Patient Package Insert according to Pharmacists' Regulations (Preparations) - 1986 The medicine is dispensed with a doctor's prescription only

Pemetrexed Taro 100 mg Powder for solution for infusion

Pemetrexed Taro 500 mg Powder for solution for infusion

Pemetrexed Taro 1000 mg Powder for solution for infusion

The active ingredient is 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 pemetrexed. Further dilution by a medical staff member is required prior to administration.

Inactive ingredients and allergens: See section 2 clause "Important information about some of the ingredients of this medicine" and section 6 "Additional information"

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

This medicine has been prescribed for the treatment of your illness. Do not pass it on to others. It might harm them, even if you think that their

illness is similar.

1. What is the medicine intended for? Pemetrexed Taro is a medicine used in the treatment of 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 any other curatible 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 lung cancer other than predominantly squamous cell histology.

Pemetrexed Taro 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 group: Folic acid analogues.

2. Before using the medicine

Do not use the medicine if:

you are hypersensitive (allergic) to pemetrexed or to any of the other ingredients this medicine contains (listed in 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.

Special warnings regarding the use of this medicine Before treatment with Pemetrexed Taro, tell the doctor:

If you currently have or have previously had problems with your kidneys, consult the doctor or hospital pharmacist, as you may not be able to receive Pemetrexed Taro.

Before each infusion, you will have samples of your blood taken to evaluate your kidney and liver functions in order to determine the suitability of receiving Pemetrexed Taro treatment. Your doctor may decide to change the dosage or delay your treatment 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 not dehydrated and that you receive appropriate treatment before and after receiving cisplatin to prevent vomiting.

If you have had or are going to have radiation therapy, inform your doctor, as there may be an early or late radiation reaction during treatment with the medicine

If you have been recently vaccinated, inform your doctor, as this can possibly cause bad effects while being treated with Pemetrexed Taro.

If you have a heart disease or a history of a heart disease, inform your doctor.

If 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

There is no relevant use for Pemetrexed Taro in children for the treatment of malignant pleural mesothelioma or for the treatment of non-small

Drug interactions If you are taking, or have recently taken other medicines, including non-prescription drugs and nutrition supplements, tell the doctor

or hospital pharmacist. Especially if you are taking: Any medicine for pain or inflammation (swelling) such as medicines called nonsteroidal anti-inflammatory drugs (NSAIDs), including medicine 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 your Pemetrexed Taro infusion and/or the status of your kidney function, your doctor will need to advise you on which medicines

If you are unsure, consult your doctor or pharmacist if any of your medicines are NSAIDs.

Pregnancy, breastfeeding, and fertility

are permitted for you and when you can take them

If you are pregnant, think you may be pregnant or are planning to become pregnant, inform your doctor. The use of Pemetrexed Taro should be avoided during pregnancy. The doctor will discuss with you the potential risk of taking Pemetrexed Taro during pregnancy Women must use effective contraception during treatment with Pemetrexed Taro.

If you are breastfeeding, inform your doctor.

Breastfeeding must be discontinued during treatment with Pemetrexed Taro.

Men are advised not to father a child during treatment and up to 6 months following treatment with Pemetrexed Taro. Therefore, men should use effective contraception during treatment with Pemetrexed Taro and up to 6 months following treatment. If you would like to father a child during treatment or in the 6 months after receiving treatment, refer to the doctor or pharmacist for advice. You may want to seek counseling on sperm storage before starting treatment.

Driving and use of machinery

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

Important information about some of the ingredients of this medicine Pemetrexed Taro 100 mg contains less than 1 mmol sodium (23 mg) per vial, i.e., essentially "sodium-free".

Pemetrexed Taro 500 mg contains 54 mg sodium (a main component of table/cooking salt) per vial. This quantity is equivalent to 2.7% of the recommended maximum daily sodium dose for adults.

Pemetrexed Taro 1000 mg contains 108 mg sodium (a main component in table/cooking salt) per vial. This quantity is equivalent to 5.4% of the recommended maximum daily sodium dose for adults.

3. How to use this medicine

The dosage and manner of treatment will be determined by the doctor only. The usual dosage is:

The dosage 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. A doctor will use this body surface area value in order to calculate the right dosage for you. This dosage may be adjusted, or treatment may be delayed depending on your blood cell counts and your general condition. A hospital pharmacist, nurse or doctor will mix 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 calculate the dosage 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 Permetexed Taro has finished.

The infusion of cisplatin will last approximately 2 hours. Usually, the infusion will be given once every 3 weeks.

Additional medicines:

Corticosteroids: The doctor will prescribe you steroid tablets (a dosage equivalent to 4 mg dexamethasone twice daily), which you will need to take on the day before the treatment, on the day of the treatment, and on the day after the treatment with Pemetrexed Taro. This medicine is given to you to reduce the frequency and severity of skin reactions that you may experience during your anticancer treatment.

Vitamin supplements: Your doctor will prescribe you oral folic acid (vitamin) or a multivitamin containing folic acid (350 to 1,000 micrograms), which you must take once a day during the treatment with Pemetrexed Taro. You must take at least 5 doses during the 7 days preceding administration of the first dose of Pemetrexed Taro. You must continue taking folic acid for 21 days after the last dose of Pemetrexed Taro. You will also receive an injection of vitamin B₁₂ (1,000 micrograms) the week before administration of **Pemetrexed Taro**, and then approximately once every 9 weeks (corresponding to 3 courses of treatment with Pemetrexed Taro). Vitamin B₁₂ and folic acid are given to you to reduce possible toxic effects of the anticancer treatment.

Do not exceed the recommended dose.

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

4. Side Effects

As with any medicine, the use of Pemetrexed Taro may cause side effects in some users. Do not be alarmed while reading the list of side effects. You might not suffer from any of them. Refer to a doctor immediately if you notice any of the following side effects:

• Fever or infection (a common or very common side effect, respectively): If you have a temperature of 38°C or higher, sweating or other signs of infection (since your white blood cell count may be lower than the normal count; this is a very common side effect). Infection (sepsis) may

- be severe and could lead to death. If you start feeling chest pain (a common side effect) or if you have a fast heart rate (an uncommon side effect).
- If you have pain, redness, swelling, or sores in your mouth (a very common side effect). Allergic reaction: if you develop a skin rash (a very common side effect) / a burning or prickling sensation (a common side effect), or fever (a common side effect). In rare cases, skin reactions may be severe and could lead to death. Contact your doctor if you get a severe rash, itching,
- or blistering (symptoms of Stevens-Johnson Syndrome or toxic epidermal necrolysis). If you experience tiredness, feeling faint, becoming breathless easily or if you look pale (since you might have less hemoglobin than normal); this is a very common side effect).
- 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, this is a common side effect).
- If you experience sudden breathlessness, intense chest pain, or a cough with bloody sputum (an uncommon side effect) (symptoms that may indicate a blood clot in the blood vessels of the lungs).

Additional Side Effects:

Very common side effects (appear in more than 1 in 10 users) Infection

Inflammation of the pharynx (pharyngitis) Low neutrophil granulocytes (a type of white blood cell) count

Low white blood cell count Low hemoglobin level

Pain, redness, swelling or sores in the mouth Loss of appetite Vomiting

Diarrhea Nausea

Flaking skin

Abnormal blood tests showing reduced functionality of the kidneys Fatigue (tiredness)

Common side effects (appear in up to 1 in 10 users) Fever with a low level of neutrophil granulocytes (a type of white blood cell)

Allergic reaction

Dehydration

Taste change

Damage to the motor nerves that may cause muscle weakness and atrophy (primarily in the arms and legs) Damage to the sensory nerves than 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

Constipation

Dryness of the conjunctiva (the membrane that lines the eyelid and covers the white of the eye) and cornea (the transparent layer in front of the

iris and pupil) Swelling of the evelids

Heart failure (a condition that affects the pumping power of the heart muscles) Irregular heart rhythm Indigestion

Abdominal pain Liver: increase in the quantity of chemicals in the blood produced by the liver Increased skin pigmentation

Eye problems including dryness, tearing and irritation and/or pain

Skin irritation and itching Skin rash that resembles a bullseye Hair loss

Hives (urticaria) Kidney failure Reduced kidney function Fever

Excessive fluids in the body tissues, causing swelling Chest pain

Inflammation and ulceration of the mucous membranes lining the digestive tract

Uncommon side effects (appear in up to 1 in 100 users)

Reduction in the level of red blood cells, white blood cells and platelets

Stroke Stroke caused by blockage of an artery to the brain

Intracranial hemorrhage Angina (chest pain caused by reduced blood flow to the heart)

Heart attack

Narrowing or blockage of the coronary arteries Increased heart rhythm

Poor blood circulation in the limbs Blockage of one of the pulmonary arteries

Inflammation and scarring of the lining of the lungs together with breathing problems

Passage of bright red blood from the anus Bleeding in the gastrointestinal tract Tear in the intestine

Inflammation of the lining of the esophagus Inflammation of the lining of the large intestine, that may be accompanied by intestinal or rectal bleeding (seen only in combination with cisplatin) Inflammation, edema, erythema and erosion of the muscle surface of the esophagus caused by radiation therapy

Rare side effects (appear in up to 1 in 1,000 users) Destruction of the red blood cells

Anaphylactic shock (severe allergic reaction)

Inflammation of the lungs caused by radiation therapy

Inflammation condition of the liver Redness of the skin Skin rash that develops throughout a previously irradiated area

Very rare side effects (appear in up to 1 in 10,000 users) Inflammation of the skin and soft tissues

Stevens-Johnson Syndrome (a severe skin and soft tissues reaction that may be life threatening) Toxic epidermal necrolysis (a severe skin reaction that may be life threatening) Autoimmune disorder that causes skin rashes and blisters on the legs, arms, and abdomen Skin inflammation characterized by the presence of bullae which are filled with fluid

Fragile skin, blisters, erosion, and scarring of the skin Redness, pain and swelling primarily in the lower limbs Inflammation of the skin and fat beneath the skin (pseudocellulitis)

Skin that becomes inflamed, itchy, red, cracked, and rough Intensely itchy spots

Side effects of unknown frequency: frequency cannot be estimated from the available data Form 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 appears, if any side effect gets worse or if you experience a side effect not mentioned in this leaflet, tell the doctor as soon as possible.

Reporting side effects Side effects can be reported to the Ministry of Health via the link "reporting side effects associated with medications" found on the home page of

Inflammation of the skin (dermatitis)

the Ministry of Health website (www.health.gov.il) directing to the online form for reporting side effects or via the following link: https://sideeffects.health.gov.il

5. How to Store the Medicine

• Avoid poisoning! This medicine, and all other medicines, must be stored in a safe place out of the reach and sight of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.

Do not use the medicine after the expiry date (exp. date) that appears on the vial and the package. The expiry date refers to the last day of that month

after being prepared. If not used immediately and if prepared as directed, in-use chemical and physical stability of reconstituted and infusion

Storage conditions Store below 25°C Reconstituted solutions and infusion solutions: from a microbiological point of view, the product must be used immediately, within 10 minutes

solutions of pemetrexed were demonstrated for 24 hours at refrigerated temperature (2°C-8°C). • This medicine is for single use only. Any unused solution residues must be disposed of in accordance with local requirement.

6. Additional Information In addition to the active ingredient, Pemetrexed Taro also contains: mannitol, hydrochloric acid, sodium hydroxide.

What Pemetrexed Taro looks like and contents of the pack: Pemetrexed Taro is a powder for the preparation of solution for infusion in a vial. It is a light yellow or green-yellow colored powder. Each pack of Pemetrexed Taro contains one vial.

Manufacturer and registration holder and its address: Taro International Ltd., 14 Hakitor St., Haifa Bay 2624761

Drug registration number in the Ministry of Health National Drug Registry: Pemetrexed Taro 100 mg: 163-33-35358-00 Pemetrexed Taro 500 mg: 163-34-35359-00

Revised in April 2021 according to MOH guidelines.

Pemetrexed Taro 1000 mg: 163-35-35360-00

Pemetrexed Taro PIL PB0321-05