Package leaflet: Information for the user

Pemetrexed 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 any 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 is and what it is used for

Pemetrexed is a medicine used in the treatment of cancer.

Pemetrexed 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 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 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

Do not use Pemetrexed
- 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
- 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 Pemetrexed

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 Pemetrexed

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 Pemetrexed.

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

Other medicines and Pemetrexed
Please 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, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or beast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before receiving this medicine.
Pregnancy
The use of Pemetrexed should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Pemetrexed during pregnancy. Women must use effective contraception during treatment with Pemetrexed.

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

Fertility
Men are advised not to father a child during and up to 6 months following treatment with Pemetrexed and should therefore use effective contraception during treatment with Pemetrexed 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
Pemetrexed may make you feel tired. Be careful when driving a car or using machines.

Pemetrexed contains sodium
Pemetrexed 500 mg contains approximately 54 mg (2.35 mmol) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.

3. How to use Pemetrexed

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

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

When using Pemetrexed 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 B12 (1000 micrograms) in the week before administration of Pemetrexed and then approximately every 9 weeks (corresponding to 3 courses of Pemetrexed treatment). Vitamin B12 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 (common): if you have a temperature of 38ºC 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 Pemetrexed 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
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
Chest pain
Muscle weakness
Conjunctivitis (inflamed eye)
Upset stomach
Pain in the abdomen
Taste change
Liver: abnormal blood tests
Watery eyes

Uncommon: may affect up to 1 in 100 people
Acute renal failure
Fast heart rate
Inflammation of the lining of the oesophagus (gullet) has been experienced with Pemetrexed / 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 Pemetrexed 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 Pemetrexed 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
Haemolytic anaemia (anaemia due to destruction of red blood cells)
Hepatitis (inflammation of the liver)
Anaphylactic shock (severe allergic reaction)

Not known: frequency cannot be estimated from the available data
Increased urine output
Thirst and increased water consumption
Hypernatraemia – increased sodium in blood

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971 Fax: +353 1 6762517, Website: www.hpra.ie e-mail: medsafety@hpra.ie.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Pemetrexed

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

This medicine does not require any special storage conditions.

Reconstituted and Infusion Solutions:
When prepared as directed, reconstituted and infusion solutions of Pemetrexed contain no antimicrobial preservatives. Chemical and physical in-use stability of reconstituted and infusion solutions of pemetrexed have been demonstrated for 24 hours at 25°C and 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 and dilution have taken place in controlled and validated aseptic conditions.

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

Do not use this medicine if you notice that the solution contains particles.

Do not throw away any medicines via wastewater. 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 contains

- The active substance is pemetrexed.

Each vial contains 500 milligrams of pemetrexed (as pemetrexed disodium 2.5 hydrate).

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 (for pH adjustment) and sodium hydroxide (for pH adjustment).

What Pemetrexed looks like and contents of the pack

Pemetrexed 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.
Each pack of Pemetrexed consists of one Pemetrexed vial.

Marketing Authorisation Holder

Generics [UK] Limited
Station Close
Potters Bar
Hertfordshire EN6 1TL
United Kingdom

Manufacturer

Wessling Hungary Kft
Anonymus u. 6
1045 Budapest
Hungary

Mylan SAS
117 Allee des Parcs
69 800 Saint-Priest
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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

Belgium	Pemetrexed Mylan Pharma 500 mg poeder voor concentraat voor oplossing voor intraveneuze infusie
Czech Republic	Pemetrexed Mylan Pharma
Germany	Pemetrexed Mylan Pharma 500 mg Pulver für ein Konzentrat zur Herstellung einer Infusionslösung
Denmark	Pemetrexed Mylan Pharma
Spain	Pemetrexed Mylan Pharma 500 mg polvo para concentrado para solución para perfusión EFG
Finland	Pemetrexed Mylan Pharma 500 mg kuiva-aine välikonsentraatiksi infuusionestettä varten, liuos
France	Pemetrexed Mylan Pharma 500 mg poudre pour solution à diluer pour solution pour perfusion
Hungary	Pemetrexed Mylan Pharma 500 mg por oldatos infúzióhoz való koncentrátumhoz
Ireland	Pemetrexed 500 mg powder for concentrate for solution for infusion
Italy	Pemetrexed Mylan Pharma
Luxembourg	Pemetrexed Mylan Pharma 500 mg Poudre pour solution à diluer pour solution pour perfusion
Norway	Pemetrexed Mylan Pharma 500 mg pulver til konsentrat til infusjonsvæske, oppløsning
Poland	Pemetrexed Mylan Pharma

Sweden	Pemetrexed Mylan 500 mg pulver till koncentrat till infusionsvätska, lösning
Slovakia	Pemetrexed Mylan Pharma 500 mg
United Kingdom	Pemetrexed 500 mg powder for concentrate for solution for infusion

This leaflet was last revised in 06/2018.

Detailed information on this medicine is available on the web site of: www.hpra.ie.

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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 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 medicinal 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.