Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) – 1986

This medicine is dispensed with a doctor's prescription only

Pemetrexed Teva 100 mg
Powder for concentrate for solution for infusion

Composition:
Each vial contains:
Pemetrexed 100 mg (as pemetrexed disodium)

Pemetrexed Teva 500 mg
Powder for concentrate for solution for infusion

Composition:
Each vial contains:
Pemetrexed 500 mg (as pemetrexed disodium)

Pemetrexed Teva 1000 mg
Powder for concentrate for solution for infusion

Composition:
Each vial contains:
Pemetrexed 1000 mg (as pemetrexed disodium)

After reconstitution, the concentrated solution contains 25 mg/ml of pemetrexed. Further dilution by a healthcare professional is required prior to administration.

For information about inactive ingredients and allergens: see section 6 - "Additional information" and section 2 - "Important information about some of this medicine's ingredients".

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.

This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

1. WHAT IS THIS MEDICINE INTENDED FOR?

Pemetrexed Teva is a medicine used in the treatment of cancer.

Pemetrexed Teva in combination with cisplatin is indicated for the treatment of patients with malignant pleural mesothelioma, whose disease is unresectable or who are otherwise not candidates for curable surgery.

Pemetrexed Teva in combination with cisplatin is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

Pemetrexed Teva is indicated as monotherapy for the second-line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

Pemetrexed Teva is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy.

Therapeutic group: folic acid analogues.

2. BEFORE USING THIS MEDICINE

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient, pemetrexed, or to any of the other ingredients in this medicine (see section 6 - "Additional information").
- You are breastfeeding; you must discontinue breastfeeding during treatment with Pemetrexed Teva.
- You have recently received or are about to receive a vaccine against yellow fever.

Special warnings about using this medicine:
Before using Pemetrexed Teva, tell your doctor:

- If you currently have or have previously had problems with your kidneys, consult your doctor or hospital pharmacist, as you may not be able to receive Pemetrexed Teva.
- Before each infusion, blood samples will be taken from you to evaluate kidney and liver function and determine suitability for the treatment. Additionally, your blood count will be checked **to determine suitability for receiving treatment** with Pemetrexed Teva. Your doctor may decide to change the dose or delay treatment depending on your general condition and whether the blood counts are too low. If you are also receiving cisplatin, your doctor will make sure that you are not dehydrated and that you are receiving appropriate treatment before and after receiving cisplatin in order to prevent vomiting.
- If you received or are about to receive radiation therapy, report this to your doctor, as there may be an early or late radiation reaction when being treated with Pemetrexed Teva.
- If you have recently been vaccinated, report this to your doctor, as this can possibly have bad implications when being treated with Pemetrexed Teva.
- If you have heart disease or a history of heart disease, report this to your doctor.
- If you have an accumulation of fluid around your lungs, your doctor may decide to remove the fluid before giving you Pemetrexed Teva.

Children and adolescents:
There is no relevant use of Pemetrexed Teva in children for treatment of malignant pleural mesothelioma and non-small cell lung cancer.

Drug interactions:
If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or hospital pharmacist. Particularly if you are taking:
Any medicine to treat pain or inflammation (swelling), such as medicines called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), including medicines purchased without a doctor's prescription (such as ibuprofen). There are many types of NSAIDs with different durations of action. Based on the planned date of your infusion of Pemetrexed Teva and/or on your kidney function status, your doctor will need to advise you on which medicines you can take and when you can take them. If you are unsure, consult your doctor or pharmacist if any of your medicines are NSAIDs.

Pregnancy, breastfeeding and fertility:
Pregnancy:
If you are pregnant, think you may be pregnant or are planning to become pregnant, **report this to your doctor**. Refrain from using Pemetrexed Teva during pregnancy. Your doctor will discuss the potential risk of taking Pemetrexed Teva during pregnancy with you. Women must use effective contraception during treatment with Pemetrexed Teva.

Breastfeeding:
If you are breastfeeding, report this to your doctor.
Breastfeeding must be discontinued during treatment with Pemetrexed Teva.

Fertility:
Men are advised not to father a child during and up to 6 months following treatment with Pemetrexed Teva. Therefore, men must use effective contraception during treatment with Pemetrexed Teva and for up to 6 months following treatment. If you would like to father a child during treatment or in the 6 months following receipt of treatment, ask your doctor or pharmacist for advice. You may want to seek counseling on sperm storage before starting treatment.

Driving and using machines:
Pemetrexed Teva may make you feel tired. Be careful when driving a car or using machines.

Important information about some of this medicine's ingredients:
Pemetrexed Teva 100 mg contains less than 1 mmol sodium (23 mg) per vial and is therefore considered sodium-free.

Pemetrexed Teva 500 mg contains approximately 54 mg sodium (main component of cooking/table salt) per vial. This amount is equivalent to 2.7% of the recommended maximum daily dietary intake of sodium for adults.

Pemetrexed Teva 1000 mg contains approximately 109 mg sodium (main component of cooking/table salt) per vial. This amount is equivalent to 5.45% of the recommended maximum daily dietary intake of sodium for adults.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.

Only your doctor will determine your dose and how you should take this medicine. The recommended dosage is usually:
The dose of Pemetrexed Teva is 500 milligrams for every square meter of your body's surface area. Your height and weight are measured to calculate the surface area of your body. Your doctor will use this body surface area to calculate 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 Teva powder with 9 mg/ml (0.9%) sodium chloride solution for injection before it is given to you.

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

When using Pemetrexed Teva in combination with cisplatin:
The doctor or hospital pharmacist will calculate the dose you need based on your height and weight. Cisplatin is also given by infusion into one of your veins, and it is given approximately 30 minutes after the infusion of Pemetrexed Teva has finished. The infusion of cisplatin will last approximately 2 hours. The infusion is usually given once every 3 weeks.

Additional medicines:
Corticosteroids: Your doctor will prescribe you steroid tablets (a dose equivalent to 4 milligrams of dexamethasone twice a day) that you will need to take on the day before, on the day of, and the day after treatment with Pemetrexed Teva. This medicine is given to you to reduce the frequency and severity of skin reactions that you may experience during your anti-cancer treatment.

Vitamin supplements:
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 being treated with Pemetrexed Teva. You must take at least 5 doses in the 7 days before administration of the first dose of Pemetrexed Teva. You must continue taking the folic acid for 21 days after the last dose of Pemetrexed Teva. You will also receive an injection of vitamin B_{12} (1,000 micrograms) in the week before administration of Pemetrexed Teva and then approximately once every 9 weeks (corresponding to 3 courses of treatment with Pemetrexed Teva). Vitamin B_{12} and folic acid are given to you to reduce the possible toxic effects of the anti-cancer treatment.

Do not exceed the recommended dose.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.

If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects

Like with all medicines, using Pemetrexed Teva may cause side effects in some users. Do not be alarmed by this list of side effects. You may not experience any of them.

Contact your doctor immediately if you notice any of the following effects:

- Fever or infection (respectively, common or very common effect): If you have a temperature of 38ºC or higher, are sweating or have other signs of infection (since you might have a lower number of white blood cells than normal, which is a very common effect). Infection (sepsis) may be severe and could lead to death.
- If you start feeling chest pain (common effect) or having a fast heart rate (uncommon effect).
- If you have pain, redness, swelling or sores in your mouth (very common effect).
- Allergic reaction: If you develop a skin rash (very common effect) / burning or prickling sensation (common effect), or fever (common effect). In rare cases, skin reactions may be severe and could lead to death. Contact your doctor if you get severe rash, 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 a lower hemoglobin level than normal, which is a very common effect).
- If you experience bleeding from the gums, nose or mouth or any other bleeding that does not stop, notice reddish or pinkish urine, have unexpected bruising (since you might have a lower number of platelets than normal, which is a common effect).
- If you experience sudden breathlessness, intense chest pain or cough with bloody sputum (uncommon effect) (symptoms that may indicate a blood clot in the blood vessels of the lungs).

Additional side effects:
Very common side effects that appear in more than one in ten users:

- Infection
- Pharyngitis
- Low count of neutrophils and granulocytes (types of white blood cells)
- Low white blood cell count
- Low hemoglobin level
- Pain, redness, swelling or sores in your mouth
- Lack of appetite
- Vomiting
- Diarrhea
- Nausea
- Skin rash
- Flaking skin
- Abnormal blood test findings indicating reduced kidney function
- Fatigue (tiredness)

Common side effects that appear in 1-10 in 100 users:

- Blood infection
- Fever with low level of neutrophils and granulocytes (types of white blood cells)
- Low platelet count
- Allergic reaction
- Dehydration
- Change in sense of taste
- Damage to the motor nerves which may cause muscle weakness and atrophy (primarily in the arms and legs)
- Damage to the sensory nerves that may cause loss of sensation, burning sensation and unsteady gait
- Dizziness
- Inflammation or swelling of the conjunctiva (the membrane that lines the eyelids and covers the white part of the eye)
- Dry eyes
- Watery eyes
- Dryness of the conjunctiva (the membrane that lines the eyelids and covers the white part of the eye) and cornea (the clear layer in front of the iris and pupil)
- Swelling of the eyelids
- Eye disorders, including dryness, tearing, irritation, and/or pain
- Heart failure (condition that affects the pumping power of your heart muscles)
- Irregular heart rhythm
- Indigestion
- Constipation
- Abdominal pain
- Liver: increase in the amount of substances made by the liver in the blood
- Increased skin pigmentation
- Skin irritation and itching
- Skin rash that resembles a bullseye
- Hair loss
- Urticaria (hives)
- Kidney failure
- Reduced kidney function
- Fever
- Pain
- Excess fluids in body tissues, causing swelling
- Chest pain
- Inflammation and ulceration of the mucous membranes lining the digestive tract

Uncommon side effects that appear in 1-10 in 1,000 users:

- Reduction in the levels of red, white blood cells and platelets
- Stroke
- Stroke caused 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 flow to the limbs
- Blockage of one of the pulmonary arteries
- 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 esophagus
- Inflammation of the lining of the large intestine, 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 lungs caused by radiation therapy

Rare side effects that appear in 1-10 in 10,000 users:

- 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 that appear in less than one in 10,000 users:

- Inflammation of skin and soft tissues
- Stevens-Johnson syndrome (a severe skin and mucous membrane reaction that may be life threatening)
- Toxic epidermal necrolysis (a 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, 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 that becomes inflamed, itchy, red, cracked, and rough
- Intensely itchy spots

Side effects of unknown frequency (the frequency of these effects has not been established yet):

- Onset of diabetes primarily due to pathology of the kidneys
- Disorder of the kidneys involving the death of tubular epithelial cells that form the renal tubules

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor as soon as possible.

Reporting side effects:
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the vial and package. The expiry date refers to the last day of that month.

Storage conditions:
Closed vials: Store below 25ºC.

Reconstituted and infusion solutions:
The chemical and physical stability of reconstituted and infusion solutions of Pemetrexed Teva were demonstrated for 24 hours under refrigeration (2ºC-8ºC). From a microbiological point of view, the product should be used immediately. If not used immediately, the duration and conditions of storage prior to use are the responsibility of the user and in no case should exceed 24 hours at a temperature of 2ºC-8ºC.

This medicine is for single use only; any unused solution must be disposed of in accordance with local requirements.

6. Additional information

In addition to the active ingredient, this medicine also contains:
Mannitol, sodium hydrochloride, hydrochloric acid (for pH adjustment).

What the medicine looks like and contents of the pack:
Powder for concentrate for solution for infusion.
White to either light yellow or green-yellow lyophilized powder.

Each pack contains one vial of Pemetrexed Teva.

Registration holder's name and address:
Abic Marketing Ltd., P.O.B 8077, Netanya

Manufacturer's name and address:
Teva Pharmaceutical Industries, P.O.Box 3190, Petach-Tikva.

The leaflet was revised in April 2021 according to MOH guidelines.

Registration number of the medicine in the Ministry of Health's National Drug Registry:
Pemetrexed Teva 100 mg: 156.39.34393
Pemetrexed Teva 500 mg: 156.40.34410
Pemetrexed Teva 1000 mg: 156.41.34411

THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY:

1. Use aseptic technique during the reconstitution and further dilution of pemetrexed for intravenous infusion administration.
2. Calculate the dose and the number of Pemetrexed Teva vials needed.

   <u>100 mg:</u> Reconstitute 100-mg vials with 4.2 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, resulting in a solution containing 25 mg/ml pemetrexed. Each vial contains an excess of pemetrexed to facilitate delivery of label amount.

   <u>500 mg:</u> Reconstitute 500-mg vials with 20 ml of sodium chloride 9 mg/ml (0.9%) solution for injection, without preservative, resulting in a solution containing 25 mg/ml pemetrexed.

   <u>1000 mg:</u> Reconstitute 1000-mg vials with 40 ml of sodium chloride 9 mg/ml (0.9%) 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. The pH of the reconstituted solution is between 6.6 and 7.8. **Further dilution is required.**
3. The appropriate volume of reconstituted pemetrexed solution must be further diluted to 100 ml with sodium chloride 9 mg/ml (0.9%) 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 polyolefin-lined administration sets and infusion bags.
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. Pemetrexed solutions are for single use only. Any unused medicinal product or waste material must 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.