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 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 [product name] is and what it is 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.

[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.

[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 hospital pharmacist before receiving [product name].

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 [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.

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 [product name].

If you have been recently vaccinated, please tell your doctor, as this can possibly cause bad effects with [product name].

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 [product name].

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 [product name]
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 [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.

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

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 [product name] should be avoided during pregnancy. Your doctor will discuss with you the potential risk of using [product name] during pregnancy. Women must use effective contraception during treatment with [product name].

Breast-feeding
If you are breast-feeding, tell your doctor.
Breast-feeding must be discontinued during treatment with [product name].

Fertility
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 powder for concentrate for solution for infusion
This medicine contains 108 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 5.4% of the recommended maximum daily dietary intake of sodium for an adult.
[product name] 500 mg powder for concentrate for solution for infusion
This medicine contains 54 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.7% of the recommended maximum daily dietary intake of sodium for an adult.
[product name] 100 mg powder for concentrate for solution for infusion
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3 How to use [product name]

The 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.

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).

Side effects with [product name] 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 number of 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 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 (may affect up to 1 in 100 people):
- Reduction in the number of red and 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 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 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 (diabetes insipidus)
- Disorder of the kidneys involving the death of tubular epithelial cells that form the renal tubules

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.

Before opening 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.

Type I glass 10 mL vial, containing 100 mg of pemetrexed, with a rubber stopper (bromobutyl- or chlorobutyl elastomer, coating of e.g. Teflon), an aluminium cap and an ivory flip-top.
Type I glass 25 mL vial, containing 500 mg of pemetrexed, with a rubber stopper (bromobutyl- or chlorobutyl

elastomer, coating of e.g. Teflon), an aluminium cap and a blue flip-top.
Type I glass 50 mL vial, containing 1000 mg of pemetrexed, with a rubber stopper (bromobutyl- or chlorobutyl elastomer, coating of e.g. Teflon), an aluminium cap and a green flip-top.

Each pack consists of one vial.

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:

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.