

Package leaflet: Information for the user

Krabbazal 100 mg powder for concentrate for solution for infusion
Krabbazal 500 mg powder for concentrate for solution for infusion
Krabbazal 1000 mg powder for concentrate for solution for infusion

pemetrexed

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 pharmacist.
- If you get any side effects, talk to your doctor or nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Krabbazal is and what it is used for
2. What you need to know before you use Krabbazal
3. How to use Krabbazal
4. Possible side effects
5. How to store Krabbazal
6. Contents of the pack and other information

1. What Krabbazal is and what it is used for

Krabbazal is a medicine used in the treatment of cancer. It contains the active substance pemetrexed. Pemetrexed belongs to a group of medicines known as folic acid analogues and disrupts processes that are essential for cell replication.

Krabbazal is given in combination with cisplatin, another anti-cancer medicine, as treatment for malignant pleural mesothelioma, a form of cancer that affects the lining of the lung, to patients who have not received prior chemotherapy.

Krabbazal is also given in combination with cisplatin for the initial treatment of patients with advanced stage of lung cancer.

Krabbazal can be prescribed to you if you have lung cancer at an advanced stage if your disease has responded to treatment or it remains largely unchanged after initial chemotherapy.

Krabbazal is also a treatment for patients with advanced stage of lung cancer whose disease has progressed after other initial chemotherapy has been used.

2. What you need to know before you use Krabbazal

Do not use Krabbazal

- if you are allergic to pemetrexed or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding; you must discontinue breast-feeding during treatment with Krabbazal.
- if you have recently received or are about to receive a vaccine against yellow fever.

Warnings and precautions

Talk to your doctor or hospital pharmacist before receiving Krabbazal.

If you currently have or have previously had problems with your kidneys, talk to your doctor or hospital pharmacist as you may not be able to receive Krabbazal.

Before each infusion you will have samples of your blood taken to evaluate if you have sufficient kidney and liver function and to check that you have enough blood cells to receive Krabbazal. Your doctor may decide to change the dose or delay treating you depending on your general condition and if your blood cell counts are too low. If you are also receiving cisplatin, your doctor will make sure that you are properly hydrated and receive appropriate treatment before and after receiving cisplatin to prevent vomiting.

If you have had or are going to have radiation therapy, please tell your doctor, as there may be an early or late radiation reaction with Krabbazal.

If you have been recently vaccinated, please tell your doctor, as this can possibly cause bad effects with Krabbazal.

If you have heart disease or a history of heart disease, please tell your doctor.

If you have an accumulation of fluid around your lungs, your doctor may decide to remove the fluid before giving you Krabbazal.

Children and adolescents

There is no relevant use of Krabbazal in the paediatric population.

Other medicines and Krabbazal

Please tell your doctor if you are taking any medicines for pain or inflammation (swelling), such as medicines called “nonsteroidal anti-inflammatory drugs” (NSAIDs), including medicines purchased without a doctor’s prescription (such as ibuprofen). There are many sorts of NSAIDs with different durations of activity. Based on the planned date of your infusion of Krabbazal and/or on the status of your kidney function, your doctor needs to advise you on which medicines you can take and when you can take them. If you are unsure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

Like other chemotherapy medicines Krabbazal is not recommended with live attenuated vaccines. Inactive vaccines should be used where possible.

Tell your doctor or hospital pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility

Pregnancy

If you are pregnant, think you may be pregnant or are planning to have a baby, **tell your doctor** and ask for advice before taking this medicine. The use of Krabbazal should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Krabbazal during pregnancy. Women must use effective contraception during treatment with Krabbazal.

Breast-feeding

If you are breast-feeding, tell your doctor.

Breast-feeding must be discontinued during Krabbazal treatment.

Fertility

Men are advised not to father a child during and up to 6 months following treatment with Krabbazal and should therefore use effective contraception during treatment with Krabbazal and for up to 6 months afterwards. If you would like to father a child during the treatment or in the 6 months following receipt of treatment, seek advice from your doctor or pharmacist. You may want to seek counselling on sperm storage before starting your therapy.

Driving and using machines

Krabbazal may make you feel tired. Be careful when driving a car or using machines.

Krabbazal contains sodium

One vial of 100 mg contains approximately 11.29 mg sodium per vial.

One vial of 500 mg contains approximately 53.77 mg sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

One vial of 1000 mg contains approximately 107.54 mg sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Krabbazal

Krabbazal powder for concentrate for solution for infusion will always be given to you by a healthcare professional. The dose of Krabbazal is 500 milligrams for every square metre of your body's surface area. Your height and weight are measured to work out the surface area of your body. Your doctor will use this body surface area to work out the right dose for you. This dose may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition. A hospital pharmacist, nurse or doctor will have mixed the Krabbazal powder with 9 mg/ml (0.9 %) sodium chloride solution for injection before it is given to you.

You will always receive Krabbazal by infusion into one of your veins. The infusion will last approximately 10 minutes.

When using Krabbazal in combination with cisplatin:

The doctor or hospital pharmacist will work out the dose you need based on your height and weight.

Cisplatin is also given by infusion into one of your veins, and is given approximately 30 minutes after the infusion of Krabbazal has finished. The infusion of cisplatin will last approximately 2 hours.

You should usually receive your infusion once every 3 weeks.

Additional medicines:

Corticosteroids: your doctor will prescribe you steroid tablets (equivalent to 4 milligram of dexamethasone twice a day) that you will need to take on the day before, on the day of, and the day after Krabbazal treatment. This medicine is given to you to reduce the frequency and severity of skin reactions that you may experience during your anticancer treatment.

Vitamin supplementation: your doctor will prescribe you oral folic acid (vitamin) or a multivitamin containing folic acid (350 to 1000 micrograms) that you must take once a day while you are taking Krabbazal. You must take at least 5 doses during the seven days before the first dose of Krabbazal. You must continue taking the folic acid for 21 days after the last dose of Krabbazal. You will also receive an injection of vitamin B₁₂ (1000 micrograms) in the week before administration of Krabbazal and then approximately every 9 weeks (corresponding to 3 courses of Krabbazal treatment). Vitamin B₁₂ and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment.

Your condition will be closely monitored during treatment. This routinely involves blood tests, including checks on your liver and kidney function. Your dose may be changed or treatment delayed depending on results from these tests.

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

4. Possible side effects

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

You must contact your doctor immediately if you notice any of the following:

- Fever or infection (common): if you have a temperature of 38°C or greater, sweating or other signs of infection (since you might have less white blood cells than normal which is very common). Infection (sepsis) may be severe and could lead to death.
- If you start feeling chest pain (common) or having a fast heart rate (uncommon).
- If you have pain, redness, swelling or sores in your mouth (very common).
- Allergic reaction: if you develop skin rash (very common) / burning or prickling sensation (common), or fever (common). Rarely, skin reactions may be severe and could lead to death. Contact your doctor if you get a severe rash, or itching, or blistering (Stevens-Johnson Syndrome or Toxic epidermal necrolysis).
- If you experience tiredness, feeling faint, becoming easily breathless or if you look pale (since you might have less haemoglobin than normal which is very common).
- If you experience bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal which is very common).
- If you experience sudden breathlessness, intense chest pain or cough with bloody sputum (uncommon) (may indicate a blood clot in the blood vessels of the lungs)

Other side effects with Krabbazal may include:

Very common (may affect more than 1 in 10 people)

Low white blood cells
 Low haemoglobin level (anaemia)
 Low platelet count
 Diarrhoea
 Vomiting
 Pain, redness, swelling or sores in your mouth
 Nausea
 Loss of appetite
 Fatigue (tiredness)
 Skin rash, peeling of the skin
 Hair loss
 Constipation
 Loss of sensation
 Kidney: abnormal blood tests

Common (may affect up to 1 in 10 people)

Allergic reaction: skin rash / burning or prickling sensation
 Infection including sepsis
 Fever
 Dehydration
 Kidney failure
 Irritation of the skin and itching
 Hives
 Chest pain
 Muscle weakness
 Conjunctivitis (inflamed eye)
 Upset stomach
 Pain in the abdomen
 Taste change
 Liver: abnormal blood tests
 Watery eyes
 Dizziness

Uncommon (may affect up to 1 in 100 people)

Acute renal failure
 Fast or irregular heart rate

Inflammation of the lining of the oesophagus (gullet) has been experienced with Krabbazal/ radiation therapy
Colitis (inflammation of the lining of the large bowel, which may be accompanied by intestinal or rectal bleeding)

Interstitial pneumonitis (scarring of the air sacs of the lung)

Oedema (excess fluid in body tissue, causing swelling)

Some patients have experienced a heart attack, stroke or “mini-stroke” while receiving Krabbazal usually in combination with another anticancer therapy

Pancytopenia- combined low counts of white cells, red cells and platelets

Radiation pneumonitis (scarring of the air sacs of the lung associated with radiation therapy) may occur in patients who are also treated with radiation either before, during or after their Krabbazal therapy.

Extremity pain, low temperature and discolouration have been reported.

Blood clots in the lung blood vessels (pulmonary embolism)

Rare (may affect up to 1 in 1,000 people)

Radiation recall (a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy, from days to years after the radiation.

Bullous conditions (blistering skin diseases)-including Stevens-Johnson syndrome and Toxic epidermal necrolysis

Immune mediated haemolytic anaemia (antibody-mediated destruction of red blood cells)

Hepatitis (inflammation of the liver)

Anaphylactic shock (severe allergic reaction)

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 the leaflet. You can also report side effects directly via <[To be completed nationally]>. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Krabbazal

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 label and carton after ‘EXP’. The expiry date refers to the last day of that month.

Keep the vial in the outer carton in order to protect from light.

This medicinal product does not require any special temperature storage conditions.

Reconstituted and infusion solutions

When prepared as directed, reconstituted and infusion solutions of Krabbazal contain no antimicrobial preservatives. Chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 3 days at room temperature at normal lighting conditions and 14 days at refrigerated temperature (2-8°C). 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 be longer than 24 hours at 2°C to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions.

Krabbazal should not be used if there are any signs of particles.

This medicine is for single use only; any unused solution must be disposed of in accordance with local requirement.

6. Contents of the pack and other information

What Krabbazal contains

The active substance is pemetrexed.

Krabbazal 100 mg: Each vial contains 100 milligrams of pemetrexed (as pemetrexed disodium hemipentahydrate).

Krabbazal 500 mg: Each vial contains 500 milligrams of pemetrexed (as pemetrexed disodium hemipentahydrate).

Krabbazal 1000 mg: Each vial contains 1000 milligram of pemetrexed (as pemetrexed disodium hemipentahydrate).

After reconstitution, the solution contains 25 mg/ml of pemetrexed. Further dilution by a healthcare provider is required prior to administration.

The other ingredients are mannitol, hydrochloric acid and sodium hydroxide.

What Krabbazal looks like and contents of the pack

Krabbazal is a powder for concentrate for solution for infusion in a vial. It is a white to either yellow or greenish-yellow lyophilisate powder.

Krabbazal is in colourless glass vials (type I) with type I rubber (bromobutyl) lyo-stopper and an aluminium cap with polypropylene disk. Vials are sheathed in protective sleeve.

Each pack of Krabbazal consists of one Krabbazal vial.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

[To be completed nationally]

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

Manufacturer

S.C. SINDAN-PHARMA S.R.L.

11th Ion Mihalache Boulevard

011171, Bucharest 1

Romania

This medicinal product is authorised in the Member States of the EEA under the following names:

[To be completed nationally]

This leaflet was last revised in

15 March 2016

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The following information is intended for medical or healthcare professionals only:

Instructions for use, handling and disposal.

1. Use aseptic techniques during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.
2. Calculate the dose and the number of Krabbazal vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of the label amount.
3. Reconstitute 100 mg vials with 4.2 ml of 9 mg/ml (0.9 %) sodium chloride solution for injection, without preservative, resulting in a solution containing 25 mg/ml pemetrexed.
 Reconstitute 500 mg vials with 20 ml of 9 mg/ml (0.9 %) sodium chloride solution for injection, without preservative, resulting in a solution containing 25 mg/ml pemetrexed.
 Reconstitute 1000 mg vials with 40 ml of 9 mg/ml (0.9 %) sodium chloride solution for injection, without preservative, resulting in a solution containing 25 mg/ml pemetrexed.

Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in colour from colourless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.6 and 7.8. **Further dilution is required.**

4. The appropriate volume of reconstituted pemetrexed solution must be further diluted to 100 ml with 9 mg/ml (0.9 %) sodium chloride solution for injection, without preservative, and administered as an intravenous infusion over 10 minutes.
5. Pemetrexed infusion solutions prepared as directed above are compatible with polyvinyl chloride and polyolefin lined administration sets and infusion bags. Pemetrexed is incompatible with diluents containing calcium, including lactated Ringer's Injection and Ringer's Injection.
6. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.
7. Pemetrexed solutions are for single use only. Any unused product or waste material should be disposed of in accordance with local requirements.

Preparation and administration precautions: As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of pemetrexed infusion solutions. The use of gloves is recommended. If a pemetrexed solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If pemetrexed solutions contact the mucous membranes, flush thoroughly with water. Pemetrexed is not a vesicant. There is not a specific antidote for extravasation of pemetrexed. There have been a few reported cases of pemetrexed extravasation, which were not assessed as serious by the investigator. Extravasation should be managed by local standard practice as with other non-vesicants.