PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

Peme Sol 25 mg/ml

Concentrate for solution for infusion

Composition:

Each 1 ml contains: 25 mg pemetrexed (as diacid monohydrate)
A 4 ml vial contains 100 mg pemetrexed diacid monohydrate
A 20 ml vial contains 500 mg pemetrexed diacid monohydrate
A 34 ml vial contains 850 mg pemetrexed diacid monohydrate
A 40 ml vial contains 1,000 mg pemetrexed diacid monohydrate
Further dilution by a healthcare professional is required before administration.

For information about inactive ingredients see section 6 – "Additional information".

Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have any other questions, refer to the doctor or the pharmacist.

This medicine has been prescribed for treatment of your illness. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Peme Sol is a medicine used for the treatment of cancer.

Peme Sol 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 any other curative surgery.

Peme Sol 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.

Peme Sol 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.

Peme Sol is indicated as monotherapy for the maintenance treatment of patients with 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 class: folic acid analogues.

2. BEFORE USING THE MEDICINE

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient (pemetrexed) or any of the additional components the medicine contains (detailed in section 6).
- You are breastfeeding; you must discontinue breastfeeding during treatment with **Peme Sol**.
- You have recently received or are about to receive a vaccine against yellow fever. See also in section 2 under "Drug interactions".

Special warnings regarding the use of the medicine

Before treatment with **Peme Sol**, inform the doctor if:

- You are currently suffering or have suffered in the past from kidney problems. Consult with the doctor or the hospital's pharmacist, as you may not be able to receive **Peme Sol**.
- Before each infusion, you will have blood samples taken in order to check your kidney and liver function and to determine whether the treatment with **Peme Sol** is appropriate for you. In addition, your blood count will be checked in order to determine whether the treatment with **Peme Sol** is appropriate for you. Depending on your general condition, and in case your blood count is too low, your doctor may decide on changing the dose or delaying your treatment. If you are also receiving cisplatin, the doctor will make sure you are not dehydrated and that you are receiving appropriate treatment before and after receiving cisplatin in order to prevent vomiting.
- You have received or are about to receive radiation therapy. Inform your doctor, as there may be an early or late radiation reaction during treatment with **Peme Sol**.
- You have been recently vaccinated. Inform your doctor, as there may be bad consequences during treatment with **Peme Sol**.
- You suffer from a heart disease or have a history of heart disease, inform the doctor.
- You suffer from fluid accumulation around the lungs, the doctor may decide to remove the fluid before giving you **Peme Sol**.

Children and adolescents

Do not give this medicine to children and adolescents, as there is no experience with this medicine in children and adolescents under the age of 18 years.

Drug interactions

If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or the hospital's pharmacist. Especially 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 types of NSAIDs with different durations of activity. Based on the planned date of **Peme Sol** infusion 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, consult your doctor or pharmacist on whether 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, **inform the doctor.** Avoid using **Peme Sol** during pregnancy. The doctor will discuss with you the potential risk of taking **Peme Sol** during pregnancy. Women must use effective contraception methods during treatment with **Peme Sol** and for 6 months after receiving the last dose.

Breastfeeding

If you are breastfeeding, inform the doctor.

Stop breastfeeding during the treatment with **Peme Sol**.

Fertility

Men are advised not to father a child during and up to 3 months following treatment with **Peme Sol**. Therefore, men should use effective contraception methods during the treatment with **Peme Sol** and for 3 months following the treatment. If you would like to father a child during the treatment or during the 3 months following the treatment, refer to the doctor or pharmacist in order to seek advice. **Peme Sol** may affect your ability to have children. Talk to the doctor to seek advice about sperm storage before starting the treatment.

Driving and operating machinery

Peme Sol may make you feel tired. You should be careful when driving a car or operating machinery.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the medicine according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and how to use the medicine. The dosage and treatment regimen will be determined by the doctor only.

The generally accepted dosage is:

The dosage of **Peme Sol** is 500 mg for every square meter of the body's surface area. Your height and weight are measured in order to calculate the surface area of your body. The doctor will use this value of body surface area in order to calculate the right dosage for you. This dosage may be adjusted or the treatment may be delayed depending on your blood cell counts and on your general condition.

Before receiving the medicine, the hospital's pharmacist, a nurse or a doctor will dilute the **Peme Sol** solution with 5% glucose solution for injection or 0.9% sodium chloride solution without preservative, at a volume of 100 ml.

Peme Sol is given by intravenous infusion, administered over 10 minutes.

Using **Peme Sol** in combination with cisplatin:

The doctor or the hospital's pharmacist will calculate the required dosage based on your height and weight. Cisplatin is given by intravenous infusion **about 30 minutes after the infusion** of **Peme Sol has finished.** The infusion of cisplatin will last approximately two hours. Usually, the infusion will be given once every 3 weeks.

Peme Sol contains an inactive ingredient called trometamol. Trometamol leads to the breakdown of cisplatin, and therefore it is not suitable for concomitant use with cisplatin. The infusion tube must be flushed after administering **Peme Sol**.

Additional medicines given during the treatment:

- Corticosteroids: the doctor will prescribe you steroid tablets (a dosage equivalent to 4 mg dexamethasone twice a day), which you will need to take a day before the treatment, on the day of the treatment and the day after the treatment with **Peme Sol**. This medicine is given to you in order to reduce the frequency and severity of skin reactions that you may suffer from during the anticancer treatment.
- Vitamin supplementation: the doctor will prescribe you oral folic acid (vitamin) or a multivitamin preparation containing folic acid (350 to 1,000 micrograms), which you will need to take once a day during the treatment with **Peme Sol**. You should take at least 5 doses during the 7 days before receiving the first dose of **Peme Sol**. You should continue taking folic acid for 21 days after the last dose of **Peme Sol**. In addition, you will receive an injection of vitamin B_{12} (1,000 micrograms) in the week before receiving **Peme Sol**, and then approximately once every 9 weeks (corresponding to 3 courses of **Peme Sol** treatment). Vitamin B_{12} and folic acid are given to you in order to reduce the possible toxic effects of the anticancer treatment.

Do not exceed the recommended dose.

If you have accidentally taken a higher dose or if you have taken an overdose or if a child has accidentally swallowed the medicine, immediately refer to a doctor or to a hospital emergency room and bring the package of the medicine with you.

Follow the treatment as recommended by the doctor.

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

If you have other questions regarding the use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, using **Peme Sol** may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.

Refer to the doctor immediately if you notice any of the following effects:

- Fever or infection (a common or very common effect, respectively): if you have a fever of 38ºC or higher, sweating or other signs of infection (since you may have less white blood cells than normal; which is a very common effect). Infection (sepsis) may be severe and could lead to death.
- If you feel chest pain (a common effect) or if you have a fast heart rate (an uncommon effect).
- If you suffer from pain, redness, swelling or sores in the mouth (very common effects).
- An allergic reaction: if you develop a skin rash (a very common effect), burning or tingling sensation (a common effect), or fever (a common effect). In rare cases, skin reactions may be severe and could lead to death. Refer to the doctor if you suffer from a severe rash, itching or blisters (Stevens-Johnson syndrome or toxic epidermal necrolysis).
- If you suffer from tiredness, feeling faint, easily develop shortness of breath or if you look pale (since your hemoglobin level might be lower than usual; which is a very common effect).
- If you suffer from bleeding from the gums, nose or mouth or any other bleeding that would not stop, notice reddish or pinkish urine, suffer from unexpected hematomas (since you might have less platelets than usual; which is a common effect).
- If you suffer from sudden shortness of breath, intense chest pain or cough with bloody sputum (uncommon effects) (symptoms that may indicate a blood clot in the blood vessels of the lungs).

Additional side effects

Very common side effects (may occur in more than 1 out of 10 users)

Infection; infection of the throat (pharyngitis); low number of neutrophil granulocytes (a type of white blood cells); low white blood cell count; low hemoglobin level; pain, redness, swelling or sores in the mouth; lack of appetite; vomiting; diarrhea; nausea; skin rash; flaking skin; abnormal findings in blood tests indicating reduced function of the kidneys; fatigue (tiredness).

Common side effects (may occur in up to 1 in 10 users)

Blood infection; fever with low number of neutrophil granulocytes (a type of white blood cells); low platelet count; an allergic reaction; dehydration; change in the 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 feeling and unsteady gait; dizziness; inflammation or swelling of the conjunctiva (the membrane that covers the white of the eye and to which the eyelid is connected); dry eyes; watery eyes; dryness of the conjunctiva (the membrane that covers the white of the eye and to which the eyelid is connected) and cornea (a clear layer located in front of the iris and pupil); swelling of the eyelids; eye problems including dryness, tearing, irritation, and/or pain; cardiac failure (a condition that affects the pumping power of your heart muscles); irregular heart rate; digestive difficulties; constipation; abdominal pain; increase in the amount of substances made by the liver in the blood; increased skin pigmentation; irritated skin; skin rash that looks like a bullseye; hair loss; hives (urticaria); kidney failure; a decrease in the function of the kidneys; fever; pain; excess fluid in body tissues, causing swelling; chest pain; inflammation and ulceration of the mucous membranes lining the digestive tract.

Uncommon side effects (may occur in up to 1 in 100 users)

Reduction in the levels of red blood cells, white blood cells and platelets; stroke; a stroke that is caused by a blockage of an artery leading to the brain; bleeding within the skull; angina (chest pain caused by reduced blood flow to the heart); heart attack; narrowing or blockage of the coronary arteries; rapid heartbeat; deficient blood flow to the limbs; blockage in one of the pulmonary arteries; inflammation and scarring of the lining of the lungs with breathing problems; anal bleeding; bleeding in the gastrointestinal tract; ruptured bowel; inflammation of the lining of the esophagus; 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 surface of the esophagus muscle caused by radiation therapy; inflammation of the lungs caused by radiation therapy.

Rare side effects (may occur in up to 1 in 1,000 users)

Destruction of red blood cells; anaphylactic shock (a severe allergic reaction); inflammation of the liver; skin redness; skin rash that develops throughout a previously irradiated area.

Very rare side effects (may occur in up to 1 in 10,000 users)

Infection of the skin and soft tissues; Stevens-Johnson syndrome (a severe skin and mucous membranes 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 blisters filled with fluid; fragile skin, blisters, erosion and skin scarring; redness, pain and swelling mainly of the lower limbs; inflammation of the skin and of the fat beneath the skin (pseudocellulitis); inflammation of the skin (dermatitis); skin that becomes inflamed, itchy, red, cracked and rough; intense localized itching.

Side effects of unknown frequency (their frequency cannot be estimated from the existing data)

Developing diabetes primarily due to pathology of the kidneys; disorder of the kidneys involving the death of the epithelial cells that form the renal tubules.

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in this leaflet, inform your doctor as soon as possible.

Reporting of side effects

Side effects may be reported to the Ministry of Health by clicking on the link "Report side effects due to medicinal treatment" found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following link: https://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE?

- Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.
- Do not use this medicine after the expiry date (exp. date) which is stated on the vial and the package. The expiry date refers to the last day of that month.
- **Store in the fridge (2°C-8°C), in the original package in order to protect the medicine from light. Do not freeze.**
- After dilution:
  From a chemical and physical point of view: after diluting with a 5% glucose solution or with a 0.9% (9 mg/ml) sodium chloride solution, **Peme Sol** solution is stable for 7 days in refrigeration, and for 24 hours at room temperature.
  From a microbiological point of view: the product should be used immediately. If not used immediately, the duration and conditions of storage before use are the responsibility of the user, and in any case should not exceed 24 hours at a temperature of 2°C-8°C, unless the dilution occurred in a controlled and aseptic environment.
- This medicine is for single use only; any unused solution must be disposed of.

6. ADDITIONAL INFORMATION

In addition to the active ingredient, Peme Sol also contains:

Trometamol, citric acid anhydrous, methionine, water for injection

What does the medicine look like and what are the contents of the package:

Peme Sol 25 mg/ml is a clear, colorless to slightly yellowish or yellow-greenish solution in a glass vial.

Each package of **Peme Sol 25 mg/ml** contains one vial.

Package sizes:

One vial containing 4 ml (100 mg/4 ml)
One vial containing 20 ml (500 mg/20 ml)
One vial containing 34 ml (850 mg/34 ml)
One vial containing 40 ml (1,000 mg/40 ml)
Not all package sizes may be marketed.

Name and address of the Manufacturer and Marketing Authorization Holder:

Teva Israel Ltd., 124 Dvora HaNevi'a St., Tel Aviv 6944020

The leaflet was revised in September 2022 in accordance with the Ministry of Health guidelines.

Registration number of the medicine in the national drug registry of the Ministry of Health: 170.40.37158

THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY:

Incompatibilities

Pemetrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection. In the absence of other compatibility studies, this medicinal product must not be mixed with other medicinal products.

Peme-Sol 25 mg/ml contains trometamol as an excipient. Trometamol is incompatible with cisplatin, resulting in degradation of cisplatin.

Intravenous lines should be flushed after administration of Peme-Sol 25 mg/ml.

Special precautions for disposal and other handling:

1. Use aseptic technique during dilution of pemetrexed for intravenous infusion administration.
2. Calculate the dose and the number of Peme-Sol 25 mg/ml vials needed.
3. **Peme-Sol 25 mg/ml must only be diluted with 5% glucose solution or 0.9% sodium chloride solution, without preservative.** The appropriate volume of pemetrexed concentrate must be diluted to 100 ml with 5% glucose solution or 0.9% sodium chloride solution 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.
5. Parenteral medicinal products must be inspected visually for particulate matter and discoloration 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 a pemetrexed solution contacts 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.

In use stability of the diluted solution

Chemical and physical in-use stability of pemetrexed infusion solution has been demonstrated in 5% glucose and 0.9% sodium chloride for 24 hours at room temperature and for 7 days at refrigerated temperature. From a microbiological point of view, the product 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 be longer than 24 hours at 2°C-8°C, unless dilution has taken place in controlled and validated aseptic conditions.

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