1.3.1 Package leaflet - Core

Package leaflet: Information for the user

[product name] <100 mg> <powder for concentrate for solution for infusion>
[product name] <500 mg> <powder for concentrate for solution for infusion>
[product name] <1000 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 [product name] is and what is it used for

[product name] is a medicine used in the treatment of cancer.

[product name] 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.

[product name] 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.

[product name] 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 [product name]

Do not use [product name]
- 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 [product name].
- 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 [product name] if:
- you currently have or have previously had problems with your kidneys, as you may not be able to receive [product name]. 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 [product name]. 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 [product name].
- you have been recently vaccinated, as this can possibly cause bad effects with [product name].
- 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 [product name].

Children and adolescents
There is no relevant use of [product name] in the paediatric population.

Other medicines and [product name]
Tell your doctor or pharmacist if you are using, have recently used or might use 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 [product name] 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
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 [product name] should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking [product name] during pregnancy. Women must use effective contraception during treatment with [product name].

You should not breast-feed while using [product name]. Discuss with your doctor when it is safe to restart breast-feeding after finishing your treatment.

Men are advised not to father a child during and up to 6 months following treatment with [product name]

and should therefore use effective contraception during treatment with [product name] 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
[product name] may make you feel tired. Be careful when driving a car or using machines.

[product name] contains sodium
[product name] 1000 mg contains approximately 108 mg (4.70 mmol) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.
[product name] 500 mg contains approximately 54 mg (2.35 mmol) sodium per vial. To be taken into consideration by patients on a controlled sodium diet.
[product name] 100 mg contains approximately 11 mg (less than 1 mmol) sodium per vial, i.e. essentially 'sodium-free'.

3 How to use [product name]

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommend dose of [product name] 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 [product name] powder with 9 mg/ml (0.9 %) sodium chloride solution for injection before it is given to you.

You will always receive [product name] by infusion into one of your veins. The infusion will last approximately 10 minutes.

When using [product name] 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 [product name] 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 [product name] 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 [product name]. You must take at least 5 doses during the seven days before the first dose of [product name]. You must continue taking the folic acid for 21 days after the last dose of [product name]. You will also receive an injection of vitamin B_{12} (1000 micrograms)

in the week before administration of [product name] and then approximately every 9 weeks (corresponding to 3 courses of [product name] 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.

Tell your doctor straight away if you notice any of the following symptoms:
- 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)

The following side effects can occur during treatment with pemetrexed:

Very common side effects (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 side effects (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 ● Increased skin pigmentation.

Uncommon side effects (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 [product name] / 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 [product name] 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 [product name] therapy ● Extremity pain, low temperature and discolouration have been reported ● Blood clots in the lung blood vessels (pulmonary embolism)

Rare side effects (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 ● Immune mediated haemolytic anaemia (anaemia due to destruction of red blood cells) ● Hepatitis (inflammation of the liver) ● Anaphylactic shock (severe allergic reaction)

Not known side effects (frequency cannot be estimated from the available data)
Lower limb swelling with pain and redness ● Increased urine output ● Thirst and increased water consumption ● Hypernatraemia – increased sodium in blood ● Inflammation of the skin, mainly of the lower limb with swelling, pain and redness.

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 the national reporting system listed in Appendix V.. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store [product name]

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 pack.

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 to 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 [product name] contains

The active substance is pemetrexed.

[product name] 100 mg: Each vial contains 100 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).
[product name] 500 mg: Each vial contains 500 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).
[product name] 1000 mg: Each vial contains 1000 mg of pemetrexed (as pemetrexed disodium hemipentahydrate).

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 [product name] looks like and contents of the pack
[product name] is a powder for concentrate for solution for infusion in a vial.

It is a white to light yellow powder.

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

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

<{Name of the Member State}> <{Name of the medicinal product}>
<{Name of the Member State}> <{Name of the medicinal product}>
<…>

This leaflet was last revised in {MM/YYYY}

[To be completed nationally]

The following information is intended for medical or 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 [product name] vials needed. Each vial contains an excess of pemetrexed to facilitate delivery of the label amount.

3. [product name] <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.
   [product name] <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.
   [product name] <1000 mg>:
   Reconstitute each 1000 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 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.