Package leaflet: Information for the user

Pemetrexed medac 100 mg powder for concentrate for solution for infusion
Pemetrexed medac 500 mg powder for concentrate for solution for infusion
Pemetrexed medac 1,000 mg powder for concentrate for solution for infusion
pemetrexed

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

What is in this leaflet

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

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

Pemetrexed medac 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.

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

Pemetrexed 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.

Pemetrexed medac 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 medac

Do not use Pemetrexed medac
- 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 Pemetrexed medac.
- if you have recently received or are about to receive a vaccine against yellow fever.

Warnings and precautions
Talk to your doctor or pharmacist before using Pemetrexed medac if:
- you currently have or have previously had problems with your kidneys, as you may not be able to receive Pemetrexed medac. 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 medac. 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.
- you have had or are going to have radiation therapy, as there may be an early or late radiation reaction with Pemetrexed medac.
- you have been recently vaccinated, as this can possibly cause bad effects with Pemetrexed medac.
- you have heart disease or a history of heart disease.
- you have an accumulation of fluid around your lungs, as your doctor may decide to remove the fluid before giving you Pemetrexed medac.

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 medac
Please tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

In particular, tell your doctor if you are using 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 Pemetrexed medac 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.

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

Breast-feeding
You should not breast-feed while using Pemetrexed medac. Discuss with your doctor when it is safe to restart breast-feeding after finishing your treatment.

Fertility
Men are advised not to father a child during and up to 3 months following treatment with Pemetrexed medac and should therefore use effective contraception during treatment with Pemetrexed medac 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 medac 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 medac may make you feel tired. Be careful when driving a car or using machines.

Pemetrexed medac contains sodium

Pemetrexed medac 100 mg
This medicine contains less than 1 mmol sodium (23 mg) per 100 mg vial, that is to say essentially 'sodium-free'.

Pemetrexed medac 500 mg
This medicine contains 54 mg sodium (main component of cooking/table salt) in each 500 mg vial. This is equivalent to 2.70% of the recommended maximum daily dietary intake of sodium for an adult.

Pemetrexed medac 1,000 mg
This medicine contains 108 mg sodium (main component of cooking/table salt) in each 1,000 mg vial. This is equivalent to 5.40% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Pemetrexed medac

The recommend dose of Pemetrexed medac is 500 mg 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 medac powder with 9 mg/ml (0.9 %) sodium chloride solution for injection before it is given to you.

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

When using Pemetrexed medac 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 medac 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 mg of dexamethasone twice a day) that you will need to take on the day before, on the day of, and the day after Pemetrexed medac 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 – 1,000 µg) that you must take once a day while you are taking Pemetrexed medac. You must take at least 5 doses during the seven days before the first dose of Pemetrexed medac. You must continue taking the folic acid for 21 days after the last dose of Pemetrexed medac. You will also receive an injection of Vitamin B_{12} (1,000 µg) in the week before administration of Pemetrexed medac and then approximately every 9 weeks (corresponding to 3 courses of Pemetrexed medac 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 °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 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)

The following side effects can occur during treatment with pemetrexed:

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
Pain, redness, swelling or sores in your mouth
Loss of appetite
Vomiting
Diarrhoea
Nausea
Skin rash
Flaking skin
Abnormal blood tests showing reduced functionality of kidneys
Fatigue (tiredness)

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

Watery eyes
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
Increased skin pigmentation
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

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 rhythm
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
Anaphylactic shock (severe allergic reaction)
Inflammatory condition of the liver
Redness of the skin
Skin rash that develops throughout a previously irradiated area

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

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 (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

United Kingdom (Northern Ireland)
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 Pemetrexed medac

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.

This medicine does not require any special storage conditions.

Reconstituted and infusion solutions: The product should be used immediately. When prepared as directed**,** chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature (2 °C – 8 °C).

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 Pemetrexed medac contains

The active substance is pemetrexed.

Pemetrexed medac 100 mg: Each vial contains 100 mg of pemetrexed (as pemetrexed disodium

hemipentahydrate).
Pemetrexed medac 500 mg: Each vial contains 500 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).
Pemetrexed medac 1,000 mg: Each vial contains 1,000 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

After reconstitution, the solution contains 25 mg/ml of pemetrexed.
The other ingredients are mannitol, hydrochloric acid and sodium hydroxide, please see section 2 "Pemetrexed medac contains sodium".

What Pemetrexed medac looks like and contents of the pack
Pemetrexed medac is a powder for concentrate for solution for infusion in a glass vial with rubber stopper.

It is a white to light yellow powder.

Each pack consists of one vial containing 100, 500 or 1,000 mg of pemetrexed.

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

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 medac vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of the label amount.

3. Pemetrexed medac 100 mg:
   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.

   Pemetrexed medac 500 mg:
   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.

   Pemetrexed medac 1,000 mg:
   Reconstitute each 1,000 mg vial 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.