Package leaflet: Information for the user

Pemetrexed Seacross 100 mg powder for concentrate for solution for infusion
Pemetrexed Seacross 500 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 further questions, please ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

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

1. What Pemetrexed Seacross is and what it is used for

Pemetrexed Seacross is a medicine used in the treatment of cancer.

This medicine 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.

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

Pemetrexed Seacross 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.

This medicine 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 Pemetrexed Seacross

Do not use Pemetrexed Seacross
- if you are allergic (hypersensitive) 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 pemetrexed.
- if you have recently received or are about to receive a vaccine against yellow fever.

Warnings and Precautions
Talk to your doctor, hospital pharmacist or nurse before using Pemetrexed Seacross.
– 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 this medicine.
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 pemetrexed. 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 pemetrexed.
- If you have been recently vaccinated, please tell your doctor, as this can possibly cause bad effects with this medicine.
- 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 pemetrexed.

Children and adolescents
This medicine should not be used in children or adolescents, since there is no experience with this medicine in children and adolescents under 18 years of age.

Other medicines and Pemetrexed Seacross
Tell your doctor if you are taking any medicine 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 pemetrexed 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.
Tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

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

Pregnancy
The use of Pemetrexed Seacross should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking this medicine during pregnancy. Women must use effective contraception during treatment with pemetrexed and for 6 months after receiving the last dose.

Breast-feeding
Breast-feeding must be discontinued during pemetrexed treatment.

Fertility
Men are advised not to father a child during and up to 3 months following treatment with pemetrexed and should therefore use effective contraception during treatment with pemetrexed and for up to 3 months afterwards. If you would like to father a child during the treatment or in the 3 months following receipt of treatment, seek advice from your doctor or pharmacist. Pemetrexed can affect your ability to have children. Talk to your doctor to seek advice about sperm storage before starting your therapy.

Driving and using machines
Pemetrexed Seacross may make you feel tired. Be careful when driving a car or using machines.

Pemetrexed Seacross contains sodium

Pemetrexed Seacross 100 mg contains less than 1 mmol (11 mg) sodium per vial and is therefore considered essentially "sodium-free".
Pemetrexed Seacross 500 mg contains approximately 2.35 mmol (54 mg) sodium (main component of cooking/table salt) per vial. This is equivalent to 2,7 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Pemetrexed Seacross

Always use this medicine exactly as your doctor or pharmacist has told you.
Check with your doctor or pharmacist if you are not sure.

The dose of Pemetrexed Seacross 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 Pemetrexed Seacross powder with 9 mg/ml (0.9 %) sodium chloride solution for injection before it is given to you.

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

When using Pemetrexed Seacross 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 pemetrexed has finished. The infusion of cisplatin will last approximately 2 hours.

You should usually receive your infusion once every 3 weeks.

Additional medicines:
Corticosteriods: 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 pemetrexed 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 pemetrexed. You must take at least 5 doses during the seven days before the first dose of pemetrexed. You must continue taking the folic acid for 21 days after the last dose of pemetrexed. You will also receive an injection of Vitamin B_{12} (1000 micrograms) in the week before administration of pemetrexed and then approximately every 9 weeks (corresponding to 3 courses of pemetrexed treatment). Vitamin B_{12} and folic acid are given to you to reduce the possible toxic effects of the anticancer treatment.

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 (respectively, common or very common): if you have a temperature

of 38 ℃ 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 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).

Side effects with pemetrexed may include:

Very common (may affect more than 1 in 10 people):
- Infection
- Pharyngitis (a sore throat)
- Low number of neutrophil granulocytes (a type of white blood cell)
- Low white blood cells
- Low haemoglobin level
- Diarrhoea
- Vomiting
- Pain, redness, swelling or sores in your mouth
- Nausea
- Loss of appetite
- Fatigue (tiredness)
- Skin rash
- Flaking skin
- Abnormal blood tests showing reduced functionality of kidneys

Common (may affect up to 1 in 10 people):
- Blood infection
- Fever with low number of neutrophil granulocytes (a type of white blood cell)
- Low platelet count
- Allergic reaction
- Loss of body fluids
- Taste change
- Damage to the motor nerves which may cause muscle weakness and atrophy (wasting primary in the arms and legs)
- Damage to the sensory nerves that may cause lost of sensation, burning pain and unsteady gait
- Dizziness
- Inflammation or swelling of the conjunctiva (the membrane that lines the eyelids and covers the white of the eye)
- Dry eye
- Dryness of the conjunctiva (the membrane that lines the eyelids and covers the white of the eye) and cornea (the clear layer in front of the iris and pupil)
- Swelling of the eyelids

- Eye disorder with dryness, tearing, irritation, and/or pain
- Cardiac Failure (Condition that affects the pumping power of your heart muscles)
- Irregular heart rhythm
- Indigestion
- Constipation
- Abdominal pain
- Liver: increases in the chemicals in the blood made by the liver
- Itchy skin
- Rash on the body where each mark resembles a bullseye
- Hair loss
- Hives
- Kidney stop working
- Reduced functionality of kidney
- Fever
- Pain
- Excess fluid in body tissue, causing swelling
- Chest pain
- Inflammation and ulceration of the mucous membranes lining the digestive tract
- Watery eyes
- Increased skin pigmentation

Uncommon (may affect up to 1 in 100 people):

- Reduction in the number of red, white blood cells and platelets
- Stroke
- Type of stroke when an artery to the brain is blocked
- Bleeding inside the skull
- Angina (Chest pain caused by reduced blood flow to the heart)
- Heart attack
- Narrowing or blockage of the coronary arteries
- Increased heart rythm
- Deficient blood distribution to the limbs
- Blockage in one of the pulmonary arteries in your lungs
- Inflammation and scarring of the lining of the lungs with breathing problems
- Passage of bright red blood from the anus
- Bleeding in the gastrointestinal tract
- Ruptured bowel
- Inflammation of the lining of the oesophagus
- Inflammation of the lining of the large bowel, which may be accompanied by intestinal or rectal bleeding (seen only in combination with cisplatin)
- Inflammation, edema, erythema, and erosion of the mucosal surface of the esophagus caused by radiation therapy
- Inflammation of the lung caused by radiation therapy

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

- Destruction of red blood cells
- Inflammatory condition of the liver
- Redness of the skin
- Skin rash that develops throughout a previously irradiated area
- Anaphylactic shock (severe allergic reaction)

Very rare (affect up to 1 of 10,000 people)

- Infections of skin and soft tissues
- Stevens-Johnson syndrome (a type of severe skin and mucous membranes reaction

that may be life threatening)
- Toxic epidermal necrolysis (a type of severe skin reaction that may be life threatening)
- Autoimmune disorder that results in skin rashes and blistering on the legs, arms, and abdomen
- Inflammation of the skin characterized by the presence of bullae which are filled with fluid
- Skin fragility, blisters and erosions and skin scarring
- Redness, pain and swelling mainly of the lower limbs
- Inflammation of the skin and fat beneath the skin (pseudocellulitis)
- Inflammation of the skin (dermatitis)
- Skin to become inflamed, itchy, red, cracked, and rough
- Intensely itchy spots

Not known: frequency cannot be estimated from the available data
- Form of diabetes primarily due to pathology of the kidney
- Disorder of the kidneys involving the death of tubular epithelial cells that form the renal tubules

You might have any of these symptoms and/or conditions. You must tell your doctor as soon as possible when you start experiencing any of these side effects.

If you are concerned about any side effects, talk to your doctor.

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 Yellow Card Scheme:
www.mhra.gov.uk/yellowcard or
HPRA Pharmacovigilance, Website: www.hpra.ie
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pemetrexed Seacross

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 & vial after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Reconstituted and diluted infusion solutions: When prepared as directed, chemical and physical in-use stability of reconstituted and further diluted infusion solutions of pemetrexed were demonstrated for 24 hours at 25 ℃ and at refrigerated temperature (2-8 ℃). From microbiological point of view, the product should be used immediately.
This medicine is for single use only; any unused solution must be disposed of in accordance with local requirement.

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 Pemetrexed Seacross contains

- The active substance is pemetrexed.
  Each vial contains 100 milligrams of pemetrexed (as pemetrexed disodium).
  Each vial contains 500 milligrams of pemetrexed (as pemetrexed disodium).
- The other ingredients are mannitol, hydrochloric acid and sodium hydroxide.

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

What Pemetrexed Seacross looks like and contents of the pack
Pemetrexed Seacross is a powder for concentrate for solution for infusion in a vial. It is a white to either light yellow or green-yellow lyophilised powder; a clear, colorless to yellow or yellow-green colored solution, once reconstituted.
Each pack of Pemetrexed Seacross consists of one vial.

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This medicinal product is authorised in the Member States of the EEA under the following names:
BG:
Pemetrexed Novamed 100 mg Прах за концентрат за инфузионен разтвор
Pemetrexed Novamed 500 mg Прах за концентрат за инфузионен разтвор
DE
Pemetrexed Seacross 100 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung
Pemetrexed Seacross 500 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung
IE
Pemetrexed Seacross 100 mg powder for concentrate for solution for infusion
Pemetrexed Seacross 500 mg powder for concentrate for solution for infusion
RO

Pemetrexed Seacross 100 mg Pulbere pentru concentrat pentru soluţie perfuzabilă
Pemetrexed Seacross 500 mg Pulbere pentru concentrat pentru soluţie perfuzabilă
CY
Pemetrexed Seacross 100 mg κόνις για πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση
Pemetrexed Seacross 500 mg κόνις για πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση

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The following information is intended for 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 pemetrexed vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of the label amount.
3. Reconstitute each 100 mg vial 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 each 500 mg vial 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.
   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 for cytotoxic medicinal products.

Preparation and administration precautions: As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of pemetrexed infusion solutions, especially by pregnant staff. 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.

The reconstituted solution is a clear, colorless to yellow or yellow-green colored solution.