Package leaflet: Information for the patient

Erwinase 10 000 U powder for solution for injection/infusion.
Crisantaspase (L-asparaginase from *Erwinia chrysanthemi*)

Read all of this leaflet carefully before you start using 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, please talk to your doctor, pharmacist or nurse.
- If you get any of the side effects listed in section 4, or if you get a side effect not listed in this leaflet, please talk to your doctor, pharmacist or nurse.

What is in this leaflet

1. What Erwinase is and what it is used for

How does Erwinase work?
Erwinase is a treatment for blood-cell cancer and belongs to a group of medicines known as 'antineoplastic and immunomodulatory agents'. It works by reducing the level of asparagine (an amino acid) in your body. Asparagine is a substance that cancer cells need in order to survive.

What is Erwinase used for?
This medicine is primarily used in children, for the treatment of cancer of the white blood cells (Acute Lymphoblastic Leukaemia), in patients who have had an allergic reaction to other similar products.

This medicine is used alongside other treatments.

2. What you need to know before you receive Erwinase

Do not use Erwinase if:
- You have previously had a severe allergic (hypersensitivity) reaction to the active substance (crisantaspase) or you are allergic to any of the other ingredients of this medicine. You can find these substances in Section 6.
- You have severe liver function impairment.
- You have or have previously had severe pancreas problems (acute pancreatitis) caused by a medicine that contains L-asparaginase.
- You have inflammation of the pancreas (pancreatitis) that is not connected to L-asparaginase.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using this medicine.
- This medicine should only be used by doctors who are specialised in this kind of treatment.
- Severe, life-threatening allergic reactions have been reported. If you experience a reaction to the treatment, the hospital will need to have special medicines and equipment in order to treat you.
- It is possible that your body will become sensitive to the active substance after repeated treatment.
- If you experience abdominal pain, this may be a symptom of pancreatitis (inflammation of the pancreas) and you must tell your doctor immediately. Pancreatitis can be fatal.

- You may suffer from too much sugar in your blood (hyperglycaemia) during the treatment. This can be treated by administering insulin.
- During the treatment, your body may be less able to prevent severe bleeding. If you suffer from severe bleeding, your treatment will be stopped. Your doctor will determine whether the treatment will be started again and when.
- Reduced liver function can be caused or exacerbated by use of this medicine. Your doctor will consider stopping the treatment in the case of a severe reaction. The treatment may be started again under strict observation, but only once you have recovered sufficiently.
- If the doctor or nurse spills this medicine on you or on themselves, particularly into the eyes, that part of the body should be flushed with plenty of water for 15 minutes.
- Neurological disorders (disorders of the nervous system) with fatal outcome have been reported. Posterior reversible encephalopathy syndrome (characterised by a headache, confusion, seizures and loss of vision) may require treatment with medicines to lower blood pressure and, in the case of a seizure, use of anti-epileptic medicines.
- The destruction of cancer cells results in high levels of uric acid (a waste substance) in your blood. This can reduce the function of your kidneys.
- A weakened immune system has been observed during treatment with this medicine. This may make you more susceptible to infection.

Blood and urine tests
During treatment, your doctor will regularly test your blood and urine to check for possible side effects, for example:
- For allergic reactions
- Whether your pancreas, kidneys and liver are still working well.
- That you have enough blood cells left.

For traceability, your healthcare professional will register the product name and the batch number of every dose of Erwinase that you receive.

Other medicines and Erwinase
- Since Erwinase can affect the function of the liver and the level of enzymes and proteins in the blood, it can alter the function of medicines that are sensitive to these.
- If Erwinase is used with other chemotherapeutic agents (medicines for the treatment of cancer), it can increase the action or the harmfulness of these medicines. This applies in particular in the case of the following chemotherapeutic agents: methotrexate, cytarabine, vincristine, imatinib and prednisone (a corticosteroid).
- Sometimes, allopurinol, a medicine for gout (a painful rheumatic inflammation), needs to be administered in order to protect the kidneys.

Erwinase must not be mixed with other medicines before being administered.

Tell your doctor or pharmacist if you are taking, have recently taken or might in the near future take any other medicines alongside Erwinase.

Pregnancy and breastfeeding
If you are pregnant, think you might be pregnant, are trying to become pregnant or are breastfeeding, please talk to your doctor or pharmacist before using this medicine.

- You should not use this medicine if you are pregnant, unless absolutely necessary. You should tell your doctor straight away if you are pregnant, become pregnant during treatment with this medicine or if you plan to become pregnant in the near future.
- You should not breastfeed during your treatment with this medicine.

Fertility and family planning
The possibility of a negative impact on male fertility cannot be ruled out.
If applicable, both men and women must use contraceptives before and for some time after treatment with Erwinase.

Driving and using machines
When driving and using machines, you should take a reduced reaction time, nausea and vomiting into account.

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

3. How to use Erwinase

Dosage
Your doctor will calculate your body surface area in square metres (m^2) and will use this to determine the dose you should receive.

Your doctor will normally treat you with 25 000 U of Erwinase per square metre.

The amount you receive can change and will depend on the amount of asparaginase (the active substance in this medicine) in your blood, which can be checked during your treatment.

Method of administration
This medicine will be administered in one of the following ways:
a) Into a vein by infusion (intravenous use).
b) Into a muscle by injection (intramuscular use).

This medicine should be administered by your doctor or nurse by injection or infusion. Before injection or infusion, the powder is dissolved very precisely (in saline).

Your treatment will normally be given without interruption. If the treatment needs to be stopped, it can be started again at a lower dose.

Duration of treatment
You will receive an injection three times a week for two weeks. This may change, depending on new results from clinical studies.

If you have received more Erwinase than you should
If you think you have received more Erwinase than you should, you must contact your doctor or another healthcare professional immediately.

If you did not receive this medicine
If you think that you did not receive a dose, you should contact your doctor or another healthcare provider immediately.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The side effects listed below have been observed when this medicine was given together with another treatment for cancer.

This medicine will be administered under strict medical observation and the doctor may give you other medicines in order to treat these side effects. Most side effects will cease as soon as you stop treatment with this medicine.

Talk to a doctor immediately if you experience any one of the following side effects:

- Blue lips, arms or legs (possible symptom of hypoxia: too little oxygen in the blood), redness or inflammation of the skin, increase or decrease in blood pressure, swelling of the face, lips and/or throat, shortness of breath, increased heart rate, gasping, difficulty swallowing, a runny nose, a rash, shivering, flushed skin, difficulty breathing, vomiting, feeling unwell (malaise) or pale skin. Repetition of the treatment increases the risk of a reaction. Redness, pain, swelling, bruising or hardness at the injection site.
- Symptoms may include: coma, encephalopathy (brain disease), seeing, hearing or feeling things that are not there (hallucinations), muscle weakness, reduced consciousness, confusion, dizziness, drowsiness, tiredness, restlessness, difficulty speaking - often as a result of other side effects.
- Erwinase can increase the risk of blood clots, which can block important blood vessels in the brain, lungs or legs (symptoms of blood clots in the arms or legs may or may not be accompanied by swelling). If you experience chest pain that spreads to the arms, neck, jaw, back or stomach, feel sweaty and are out of breath, these may be symptoms of a heart attack (myocardial infarction).
- Bleeding more often and getting bruises, even if you have not been injured.
- If you have symptoms of severe inflammation of the pancreas (pancreatitis), such as severe abdominal pain with nausea and diarrhoea, the treatment must be stopped and not restarted at a later date.
- High blood sugar levels (hyper glycaemia).
- Change in the function of the liver (established by laboratory tests).

The other side effects that have been observed with this medicine are listed below, in order of how often they occur:
Contact your doctor if you experience any one of the following side effects:

Very common (affects more than 1 in 10 users)

- Generalised infection or septic shock (shock as a result of infection, including life-threatening shock) and other infections
- Fewer blood cells (including platelets and both white and red blood cells). Some of these can be caused by reduced function of the bone marrow.
- Increase in the concentration of fat, bilirubin (a waste substance that occurs in your blood when red blood cells stop working) and certain digestive enzymes in the blood (your doctor will monitor this)
- Weight loss
- Pain all over the body, including muscle and joint pain
- Nausea

Common (affects less than 1 in 10 users)

- Diarrhoea
- Mucositis (inflammation of the digestive tract)
- Stomach complaints
- Fever
- Tiredness
- Headaches

Uncommon (affects less than 1 in 100 users)
- Complications of diabetes (high blood sugar)
- Increase in the level of ammonium in the blood
- Seizures
- Fatty liver
- Reduced kidney function

Rare (affects less than 1 in 1 000 users)
- Posterior reversible encephalopathy syndrome (a condition characterised by headache, confusion, seizures and loss of vision)
- Liver failure

Very rare (affects less than 1 in 10 000 users)
- A painful joint condition known as reactive arthritis

Not known (cannot be determined from available data)
- Loss of appetite (anorexia)
- Inflammation of the salivary glands at the back of the throat
- Reduced levels of albumin (a protein) in the blood, resulting in water retention
- Formation of blisters and peeling of the skin (toxic epidermal necrolysis)
- Muscle pain
- Kidney disorders with abnormal results in the urine tests (high protein level)

The side effects are generally reversible (they disappear once you stop taking the medicine).

Additional side effects in children and young adults
Side effects affecting the liver, pancreas and clotting of the blood are more common in adults than in children and young adults.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie. By reporting side effects, you can help us to obtain more information about the safety of this medicine.

5. How to store this medicine

Keep this medicine out of the sight and reach of children.

The hospital will store this medicine in a refrigerator (between 2 °C and 8 °C) and it must not be used after the expiry date, which can be found on the pack after "EXP". A month and a year are stated here. The expiry date refers to the last day of that month.

6. Contents of the pack and other information

What this medicine contains

- The active substance in this medicine is Crisantaspase (L-asparaginase from *Erwinia chrysanthemi*)
- Each vial contains 10 000 U (units) of crisantaspase.
- The other ingredients are: sodium chloride, glucose monohydrate, sodium hydroxide, acetic acid

What Erwinase looks like and contents of the pack
Erwinase is a white powder contained in a small glass bottle.
Each pack has 5 small glass bottles.

Marketing Authorisation Holder
Porton Biopharma Limited
Lee View House, 13 South Terrace
Cork, T12 T0CT
Ireland
Email: medinfo@portonbiopharma.com

Manufacturer
Almac Pharma Services Limited
Seagoe Industrial Estate
Portadown, Craigavon
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DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

The following information is intended for healthcare professionals only:

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

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 for injection should be administered within 15 minutes of reconstitution. If a delay of more than 15 minutes between reconstitution and administration is unavoidable, then the solution should be withdrawn into an aseptic glass or polypropylene syringe under sterile conditions. The syringe containing 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 a polyvinylchloride (PVC) infusion bag. The infusion bag should be stored below 25 °C and used within 4 hours.

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.

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.

In the absence of compatibility studies, this medicinal product should not be mixed with other medicinal products. Accordingly, other intravenous medicinal products must not be infused through the same intravenous line as when administering Erwinase.