycemia). This can be controlled by receiving insulin.
- Bleeding and blood clot disorders. During treatment your body's ability to prevent excessive bleeding may be affected. In the case you experience any significant bleeding your treatment will be stopped. Your doctor will determine if, and when, treatment can be restarted.
- Liver dysfunctions can be caused or worsened. Discontinuation of Erwinase will be considered in the event of a severe reaction. Treatment can be restarted under close monitoring, but only once at least near complete recovery is achieved.
- Neurological disorders have been reported with fatal outcomes. Posterior reversible encephalopathy syndrome (characterised by headache, confusion, seizures and visual loss) may require blood-pressure lowering medicines and in case of seizure, anti-epileptic treatment.
- Kidney impairment due to high levels of a substance called uric acid in your blood from the chemotherapy.
- Reduced immune system that may increase your chances of an infection.

Monitoring during treatment with Erwinase
You will be monitored closely during and after treatment with Erwinase for:
- Allergic reactions
- Pancreas, kidney and liver functions
- Normal blood content

For traceability purposes your health care professional will record the product name and batch number for each dose of Erwinase you receive.

Other medicines and Erwinase
Tell your doctor or your pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, particularly any of the following:
- Types of medicines used to treat cancer called 'methotrexate' or 'cytarabine' as they can affect the way Erwinase works.
- Prednisone which is used in cancer treatment may increase the risk of a change in clotting.
- Vincristine which is used in cancer treatment, this can increase the toxic effects of both medicinal products and increase the risk of anaphylaxis.
- Oral contraceptives.

Your doctor or your nurse will not mix Erwinase with other medicines in the same infusion.
However you will probably be given other medicines before, during or after Erwinase treatment as part of your course of therapy.

Pregnancy
If you are pregnant, think you may be pregnant, or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breastfeeding
You must not breast-feed your baby during your treatment with Erwinase, there may be a risk to the feeding child.

Fertility & Family planning
Potential for a decrease in male fertility cannot be out ruled.
When appropriate both men and women should use necessary contraceptive measures before, and for at least three months after treatment with Erwinase. Women should use a form of contraception other than oral contraceptives.

Driving and using machines
Erwinase can cause dizziness and drowsiness. This can affect your coordination and therefore your ability to drive and operate machinery.

Erwinase contains sodium and glucose
Erwinase contains the following ingredients :
- **sodium** (less than 23 mg per dose). You can consider this medicine as essentially sodium free if you are on a salt-free or low-salt diet.
- **glucose.** If you are diabetic, please note that each bottle of Erwinase contains 5 mg glucose.

3. How Erwinase is given

Dosage
Erwinase will only be given to you by health care professionals who are experienced in giving chemotherapy.
Your doctor will decide what dose to administer, how often you will be given Erwinase and for how long. It varies according to your body weight, your specific condition being treated, and your response to therapy.

Method of administration
Erwinase can be given to you in one of the following ways:
a) Into a vein (intravenous use). This may be given over 1 to 2 hours.
b) Into a muscle (intramuscular use).

If you are given more Erwinase than you should
If you are concerned that you have been given too much Erwinase, contact your doctor or another healthcare professional immediately.

If you think you have missed a dose of Erwinase
If you are concerned that you have missed a dose, contact your doctor or another healthcare professional immediately.
If you have any further questions on this product, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, Erwinase can cause side effects, although not everybody gets them.
Erwinase will be given under strict medical supervision and your doctor may give you other medicines to treat these side effects. Most of the side effects will stop once you stop taking Erwinase.

Serious side effects
Tell your doctor immediately if you experience:
- Severe allergic reactions including blue discolouration of the lips and extremities (possible symptoms of hypoxia), swelling of the face and/or, shortness of breath, increased heart rate; wheezing, difficulty swallowing, hay fever like symptoms, rash, chills, flushing, high or low blood pressure, vomiting
- Redness, pain, swelling, bruising, or hardening of the skin at the site of the injection
- Damage to the Central Nervous System symptoms may include coma, encephalopathy, hallucinations, muscle weakness, confusion, dizziness, drowsiness, agitation, difficulty speaking
- Arm, leg or calf pain with or without swelling (symptoms of blood clots in the arm or leg), abdominal pain (symptoms of a blood clot in the area of the stomach, intestines, and kidneys) chest pain spreading to the arms, neck, jaw, back or stomach, feeling sweaty and breathless (which may be symptoms of a heart attack/ myocardial infarction)
- Pain near your stomach or in your back (this may be inflammation of your pancreas)
- High blood sugar levels (hyperglycemia)
- Increased frequency of bleeding events including bruising even if you have not been injured
- Changes in liver functions (identified by laboratory testing)

Other side effects
Talk to your doctor if you get any of the following:

Very common side effects (may affect more than 1 in 10 people):
- Infections, including blood infections caused by bacteria (sepsis). This may be due to low levels of white cells in your blood. You may experience fever, a rapid heart rate, confusion or a rash.
- Decreases in normal blood content. Some of which may be due to reduced bone marrow activity.
- Increase in blood fats, bilirubin, creatinine, urea levels and certain liver enzymes- your doctor will monitor these.
- Weight loss
- Generalised pain/Muscle pains
- Nausea

Common (may affect up to 1 in 10 people) side effects include:
- Difficulty breathing or stopping breathing
- Mucositis (inflammation of the digestive tract)
- Diarrhoea
- Abdominal pain/discomfort
- tiredness or headache
- High temperature

Uncommon (may affect up to 1 in 100 people) side effects include:
- Life threatening complications of uncontrolled diabetes
- High blood levels of ammonia
- Fits (convulsions)
- Build up of fats in the liver
- Kidney dysfunction

Rare (may affect up to 1 in 1,000 people) side effects include:
- Posterior reversible encephalopathy syndrome (a condition characterised by headache, confusion, seizures and visual loss).

Not known (frequency cannot be estimated from the available data)
- Inflammation of the salivary gland at the back of the throat
- Liver failure, increased mass of liver, jaundice
- Decreased albumin levels in the blood causing water retention
- Blistering and peeling of the skin (Toxic epidermal necrolysis)
- Joint pain

Additional side effects in children and adolescents
Liver, pancreas and blood clotting side effects may be higher in adults compared to children.

Reporting of side effects
If you get any side effects, talk to your doctor or, pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via MHRA Yellow Card in Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Erwinase

Keep this medicine out of the sight and reach of children.
Erwinase will not be used after the expiry date printed on the label after "EXP". The expiry date refers to the last day of the month.
The unopened Erwinase vials will be stored in a refrigerator (between +2°C to +8°C) by the hospital. After reconstitution, the product should be used within 15 minutes. If the delay is more than 15 minutes, the solution should be withdrawn into a glass or polypropylene syringe and used within 8 hours. The reconstituted product should be stored below 25°C.

6. Contents of the pack and other information

What Erwinase contains
The active substance is crisantaspase (L-asparaginase from Erwinia chrysanthemi). Each vial contains 10,000 International units of cristanaspase (L-asparaginase from Erwinia chrysanthemi).
The other excipients are sodium chloride (See section 2) and glucose monohydrate (See section 2).

What Erwinase looks like and contents of the pack
Erwinase is provided as a powder for solution for injection/infusion.
It comes as a white lyophilized powder in a clear glass bottle with a rubber stopper and an aluminium seal.
Each pack contains 5 glass bottles of powder.

Marketing Authorisation Holder and Manufacturer
Porton Biopharma Limited,
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Porton Down, Salisbury, SP4 0JG
United Kingdom

This leaflet was last revised in June 2020
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DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

Metabolism and nutrition disorders	Hyperlipidemia, including Increased cholesterol, and hypertriglyceridemia	Very common
	Increased amylase and/or lipase	Very common
	Weight loss[8]	Very common
	Hyperglycemia	Very common
	Diabetic ketoacidosis	Uncommon
	Hyperammonemia	Uncommon
Nervous system disorders	Central nervous system (CNS) depression or toxicity[9]	Common
	• Convulsions (grand mal, partial seizures)[10]	Uncommon
	• Encephalopathy[11]	Common
	• Posterior reversible encephalopathy syndrome*	Rare
	Headache	Common
Vascular disorders	Venous and arterial thrombotic, embolic and ischemic events[7,12]	Common
	Haemorrhage[2]	Common
	Hypotension	Uncommon
	Hypertension	Not known
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Common
Gastrointestinal disorders	Pancreatitis[2,13]	Common
	Vomiting	Very common
	Diarrhoea	Common
	Abdominal pain/ discomfort	Common
	Nausea	Very common
	Parotitis	Not known
Hepatobiliary disorders	Increased blood bilirubin, transaminases, alkaline phosphatase	Very common
	Hepatotoxicity	Very common
	• Hepatic steatosis	Uncommon
	• Hepatic failure	Not known
	• Cholestatic jaundice	Not known
	• Hepatomegaly	Not known
	Hypoalbuminemia[14]	Not known
	Increased BSP retention	Not known
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis[2]	Not known
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[15]	Very common
	Reactive arthritis	Not known
Renal and urinary disorders	Renal impairment	Uncommon
General disorders and administration site conditions	Mucositis	Common
	Pyrexia	Common
	Injection site and local hypersensitivity reactions[16] including late-onset reactions[17]	Common
	Fatigue	Common
Investigations	Increases in blood urea nitrogen, and/or serum creatinine[18]	Very common

* See "Description of selected adverse reactions"

[1] Including, for example, bacterial, viral, fungal, and opportunistic infections.
[2] Including fatal outcomes
[3] Resulting from bone marrow depression.
[4] The following have been documented with Erwinase: decreased antithrombin III, Protein C and Protein S activity; decreased fibrinogen levels (As a consequence of inhibition protein synthesis) Decreased plasminogen levels have been reported with *E. coli*-derived L-asparaginase.
[5] Including prolonged activated partial thromboplastin time, prothrombin time, and INR.
[6] Including reactions consistent with anaphylactic reactions (e.g., hypotension, bronchospasm/wheezing, hypoxia, respiratory distress/ dyspnoea, dysphagia, rhinitis, angioedema, urticaria, rash, pruritus, erythema, pallor, and/or malaise); febrile reactions, e.g., with chills, flushing, hypertension, tachycardia, vomiting, nausea, and/or headache; and reactions e.g., with musculoskeletal symptoms such as arthralgia and skin manifestations, such as purpura/petechiae
[7] Severe and immediate systemic reaction.
[8] Severe weight loss (>20%) has also been reported.
[9] CNS depression (e.g., coma, somnolence, lethargy), and other manifestations of neurotoxicity including paresis, aphasia, hallucinations, confusion, agitation, dizziness, headache, possibly secondary to a primary adverse reaction such as hyperglycemia, hyperammonemia, encephalopathy, sepsis, cerebrovascular event, hypersensitivity reactions, or effects of other concurrent drug therapy. Neurotoxicity (e.g., somnolence, lethargy, confusion, dizziness, headache) unrelated to an underlying clinical condition has been reported with other L-asparaginase products.
[10] Seizures can be associated with a cerebrovascular event or metabolic encephalopathy.
[11] Encephalopathy can be a consequence of hyperammonemia.
[12] Including peripheral, pulmonary, cerebral (e.g., sinus thrombosis), cardiac (e.g., myocardial infarction), intestinal, renal, hepatic
[13] Including acute, necrotizing, hemorrhagic, and pseudocyst formation
[14] Hypoalbuminemia can be symptomatic with peripheral edema
[15] Including myalgia, arthralgia, pain in extremity
[16] Including injection site urticaria, rash, pruritus, erythema, pain, edema, swelling, induration, hematoma
[17] A delayed local skin reaction with blisters has been reported with another L-asparaginase product.
[18] Including increases within the laboratory normal range.

c. Description of selected adverse reactions

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

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. Pediatric population
Compared with children, the incidence of hepatic and pancreatic toxicities and of venous thromboembolic events may be increased in adolescents and young adults.

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

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

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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.
Asparagine is an amino acid 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.
As lymphoblastic cells are lacking asparagine synthetase activity they are dependent upon exogenous asparagine. The anti-tumour activity of L-asparaginase is a result of the sustained depletion of exogenous asparagine.
It has also been noted that asparaginase, in addition to its asparaginase activity, has significant glutaminase activity. It catalyses the deamination of glutamine in glutamic acid with the release of ammonia.
Glutamine may lead to alternative asparagine synthesis and therefore glutamine depletion may complement asparagine depletion. However, exact potential of this glutaminase activity remains unknown.

5.2 Pharmacokinetic properties
Based on a population PK model, the mean (%CV) half-life of crisantaspase is 7.5 (24%) hours after intravenous infusion in contrast to 15.6 (20%) hours after intramuscular injection. L-asparaginase penetrates through to the cerebrospinal fluid to a small degree and is also found in lymph.
Serum trough asparaginase activity ≥ 0.1 U/mL has been demonstrated to correlate with asparagine depletion (asparagine < 0.4 mcg/mL or 3 µM) and to serum levels that predict clinical efficacy.

Clinical trials
Study 1 (AALL07P2) was a single-arm, multicentre, open-label, safety and clinical pharmacology trial, which enrolled ALL patients who were unable to continue to receive pegaspargase due to hypersensitivity reactions. The main outcome measure was the proportion of patients who achieved a serum trough asparaginase level ≥ 0.1 IU/mL, which correlates with asparagine depletion and predicts clinical efficacy. Patients received Erwinase 25,000 IU/m^2 intramuscularly for two weeks (total 6 doses) as a replacement for each scheduled dose of pegaspargase.
Out of 58 patients enrolled, 48 were evaluable for the main outcome measure in the first treatment course. The median age was 11 years (2 to 18 years) and 59% were male.
Study 2 (100EUSA12) was a single-arm, multicentre pharmacokinetic study in patients with ALL/LBL who had developed hypersensitivity to native *E. coli* asparaginase, pegaspargase, or calaspargase pegol. Patients received Erwinase 25,000 IU/m^2 intravenously 3 days per week for up to 30 weeks. The main outcome measure was the proportion of patients with 2-day nadir serum asparaginase activity (NSAA) levels after the fifth dose ≥ 0.1 IU/mL.
Out of 30 patients enrolled, 24 were evaluable for the main outcome measure in the first treatment course. The median age was 7 years (1-17 years) and 63% were male.
The results of the two studies are presented in the table below.
Proportion of patients with sustained asparaginase activity

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

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

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

5.3 Preclinical safety data
Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:
Reproduction and development toxicity
Embryotoxicity studies with *Erwinia* L-asparaginase have given evidence of teratogenic potential in rabbits. In addition, pre-clinical experience with other asparaginase preparations has shown teratogenic potential in rats, mice and rabbits with doses in the therapeutic ranges.
In a fertility and early embryonic development study in rats, IM administration of crisantaspase had no effect on male and female fertility at doses approximately 50% of the recommended human dose (based on body surface area). However, a 12 to 15% decrease in sperm count was observed at doses approximately 12 to 50% of the recommended human dose.

Carcinogenicity
Non-clinical studies have not been conducted to evaluate the carcinogenic or mutagenic potential of crisantaspase. Crisantaspase is an enzyme for which the structure and well documented activity do not suggest any carcinogenic or mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium Chloride
Glucose Monohydrate

6.2 Incompatibilities
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Accordingly, other intravenous medicinal products must not be infused through the same intravenous line while infusing Erwinase.

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.
Chemical and physical stability of the reconstituted solution when stored in a glass or transparent polypropylene syringe at a temperature below 25 °C was demonstrated for up to 8 hours.
From a microbiological perspective, the reconstituted solution for injection must be used immediately unless the method of dilution excludes the risk of microbiological contamination. If the reconstituted solution is not used immediately, the duration and conditions of storage are the responsibility of the user.
For instructions on reconstitution of the medicinal product, see section 6.6.

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

6.5 Nature and contents of container
Type 1 clear neutral glass vials of 3 ml nominal capacity, closed with 13 mm halobutyl freeze-drying stoppers and aluminium overseals, containing a white lyophilised solid.
Pack size: 5 vials.

6.6 Special precautions for disposal and other handling
The contents of each vial should be reconstituted in 1 ml to 2 ml of sodium chloride (0.9%) solution for injection.
When reconstituted with 1 mL the resultant concentration is 10,000 IU/mL. When reconstituted with 2 mL, the resultant concentration is 5,000 IU/mL
Slowly add the sodium chloride (0.9%) solution for injection. against the inner vial wall, do not squirt directly onto or into the powder.
Allow the contents to dissolve by gentle mixing or swirling maintaining the vial in an upright position, avoiding contact of the solution with the stopper. Avoid froth formation due to excessive or vigorous shaking.
The solution should be clear without any visible particles. Fine crystalline or thread-like wisps of protein aggregates may be visible if shaking is excessive. If there are any visible particles or protein aggregates present the reconstituted solution should be rejected.
The solution should be administered within 15 minutes of reconstitution. If a delay of more than 15 minutes between reconstitution and administration is unavoidable, the solution should be withdrawn into a glass or polypropylene syringe for the period of the delay. The solution should be used within 8 hours.
Erwinase is not a cytotoxic medicinal product (such as vincristine or methotrexate) and does not require the special precautions needed for manipulating such agents. It should be handled in the same way as other therapeutic enzymes such as hyaluronidase.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
Porton Biopharma Limited
Manor Farm Road
Porton Down, Salisbury, SP4 0JG
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)
PL 44403/0002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
First authorisation: 19 July 1985
Latest renewal: 25 May 2006

10. DATE OF REVISION OF THE TEXT
06/2020
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