PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pemetrexed 5 mg/ml solution for infusion
Pemetrexed 6 mg/ml solution for infusion
Pemetrexed 6.5 mg/ml solution for infusion
Pemetrexed 7 mg/ml solution for infusion
Pemetrexed 7.5 mg/ml solution for infusion
Pemetrexed 8 mg/ml solution for infusion
Pemetrexed 8.5 mg/ml solution for infusion
Pemetrexed 9 mg/ml solution for infusion
Pemetrexed 10 mg/ml solution for infusion
Pemetrexed 11 mg/ml solution for infusion

pemetrexed

Read all of this leaflet carefully before you are given 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, 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 is and what it is used for

Pemetrexed contains the active substance pemetrexed, which belongs to the group of medicines used in the treatment of cancer. It is used:
- 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
- in combination with cisplatin for the initial treatment of patients with advanced stage of lung cancer
- as a treatment for patients with lung cancer at an advanced stage if their disease has responded to treatment or it remains largely unchanged after initial chemotherapy
- as 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 are given Pemetrexed

You should NOT be given 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 before you are given 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 see 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 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 or adolescents under 18 years of age.

Other medicines and Pemetrexed
Tell your doctor if you are taking, have recently taken or might take 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.

Pregnancy, breast-feeding and fertility

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

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 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 5 mg/ml contains 407.9 mg (17.7 mmol) sodium (main component of cooking/table salt) per infusion bag. This is equivalent to 20.4 % of the maximum daily dietary intake of sodium for an adult.

Pemetrexed 6 mg/ml contains 418.6 mg (18.2 mmol) sodium (main component of cooking/table salt) per infusion bag. This is equivalent to 20.9 % of the maximum daily dietary intake of sodium for an adult.

Pemetrexed 6.5 mg/ml contains 424.0 mg (18.4 mmol) sodium (main component of cooking/table salt) per infusion bag. This is equivalent to 21.2 % of the maximum daily dietary intake of sodium for an adult.

Pemetrexed 7 mg/ml contains 429.4 mg (18.7 mmol) sodium (main component of cooking/table salt) per infusion bag. This is equivalent to 21.5 % of the maximum daily dietary intake of sodium for an adult.

Pemetrexed 7.5 mg/ml contains 434.8 mg (18.9 mmol) sodium (main component of cooking/table salt) per infusion bag. This is equivalent to 21.7 % of the maximum daily dietary intake of sodium for an adult.

Pemetrexed 8 mg/ml contains 440.1 mg (19.1 mmol) sodium (main component of cooking/table salt) per infusion bag. This is equivalent to 22.0 % of the maximum daily dietary intake of sodium for an adult.

Pemetrexed 8.5 mg/ml contains 445.5 mg (19.4 mmol) sodium (main component of cooking/table salt) per infusion bag. This is equivalent to 22.3 % of the maximum daily dietary intake of sodium for an adult.

Pemetrexed 9 mg/ml contains 450.9 mg (19.6 mmol) sodium (main component of cooking/table salt) per infusion bag. This is equivalent to 22.5 % of the maximum daily dietary intake of sodium for an adult.

Pemetrexed 10 mg/ml contains 461.7 mg (20.1 mmol) sodium (main component of cooking/table salt) per infusion bag. This is equivalent to 23.1 % of the maximum daily dietary intake of sodium for an adult.

Pemetrexed 11 mg/ml contains 472.4 mg (20.5 mmol) sodium (main component of cooking/table salt) per infusion bag. This is equivalent to 23.6 % of the maximum daily dietary intake of sodium for an adult.

3. How Pemetrexed will be given

The recommended dose of Pemetrexed is 500 milligrams for every square meter 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.

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 pharmacist will work out the dose you need based on your height and weight. Cisplatin (75 milligrams for every square meter of your body's surface area) 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 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 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, pharmacist or nurse.

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).

Serious side effects

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
- abnormal 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
- 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 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. 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 infusion bag and the outer packaging after EXP. The expiry date refers to the last day of that month.

Store in the original packaging in order to protect from light.

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 contains
- The active substance is pemetrexed (as disodium, heptahydrate).
- The other ingredients are sodium chloride, hydrochloric acid, concentrated (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injection.

One 100 ml infusion bag contains 500 mg pemetrexed (equivalent to 551.43 mg pemetrexed disodium and 699.0 mg of pemetrexed disodium heptahydrate).
One 100 ml infusion bag contains 600 mg pemetrexed (equivalent to 661.71 mg pemetrexed disodium and 838.8 mg of pemetrexed disodium heptahydrate).
One 100 ml infusion bag contains 650 mg pemetrexed (equivalent to 716.85 mg pemetrexed disodium and 908.7 mg of pemetrexed disodium heptahydrate).
One 100 ml infusion bag contains 700 mg pemetrexed (equivalent to 772.0 mg pemetrexed disodium and 978.6 mg of pemetrexed disodium heptahydrate).
One 100 ml infusion bag contains 750 mg pemetrexed (equivalent to 827.14 mg pemetrexed disodium and 1048.5 mg of pemetrexed disodium heptahydrate).
One 100 ml infusion bag contains 800 mg pemetrexed (equivalent to 882.28 mg pemetrexed disodium and 1118.4 mg of pemetrexed disodium heptahydrate).
One 100 ml infusion bag contains 850 mg pemetrexed (equivalent to 937.42 mg pemetrexed disodium and 1188.3 mg of pemetrexed disodium heptahydrate).
One 100 ml infusion bag contains 900 mg pemetrexed (equivalent to 992.57 mg pemetrexed disodium and 1258.2 mg of pemetrexed disodium heptahydrate).
One 100 ml infusion bag contains 1000 mg pemetrexed (equivalent to 1102.85 mg pemetrexed disodium and 1398.0 mg of pemetrexed disodium heptahydrate).
One 100 ml infusion bag contains 1100 mg pemetrexed (equivalent to 1213.14 mg pemetrexed disodium and 1537.8 mg of pemetrexed disodium heptahydrate).

What Pemetrexed looks like and contents of the pack
Pemetrexed solution for infusion is a clear colourless to yellow or green-yellow solution, free from visible particulate matter.

Pemetrexed solution for infusion is packed in cartons each holding 1 or 5 single-dose infusion bags of 100 ml.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Sun Pharmaceutical Industries Europe BV
Polarisavenue 87
2132 JH Hoofddorp
The Netherlands

Manufacturer
Sun Pharmaceutical Industries Europe BV
Polarisavenue 87

2132 JH Hoofddorp
The Netherlands

Terapia S.A.
124 Fabricii Street
400632, Cluj-Napoca
Cluj County
Romania

This medicine is authorised in the Member states of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

France:	Pemetrexed SUN
Germany:	Pemetrexed SUN
Italy:	Pemetrexed SUN Pharma
The Netherlands:	Pemetrexed SUN
Spain:	Pemetrexed SUN
United Kingdom (Northern Ireland):	Pemetrexed SUN

This leaflet was last revised in August 2021.

The following information is intended for medical or healthcare professionals only

Instructions for use, handling and disposal

Handling
- calculate the dose, and decide which strength of the Pemetrexed infusion bag is needed
- inspect the product pack for any damage. Do not use if there are signs of tampering
- apply patient-specific label on the overwrap.

Removal of infusion bag from overwrap and infusion bag inspection
- **for overwrap with window:** use the drug product if the colour of oxygen indicator is pink prior to opening the overwrap to remove the infusion bag; do not use the drug product if the colour of the oxygen indicator is blue prior to opening the overwrap. (The oxygen indicator is present in the bags overwrapped with an aluminium pouch with a transparent window.)
- tear overwrap at notch. Do not use if overwrap has been previously opened or damaged
- remove infusion bag from overwrap
- use only if infusion bag and seal are intact. Prior to administration check for minute leaks by squeezing bag firmly. If leaks are found, discard the bag and solution as sterility may be impaired
- parenteral medicinal products must be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

Administration
- break the stopper seal by applying pressure on one side with hand
- using aseptic technique, attach sterile administration set
- refer to directions for use accompanying the administration set.

Precautions
- do not use in series connection
- do not introduce additives into the infusion bag
- the solution for infusion is ready to use and must not be mixed with other medicinal products
- Pemetrexed solution for infusion is for single use only.

As with other potentially toxic anticancer agents, care should be exercised in the handling Pemetrexed solution for infusion. 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 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.

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.