Package leaflet: Information for the patient

Spectrila 10,000 U powder for concentrate for solution for infusion
asparaginase

Read all of this leaflet carefully before you are given 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 nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Spectrila is and what it is used for

Spectrila contains asparaginase, which is an enzyme that interferes with natural substances necessary for cancer cell growth. All cells need an amino acid called asparagine to stay alive. Normal cells can make asparagine for themselves, while some cancer cells cannot. Asparaginase lowers asparagine level in blood cancer cells and stops the cancer growing.

Spectrila is used to treat adults and children with acute lymphoblastic leukaemia (ALL) which is a form of blood cancer. Spectrila is used as part of a combination therapy.

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

Spectrila must not be used
- if you are allergic to asparaginase or to the other ingredient of this medicine (listed in section 6),
- if you have or previously had inflammation of the pancreas (pancreatitis),
- if you have severe liver function problems,
- if you have a blood clotting disorder (such as haemophilia),
- if you had severe bleeding (haemorrhage) or severe blood clotting (thrombosis) under previous asparaginase treatment.

Warnings and precautions
Talk to your doctor or nurse before you are given Spectrila.

The following life-threatening situations could arise during treatment with Spectrila:
- severe inflammation of the pancreas (acute pancreatitis),
- liver problems,
- a serious allergic reaction which causes difficulty in breathing or dizziness,
- blood clotting disorders (bleeding or formation of blood clots),
- high blood sugar levels.

Before and during treatment with Spectrila your doctor will carry out blood tests.

If severe liver problems occur, treatment with Spectrila must be interrupted immediately.

If allergic symptoms occur, intravenous infusion of Spectrila must be discontinued immediately. You may be given anti-allergic medicines and, if necessary, medicines to stabilise your circulation. In the majority of cases, your treatment can be continued by switching to other medicines containing different forms of asparaginase.

Blood clotting disorders may require you to receive fresh plasma or a certain type of protein (antithrombin III) in order to reduce the risk of bleeding or formation of blood clots (thrombosis).

High blood sugar levels may require treatment with intravenous fluids and/or insulin.

Reversible posterior leukoencephalopathy syndrome (characterised by headache, confusion, seizures and visual loss) may require blood-pressure lowering medicines and in case of seizure, anti-epileptic treatment.

Other medicines and Spectrila
Tell your doctor if you are using, have recently used or might use any other medicines. This is important as Spectrila may increase the side effects of other medicines through its effect on the liver which plays an important role in removing medicines from the body.

In addition, it is especially important to tell your doctor if you are also using any of the following medicines:
- Vincristine (used to treat certain types of cancer) since the simultaneous use of vincristine and asparaginase may increase the risk of certain side effects. To avoid this, vincristine is usually given 3–24 hours before asparaginase.
- Glucocorticoids (anti-inflammation medicines that dampen down your immune system) since the simultaneous use of glucocorticoids and asparaginase may increase the formation of blood clots (thrombosis).
- Medicines that reduce the ability of blood to clot, such as anticoagulants (e.g. warfarin and heparin), dipyridamole, acetylsalicylic acid or medicines to treat pain and inflammation, since using these medicines with asparaginase may increase the risk of bleeding.
- Medicines which are metabolised in the liver (e.g. paracetamol, acetylsalicylic acid, tetracycline) because the risk of side effects may increase.
- Asparaginase may influence the efficacy of methotrexate or cytarabine (used to treat certain types of cancer):
  - if asparaginase is given after these medicines their effect may be increased.
  - if asparaginase is given before these medicines their effect may be weakened.
- Medicines which may have a negative effect on liver function (e.g. paracetamol, acetylsalicylic acid, tetracycline) since these negative effects may be worsened by parallel treatment with asparaginase.
- Medicines which may suppress bone marrow function (e.g. cyclophosphamide, doxorubicin, methotrexate) as these effects may be enhanced by parallel use of asparaginase. You may be more prone to infections.
- Other anti-cancer medicines as they may contribute to the release of too much uric acid when tumour cells are destroyed by asparaginase.

Vaccination
Simultaneous vaccination with live vaccines may increase the risk of a serious infection. You should therefore not receive vaccination with live vaccines until at least 3 months after the end of treatment with Spectrila.

Pregnancy and breast-feeding
There are no data on the use of asparaginase in pregnant women. Spectrila should not be used during pregnancy unless the clinical condition of the woman requires treatment with asparaginase.
It is unknown whether asparaginase is present in human breast milk. Therefore, Spectrila must not be used during breast-feeding.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

If you are a woman you must use contraceptives or remain abstinent during chemotherapy and for 7 months after the end of treatment. Since an indirect interaction between components of the oral contraception and asparaginase cannot be ruled out, oral contraceptives are not considered sufficiently safe. A method other than oral contraceptives should be used in women of childbearing potential.

If you are a man, you should take adequate precautions to ensure that your partner does not become pregnant during your treatment with Spectrila and for 4 months after the last dose.

Driving and using machines
Do not drive or use machines when taking this medicine because it may make you feel drowsy, tired or confused.

3. How to use Spectrila

Spectrila is prepared and given by healthcare personnel. Your doctor decides on the dose you receive. The dose depends on your body surface area (BSA) which is calculated from your height and weight.

Spectrila is given into a vein. It is usually given with other anti-cancer medicines. The duration of treatment depends on the specific chemotherapy protocol that is used to treat your disease.

Use in adults
The recommended dose of Spectrila for adults is 5,000 U per m² body surface area (BSA) given every third day.

Use in children and adolescents
The recommended dose in children and adolescents aged 1–18 years is 5,000 U per m² BSA given every third day.

The recommended dose in infants aged 0–12 months is as follows:
- age less than 6 months: 6,700 U/m² BSA,
- age 6–12 months: 7,500 U/m² BSA.

If you were given more Spectrila than you should
If you think that you received too much Spectrila, tell your doctor or nurse as soon as possible.

Up to date it is not known that an overdose with asparaginase led to any signs of an overdose. If necessary, your doctor will treat your symptoms and will give you supportive care.

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

4. Possible side effects

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

Tell your doctor immediately and stop taking Spectrila if you experience:
- inflammation of the pancreas, which causes severe pain in the abdomen and back,
- severe liver function abnormalities (determined by laboratory tests),
- allergic reactions including serious allergic reaction (anaphylactic shock), flushing, rash, low blood pressure, swelling of face and throat, hives, shortness of breath,

- blood clotting disorders such as bleeding, disseminated intravascular coagulation (DIC) or formation of blood clots (thrombosis),
- high blood sugar level (hyperglycaemia).

A list of all other side effects is set out below according to how common they are:

Very common side effects (may affect more than 1 in 10 people)
- feeling sick (nausea), being sick (vomiting), stomachache or watery stools (diarrhoea)
- accumulation of fluid (oedema)
- feeling of tiredness
- abnormal laboratory tests including changes in protein levels in the blood, changes in blood fat or in liver enzyme values or high level of urea in the blood

Common side effects (may affect up to 1 in 10 people)
- mild to moderate reduction in all blood cell counts
- allergic reactions including wheezing (bronchospasm) or difficulty in breathing
- low blood sugar level (hypoglycaemia)
- loss of appetite or weight loss
- depression, hallucination or confusion
- nervousness (agitation) or somnolence (sleepiness)
- changes in the electroencephalogram (a trace of the electrical activity of your brain)
- high blood levels of amylase and lipase
- pain (back pain, joint pain, stomach ache)

Uncommon side effects (may affect up to 1 in 100 people)
- high blood levels of uric acid (hyperuricaemia)
- high blood levels of ammonia (hyperammonaemia)
- headache

Rare (may affect up to 1 in 1,000 people)
- diabetic ketoacidosis (complication due to uncontrolled blood sugar)
- seizures, severe impairment of consciousness including coma, and stroke
- reversible posterior leukoencephalopathy syndrome (a condition characterised by headache, confusion, seizures and visual loss)
- inflammation of the salivary glands (parotitis)
- cholestasis (blocked bile flow from the liver)
- jaundice
- destruction of liver cells (liver cell necrosis)
- liver failure which may lead to death

Very rare (may affect up to 1 in 10,000 people)
- decreased function of the thyroid gland or the parathyroid glands
- mild tremor (shaking) of the fingers
- pseudocysts of the pancreas (collections of fluid after acute inflammation of the pancreas)

Not known (frequency cannot be estimated from the available data):
- infections
- fatty liver

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

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

5. How to store Spectrila

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

Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C–8 °C).
Keep the vial in the outer carton in order to protect from light.

The reconstituted solution is stable for 2 days when stored at 2 °C–8 °C. If the medicine is not used immediately, the user preparing this medicine is responsible for storage times and conditions to ensure sterility of the product. Storage would normally not be longer than 24 hours at 2 °C–8 °C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Spectrila contains
- The active substance is asparaginase. One vial of powder contains 10,000 units of asparaginase. After reconstitution, one ml of solution contains 2,500 units of asparaginase.
- The other ingredient is sucrose.

What Spectrila looks like and contents of the pack
Spectrila is provided as a powder for concentrate for solution for infusion.

The powder is white and it is supplied in a clear glass vial with a rubber stopper and an aluminium seal and a plastic flip-off cap.

Spectrila is available in packs containing 1 or 5 vials.
Not all pack sizes may be marketed.

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The following information is intended for healthcare professionals only:

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Spectrila should only be used by physicians who are experienced in such treatment protocols.

Recommended control examinations and safety precautions

Before initiating therapy bilirubin, hepatic transaminases, and coagulation parameters (partial thromboplastin time [PTT], prothrombin time [PT], antithrombin, fibrinogen, and D-dimer) should be determined.

After administration of asparaginase, close monitoring of bilirubin, hepatic transaminases, of blood/urinary glucose, coagulation parameters (PTT, PT, antithrombin III, fibrinogen, and D-dimer), amylase, lipase, triglycerides, and cholesterol is recommended.

Acute pancreatitis
Treatment with asparaginase should be discontinued in patients developing acute pancreatitis. Acute pancreatitis has developed in less than 10% of patients. In rare cases, haemorrhagic or necrotising pancreatitis occurs. There have been isolated reports of fatal outcomes. Clinical symptoms include abdominal pain, nausea, vomiting and anorexia. Serum amylase and lipase are usually elevated, although in some patients they can be normal due to impaired protein synthesis. Patients with severe hypertriglyceridaemia are at increased risk of developing acute pancreatitis. These patients should no longer be treated with any asparaginase preparation.

Hepatotoxicity
In rare cases severe liver impairment has been described, including cholestasis, icterus, hepatic necrosis and hepatic failure with fatal outcome (see sections 4.8 and 4.5). Liver parameters should be monitored closely before and during treatment with asparaginase.
Treatment with asparaginase should be interrupted if patients develop severe hepatic impairment (bilirubin > 3 times the upper limit of normal [ULN]; transaminases > 10 times ULN), severe hypertriglyceridaemia, hyperglycaemia or coagulation disorder (e.g. sinus vein thrombosis, severe bleeding).

Allergy and anaphylaxis
Because of the risk of severe anaphylactic reactions asparaginase should not be administered as a bolus intravenous injection. If allergic symptoms occur, administration of asparaginase must be discontinued immediately and appropriate treatment given, which may include antihistamines and corticosteroids.

Coagulation disorders
Due to the inhibition of protein synthesis (decreased synthesis of factors II, V, VII, VIII, and IX, proteins C and S, antithrombin III [AT III]) caused by asparaginase, coagulation disorders can occur which can manifest either as thrombosis, disseminated intravascular coagulation (DIC), or bleeding. The risk of thrombosis seems to be higher than the risk of bleeding. Symptomatic thromboses related to the use of central venous catheters have been described, too. Frequent evaluation of coagulation parameters is important before and during asparaginase treatment. Expert advice should be sought in cases where AT III is decreased.

Hyperglycaemic conditions

Asparaginase may induce hyperglycaemia as a consequence of decreased insulin production. Additionally it may decrease insulin secretion from pancreatic β-cells and impair insulin receptor function. The syndrome is generally self-limiting. However, in rare cases it can result in diabetic ketoacidosis. Concomitant treatment with corticosteroids contributes to this effect. Serum and urine glucose levels should be regularly monitored and managed as clinically indicated.

Antineoplastic agents
Asparaginase-induced tumour cell destruction may release large amounts of uric acid, resulting in hyperuricaemia. Co-administration of other antineoplastic medicinal products contributes to this effect. Aggressive alkalinisation of the urine and use of allopurinol can prevent urate nephropathy.

Glucocorticoids
A higher risk of thrombosis during induction therapy with asparaginase and prednisone was seen in children with a genetic prothrombotic risk factor (factor V G1691A-mutations, prothrombin G20210A-variation, methylenetetrahydrofolate reductase [MTHFR] T677T-genotype, increased lipoprotein A, hyperhomocysteinaemia).

Contraceptives
Woman of childbearing potential have to use effective contraception during treatment and for 7months after asparaginase discontinuation. 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.
Men should use effective contraceptive measures and be advised to not father a child while receiving asparaginase and for 4 months following completion of treatment.

Philadelphia chromosome-positive patients
Efficacy and safety of Spectrila have not been established in Philadelphia chromosome-positive patients.

Asparaginase activity
Measurement of the asparaginase activity level in serum or plasma may be undertaken in order to rule out accelerated elimination of asparaginase activity. Preferably, levels should be measured three days after the last asparaginase administration, i.e. usually directly before the next dose of asparaginase is given. Low asparaginase activity levels are often accompanied by the appearance of anti-asparaginase antibodies. In such cases, a switch to a different asparaginase preparation should be considered. Expert advice should first be sought.

Hypoalbuminaemia
As a result of impaired protein synthesis, the serum protein level (especially albumin) decreases very commonly in patients treated with asparaginase. Since serum protein is important for the binding and transport function of some active substances, the serum protein level should be monitored regularly.

Hyperammonaemia
Plasma ammonia levels should be determined in all patients with unexplained neurologic symptoms or severe and prolonged vomiting. In case of hyperammonaemia with severe clinical symptoms, therapeutic and pharmacological measures that rapidly reduce plasma ammonia levels (e.g. protein restriction and haemodialysis), reverse catabolic states and increase removal of nitrogen wastes should be initiated and expert advice sought.

Reversible posterior leukoencephalopathy syndrome
Reversible posterior leukoencephalopathy syndrome (RPLS) may occur rarely during treatment with any asparaginase. This syndrome 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 RPLS 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 RPLS is caused by asparaginase, concomitant treatment or the underlying diseases.

RPLS 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

Handling

To dissolve the powder, 3.7 ml of water for injection is **carefully squirted against the inner wall of the vial** with an injection syringe (do not squirt directly on or into the powder). The dissolution of the contents is achieved by slow turning (avoid froth formation due to shaking). The ready-to-use solution may exhibit a slight opalescence.

The calculated quantity of asparaginase is dissolved further in 50 to 250 ml of sodium chloride 9 mg/ml (0.9%) solution for infusion.

Method of administration

For intravenous use only. The daily amount of asparaginase needed per patient can be diluted in a final volume of 50–250 ml sodium chloride 9 mg/ml (0.9%) solution for infusion.

Duration of administration

The diluted solution of asparaginase should be infused over 0.5 to 2 hours.
Asparaginase must not be administered as a bolus dose.

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