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

The medicine is dispensed with a doctor's prescription only

PEMETREXED TARO 100 mg

Powder for concentrate for solution for infusion

PEMETREXED TARO 500 mg

Powder for concentrate for solution for infusion

PEMETREXED TARO 1000 mg

Powder for concentrate for solution for infusion

Active ingredient: pemetrexed.

Pemetrexed Taro 100 mg: Each vial contains 100 mg pemetrexed (as pemetrexed disodium heptahydrate)
Pemetrexed Taro 500 mg: Each vial contains 500 mg pemetrexed (as pemetrexed disodium heptahydrate)
Pemetrexed Taro 1000 mg: Each vial contains 1000 mg pemetrexed (as pemetrexed disodium heptahydrate).

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

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

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have any further questions, please contact 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 Taro is a medicine used to treat cancer.

Pemetrexed Taro 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 curative surgery.
Pemetrexed Taro 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 Taro 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 Taro 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 hypersensitive (allergic) to pemetrexed or any of the other ingredients in this medicine (see section 6).
- you are breastfeeding; you must discontinue breastfeeding during treatment with **Pemetrexed Taro**.
- 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 this medicine
Before starting treatment with Pemetrexed Taro, tell your doctor if:

- you currently have or have previously had problems with your kidneys; talk to your doctor or pharmacist at the hospital, as you may not be able to receive **Pemetrexed Taro**.
- Before each infusion, you will have samples of your blood taken to evaluate kidney and liver function and determine the suitability of receiving treatment. You will also have a blood cell count to determine the suitability of receiving **Pemetrexed Taro**. 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; please tell your doctor, as there may be an early or late radiation reaction with **Pemetrexed Taro** therapy.
- you have been vaccinated recently; please tell your doctor, as this could have undesirable effects with **Pemetrexed Taro** therapy.
- you have heart disease or a history of heart disease; please tell your doctor.
- you have an accumulation of fluid around your lungs; your doctor may decide to remove the fluid before giving you **Pemetrexed Taro**.

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 the age of 18.

Drug interactions
If you are taking or have recently taken other medicines, **including non-prescription medicines and dietary supplements, inform the hospital doctor or pharmacist.**
Particularly 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 Taro** 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 the medicines you take are NSAIDs.

Pregnancy, breastfeeding, and fertility

Pregnancy

If you are pregnant, think you may be pregnant or are planning a pregnancy, **tell your doctor**. The use of **Pemetrexed Taro** should be avoided during pregnancy. Your doctor will discuss with you the risk of taking **Pemetrexed Taro** during pregnancy.
Women must use effective contraception during treatment with **Pemetrexed Taro** and for 6 months after receiving the last dose.

Breastfeeding
If you are breastfeeding, tell your doctor .

Breastfeeding must be discontinued during treatment with **Pemetrexed Taro**.

Fertility
Men are advised not to father a child during and up to 3 months following treatment with **Pemetrexed Taro** and should therefore use effective contraception during treatment with **Pemetrexed Taro** and for up to 3 months afterwards. If you would like to father a child during the treatment or in the 3 months following receipt of treatment, seek advice from your doctor or pharmacist. Pemetrexed Taro can affect your ability to have children. Talk to your doctor to seek advice about sperm storage before starting your therapy.

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

Important information about some of this medicine's ingredients
Pemetrexed Taro 100 mg contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.
Pemetrexed Taro 500 mg contains 54 mg sodium (the main ingredient in table salt) per vial. This quantity is equivalent to 2.7% of the maximum recommended daily allowance of sodium for adults.
Pemetrexed Taro 1000 mg contains 108 mg sodium (the main ingredient in table salt) per vial. This quantity is equivalent to 5.4% of the recommended daily allowance of sodium for adults.

3. HOW SHOULD YOU USE THIS MEDICINE?

Always use the 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 usual dosage is:

The dose of **Pemetrexed Taro** is 500 mg 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.
A hospital pharmacist, nurse, or doctor will have mixed the **Pemetrexed Taro** powder with 9 mg/ml (0.9%) sodium chloride solution for injection before it is given to you.

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

When using **Pemetrexed Taro** 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 **Pemetrexed Taro** has finished. The infusion of cisplatin will last approximately 2 hours.

You should usually receive your infusion once every 3 weeks.

Additional medicines given during treatment:

Corticosteriods: your doctor will prescribe you steroid tablets (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 **Pemetrexed Taro** 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 1,000 micrograms) that you must take once a day while you are taking **Pemetrexed Taro**. You must take at least 5 doses during the seven days before the first dose of **Pemetrexed Taro**. You must continue taking the folic acid for 21 days after the last dose of **Pemetrexed Taro**. You will also receive an injection of vitamin B_{12} (1,000 micrograms) in the week before administration of **Pemetrexed Taro** and then approximately every 9 weeks (corresponding to 3 courses of **Pemetrexed Taro** treatment). Vitamin B_{12} and folic acid are given to you 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, contact a doctor or hospital emergency room immediately and bring the medicine package with you.
Treatment should be continued as recommended by your doctor.

Do not take medicines in the dark! Check the label and the dose <u>every time</u> you take medicine. Wear glasses if you need them.
If you have further questions regarding the use of this medicine, consult your doctor or pharmacist.

4. <u>SIDE EFFECTS</u>

As with any medicine, the use of **Pemetrexed Taro** 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.

You must contact your doctor immediately if you notice any of the following:
- Fever (common) or infection (very 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 have a fast heart rate (uncommon).
- If you have pain, redness, swelling, or sores in your mouth (very common).
- Allergic reaction: if you develop a 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 will not stop, notice reddish or pinkish urine, experience unexpected bruising (since you might have less platelets than normal which is 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).

Additional side effects

<u>Very common side effects (affect more than 1 in 10 users)</u>
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 side effects (affect up to 1 in 10 users)
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 (primarily in the arms and legs)
damage to the sensory nerves that may cause loss of sensation, burning sensation and unsteady gait
dizziness
swelling or inflammation of the conjunctiva (the membrane that lines the eyelid and covers the white of the eye)
dry eyes
watery eyes
dryness of the conjunctiva (the membrane that lines the eyelid and covers the white of the eye) and cornea (the clear layer in front of the iris and pupil)
swelling of the eyelids
eye problems including dryness, tearing, irritation, and/or pain
heart failure (a 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
skin irritation
skin rash where each mark resembles a bullseye
hair loss
hives (urticaria)
kidney stops 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 side effects (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
increased 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

bleeding 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 lungs caused by radiation therapy.

Rare side effects (affect up to 1 in 1,000 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 (may affect up to 1 in 10,000 users)
infections of skin and soft tissues
Stevens-Johnson syndrome (a type of severe skin and soft tissue 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, 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 becomes inflamed, itchy, red, cracked, and rough
intensely itchy spots.

Not known: frequency cannot be estimated from the available data
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 a side effect occurs, if any of the side effects worsen, or if you experience a side effect not mentioned in this leaflet, consult the doctor.

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 this medicine after the expiry date (exp. date) which is stated on the vial and carton. The expiry date refers to the last day of that month.

Storage conditions
Do not store over 25˚C.
Shelf-life after reconstitution (dissolving): 24 hours when the concentrated solution is stored in the refrigerator (2°C-8°C).
Shelf-life after dilution: Use the product immediately, within 10 minutes of preparation.

This medicine is for single use only. Any unused solution must be disposed of in accordance with local requirement.

6. ADDITIONAL INFORMATION

In addition to the active ingredient, this medicine also contains:
mannitol, hydrochloric acid, sodium hydroxide.

What the medicine looks like and contents of the pack:
A powder for solution for infusion in a vial. It is a white to either light yellow or green-yellow lyophilized powder.
Each pack of **Pemetrexed Taro** contains one vial.

Name and address of manufacturer and license holder: Taro International Ltd., 14 Hakitor Street, Haifa Bay 2624761

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Pemetrexed Taro 100 mg: 163-33-35358-00
Pemetrexed Taro 500 mg: 163-34-35359-00
Pemetrexed Taro 1000 mg: 163-35-35360-00

Revised in October 2022 according to MOH guidelines.

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

Special precautions for disposal and other handling

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 Taro** vials needed. The vial contains an excess of pemetrexed to facilitate delivery of label amount.

3. **Pemetrexed Taro 100 mg**
   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.
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   – **Pemetrexed Taro 500 mg**
   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.
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   – **Pemetrexed Taro 1000 mg**
   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 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 sodium chloride 9 mg/ml (0.9%) 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.

6. Parenteral medicinal products must 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 medicinal product or waste material must be disposed of in accordance with local requirements.