Package leaflet: Information for the user

Pemetrexed Clonmel 25 mg/ml 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 Clonmel is and what it is used for
Pemetrexed Clonmel is a medicine used in the treatment of cancer.

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

Product name 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 Clonmel is also a treatment for patients with an 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 Clonmel
DO NOT use Pemetrexed Clonmel
- 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 Clonmel
- 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 or nurse before receiving Pemetrexed Clonmel.

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 Clonmel.
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 Clonmel. 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 Clonmel.

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

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 Clonmel.

Children and adolescents
Pemetrexed ClonmelThis 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 Clonmel
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 Clonmel 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

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor. The use of Pemetrexed Clonmel should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Pemetrexed Clonmel during pregnancy. Women must use effective contraception during treatment with Pemetrexed Clonmel 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 Pemetrexed Clonmeltreatment with Pemetrexed Clonmel.

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

Pemetrexed Clonmel contains sodium
This medicine contains 110.03 mg sodium (main component of cooking/table salt) in each dose (500 milligrams pemetrexed for every square metre of your body's surface area). This is equivalent to 5.51 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Pemetrexed Clonmel

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

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

Duration of use
You should usually receive your infusion once every 3 weeks.

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

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 Clonmel 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:
- Folic acid: your doctor will prescribe you oral folic acid (vitamin) or a multivitamin containing folic acid (350 to 1 000 micrograms) that you must take once a day while you are taking Pemetrexed Clonmel. You must take at least 5 doses during the seven days before the first dose of Pemetrexed Clonmel. You must continue taking the folic acid for 21 days after the last dose of Pemetrexed Clonmel.
- Vitamin B12: you will also receive an injection of vitamin B12 (1 000 micrograms) in the week before administration of Pemetrexed Clonmel and then approximately every 9 weeks (corresponding to 3 courses of Pemetrexed Clonmel 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 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)

Side effects with Pemetrexed Clonmel 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
- 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, oedema, erythema, and erosion of the mucosal surface of the oesophagus 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 (may affect up to 1 in 10 000 people)
- infections of skin and soft tissues
- Stevens-Johnson syndrome (a type of severe skin and mucous membrane 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 characterised 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, pharmacist or nurse. 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 Clonmel
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 vial. The expiry date refers to the last day of that month.

Store unopened vial in a refrigerator (2 °C - 8 °C)
Do not freeze.
After first opening, use immediately.

Diluted solutions: The product should be used immediately. When prepared as directed, chemical and physical in-use stability of the infusion solutions of pemetrexed were demonstrated for 72 hours at refrigerated temperature (2 °C to 8 °C).

The solution is clear and ranges in colour from colourless to yellow or green - yellow without adversely affecting product quality.
Do not use if particulate matter is present.

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 Clonmel contains
The active substance is pemetrexed.

Each ml of the concentrate for solution for infusion contains 25 mg of pemetrexed (as 30.21 mg pemetrexed disodium hemipentahydrate).

The 4 ml vial contains either 100 mg of pemetrexed (as 120.83 mg pemetrexed disodium hemipentahydrate).
The 20 ml vial contains either 500 mg of pemetrexed (as 604.13 mg pemetrexed disodium hemipentahydrate).
The 40 ml vial contains either 1 000 mg of pemetrexed (as 1 208.26 mg pemetrexed disodium hemipentahydrate).

The other ingredients are mannitol, acetylcysteine, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections.

Further dilution by a healthcare provider is required prior to administration.

What Pemetrexed Clonmel looks like and contents of the pack
This medicine is a concentrate for solution for infusion.

The concentrate is a clear, colourless or light yellow or light green-yellow solution. It is filled in clear glass vials sealed with fluoropolymer-coated chlorobutyl/butyl rubber stoppers Type I and aluminium snap-off caps.

[Each vial is packed in a transparent PC container with reclosable tamper-proof PP flip-off cap.]

Each vial contains 25 mg/ml pemetrexed.

Each pack contains 1 x 4 ml vial.
Each pack contains 1 x 20 ml vial.
Each pack contains 1 x 40 ml vial.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Clonmel Healthcare Ltd, Waterford Road, Clonmel, Co. Tipperary, Ireland

Manufacturer
STADA Arzneimittel AG, Stadastrasse 2-18, D-61118 Bad Vilbel, Germany

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

DE	Pemetrexed STADA 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung
AT	Pemetrexed STADA 25 mg/ml Konzentrat zur Herstellung einer Infusionslösung
BE	Pemetrexed EG 25 mg/ml concentraat voor oplossing voor infusie
CZ	Pemetrexed STADA 25 mg/ml koncentrát pro infuzní roztok
DK	Pemetrexed STADA
FI	Pemetrexed STADA
FR	Pemetrexed EG 25 mg/ml, solution à diluer pour perfusion
HR	Pemetreksed STADA 25 mg/ml koncentrat za otopinu za infuziju
HU	Pemetrexed Stada 25 mg/ml koncentrátum oldatos infúzióhoz
IE	Pemetrexed Clonmel 25 mg/ml concentrate for solution for infusion
IT	Pemetrexed EG
LU	Pemetrexed EG 25 mg/ml solution à diluer pour solution
NL	Pemetrexed CF 25 mg/ml, concentraat voor oplossing voor infusie
PL	Pemetrexed STADA
RO	Pemetrexed STADA 25 mg/ml concentrat pentru soluţie perfuzabilă
SE	Pemetrexed STADA
SK	Pemetrexed STADA 25 mg/ml infúzny koncentrát
UK	Pemetrexed 25 mg/ml concentrate for solution for infusion

This leaflet was last revised in September 2022.

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

Instructions for use, handling and disposal

1. Use aseptic techniques during dilution of pemetrexed for intravenous infusion administration.

2. Calculate the dose and the number of Pemetrexed Clonmel vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of the label amount.

3. The appropriate volume of 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.

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

5. Parenteral medicinal products must be inspected visually for particulate matter and

discolouration prior to administration. If particulate matter is observed, do not administer.

6. Chemical and physical in-use stability of the solution for infusion has been demonstrated for 72 hours at 2 °C to 8 °C. From a microbiological point of view, the solution for infusion 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 normally not be longer than 24 hours at 2 °C to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

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.