

Package leaflet: Information for the user

Pemetrexed 25 mg/ml 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 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
2. What you need to know before you use Pemetrexed
3. How to use Pemetrexed
4. Possible side effects
5. How to store Pemetrexed
6. Contents of the pack and other information

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 using Pemetrexed.

- if you currently have or have previously had problems with your kidneys, 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, as there may be an early or late radiation reaction with Pemetrexed.
- if you have been recently vaccinated, as this can possibly cause bad effects with Pemetrexed.
- if you have heart disease or a history of heart disease.
- 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

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

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.

Please inform your doctor if you are taking medicines called proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole) used to treat heartburn and acid regurgitation.

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. 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 and for 6 months after receiving the last dose.

Breast-feeding

If you are breast-feeding, tell your doctor.

Breast-feeding must be discontinued during treatment with Pemetrexed.

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

Pemetrexed contains propylene glycol

This medicine contains 140 mg propylene glycol in each 4 ml vial which is equivalent to 35 mg/ml.

This medicine contains 700 mg propylene glycol in each 20 ml vial which is equivalent to 35 mg/ml.

This medicine contains 1400 mg propylene glycol in each 40 ml vial which is equivalent to 35 mg/ml.

3 How to use Pemetrexed

The 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 solution with sodium chloride 9 mg/ml (0.9 %) solution for injection or 5% dextrose 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

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 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** (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)

Side effects with Pemetrexed may include:

Very common side effects (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 side effects (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: • 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 loss 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 side effects (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 side effects (may affect up to 1 in 1000 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 side effects (may affect up to 1 in 10000 people)

infection 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, cracked and rough • intensely itchy spots

Not known side effects (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 this leaflet. You can also report side effects directly via:

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

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

This medicine does not require any special storage conditions.

Do not freeze.

Diluted solutions: the product should be used immediately. When prepared as directed, chemical and physical

in-use stability of the diluted solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature. Store protected from light.

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 contains

The active substance is pemetrexed.

One vial of 4 ml concentrate contains 100 mg pemetrexed (as pemetrexed diarginine).

One vial of 20 ml concentrate contains 500 mg pemetrexed (as pemetrexed diarginine).

One vial of 40 ml concentrate contains 1000 mg pemetrexed (as pemetrexed diarginine).

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

The other ingredients are L-Arginine, L-Cysteine, propylene glycol, citric acid and water for injections.

What Pemetrexed looks like and contents of the pack

Pemetrexed is a clear, colourless to slightly yellow to brown, brown yellow or green yellow solution. It is provided in glass vials. Each pack contains:

1 x 4 ml vial (100 mg/4 ml)

1 x 20 ml vial (500 mg/ 20 ml)

1 x 40 ml vial (1000 mg/ 40 ml)

The vials are closed with a rubber stopper (bromobutyl), a cap and a flip-top.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

BioOrganics BV
Microweg 22
6545 CM Nijmegen
The Netherlands

Manufacturer(s):

Synthon BV
Microweg 22
6545 CM Nijmegen
The Netherlands

Synthon Hispania S.L.
Castello, 1
Poligono Las Salinas
08830 Sant Boi de Llobregat
Spain

Synthon s.r.o.

Brněnská 32 /čp. 597
678 01 Blansko
Czech Republic

STADAPHARM GmbH
Stadastrasse 2-18
61118 Bad Vilbel
Germany

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

Austria	Pemetrexed BioOrganics 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Germany	Pemetrexed STADA 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Spain	Pemetrexed BioOrganics 25 mg/ml concentrado para solución para perfusion
France	Pemetrexed BioOrganics 25 mg/ml solution à diluer pour perfusion
Italy	Pemetrexed Synthon
The Netherlands	Pemetrexed BioOrganics 25 mg/ml, concentraat voor oplossing voor infusie
Ireland	Pemetrexed 25 mg/ml concentrate for solution for infusion
Great Britain	Pemetrexed 25 mg/ml concentrate for solution for infusion

This leaflet was last revised in

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

Instructions for use, handling and disposal.

1. Use aseptic techniques during the 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. Each vial contains a solution containing 25 mg/ml pemetrexed.
3. The appropriate volume of the solution must be further diluted to 100 ml with sodium chloride 9 mg/ml (0.9 %) solution for injection or 5% dextrose solution for injection, without preservative, and administered as an intravenous infusion over 10 minutes.
4. 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.

Pemetrexed contains L-Arginine as an excipient. L-Arginine is incompatible with cisplatin resulting in degradation of cisplatin. This medicinal product must not be mixed with other medicinal products. Intravenous lines should be flushed after administration of Pemetrexed.

5. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.
6. Pemetrexed solutions are for single use only. Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

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.