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

The medicine is dispensed with a doctor's prescription only

Sunitinib Taro 12.5 mg
Sunitinib Taro 25 mg
Sunitinib Taro 37.5 mg
Sunitinib Taro 50 mg
Hard capsules

Active ingredient
Sunitinib 12.5 mg, 25 mg, 37.5 mg, 50 mg

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

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about the medicine. If you have 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.

This medicine is intended for adults above the age of 18.

1. What is this medicine intended for?

- For treatment of gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to imatinib mesylate.
- For treatment of advanced renal cell carcinoma (aRCC).
- For treatment of differentiated pancreatic neuroendocrine tumors (pNET), metastatic or unresectable.

Therapeutic group:
Targeted tyrosine kinase receptor inhibitor.

2. Before using this medicine

Do not use this medicine if:

You are sensitive (allergic) to the active ingredient or to any of the other ingredients in this medicine (see section 6).

Special warnings about using this medicine

Before treatment with Sunitinib Taro, tell your doctor if:

- **You have high blood pressure.** Sunitinib Taro can raise blood pressure. Your doctor may check your blood pressure during treatment with Sunitinib Taro, and you may be treated with medicines to reduce the blood pressure, if needed.
- **You have or have had a blood disease, bleeding problems or bruising.** Treatment with Sunitinib Taro may increase the risk of bleeding or lead to changes in the number of certain cells in the blood which may lead to anemia or affect the ability of your blood

to clot. If you are taking warfarin or acenocoumarole, medicines which thin the blood to prevent blood clots, there may be a greater risk of bleeding. Tell your doctor if you have bleeding during treatment with Sunitinib Taro.

- **You have heart problems.** Sunitinib Taro can cause heart problems. Tell your doctor if you feel very tired, have shortness of breath, or swollen feet and ankles.
- **You have abnormal heart rhythm changes.** Sunitinib Taro can cause abnormality of your heart rhythm. Your doctor may perform an electrocardiogram to evaluate these problems during your treatment with Sunitinib Taro. Tell your doctor if you feel dizzy, faint, or have abnormal heartbeats while taking Sunitinib Taro.
- **You have had recent problems with blood clots in your veins or arteries (types of blood vessels), including stroke, heart attack, embolism, or thrombosis.** Contact your doctor immediately if you have symptoms such as chest pain or pressure, pain in your arms, back, neck or jaw, shortness of breath, numbness or weakness on one side of your body, trouble talking, headache, or dizziness while on treatment with Sunitinib Taro.
- **You have or have had damage in the small blood vessels, a condition called TMA** (thrombotic microangiopathy). Tell your doctor if you develop fever, tiredness, bruising, bleeding, swelling, confusion, loss of sight, and seizures.
- **You have or have had an aneurysm** (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- **You have thyroid gland problems.** Sunitinib Taro can cause thyroid gland problems. Tell your doctor if you get tired more easily, generally feel colder than other people, or your voice deepens whilst taking Sunitinib Taro. Your thyroid function should be checked before you take Sunitinib Taro and during treatment with it. If your thyroid gland is not producing enough thyroid hormone, you may be treated with thyroid hormone replacement.
- **You have or have had pancreatic or gallbladder disorders.** Tell your doctor if you develop any of the following symptoms and signs: pain in the area of the stomach (upper abdomen), nausea, vomiting, and fever. These may be caused by inflammation of the pancreas or gallbladder.
- **You have or have had liver problems.** Tell your doctor if you develop any of the following symptoms and signs of liver problems during Sunitinib Taro treatment: itching, yellow eyes or skin, dark urine, and pain or discomfort in the right upper stomach area. Your doctor will do blood tests to check your liver function before and during treatment with Sunitinib Taro, and as clinically indicated.
- **You have or have had kidney problems.** Your doctor will monitor your kidney function.
- **You are going to have or have recently had surgery.** Sunitinib Taro may affect the way your wounds heal. You will usually stop treatment with Sunitinib Taro if you are having an operation. Your doctor will decide when to start taking Sunitinib Taro again.
- **You may be advised to have a dental check-up before you start treatment with Sunitinib Taro.**
  - If you have or have had pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or feel that a tooth is loose, tell your doctor and dentist immediately.
  - If you need to undergo an invasive dental treatment or dental surgery, tell your dentist that you are being treated with Sunitinib Taro, in particular when you are also taking or have taken intravenous bisphosphonates. Bisphosphonates are medicines used to prevent bone complications that may have been given for another medical condition.
- **You have or have had skin and subcutaneous tissue disorders.** During treatment with Sunitinib Taro, pyoderma gangrenosum (painful skin ulceration) or necrotizing fasciitis (rapidly spreading infection of the skin/soft tissues that may be life-threatening) may occur. Contact your doctor immediately if symptoms of infection occur around a skin injury, including fever, pain, redness, swelling, or drainage of pus

or blood. This event is generally reversible after Sunitinib Taro discontinuation. Severe skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) have been reported with the use of Sunitinib Taro, appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk. The rash may progress to widespread blistering or peeling of the skin and may be life-threatening. If you develop a rash or these skin symptoms, contact your doctor immediately.

- **You have or have had seizures.** Tell your doctor as soon as possible if you have high blood pressure, headache, or loss of sight.
- **You have diabetes.** Blood sugar levels in diabetic patients should be checked regularly in order to assess if the dosage of your antidiabetic medications needs to be adjusted to minimize the risk of low blood sugar. Notify your doctor as soon as possible if you experience signs and symptoms of low blood sugar levels (fatigue, palpitations, sweating, hunger and loss of consciousness).

Children and adolescents

Sunitinib Taro is not intended for people aged under 18.

Interactions with other medicines

If you are taking or have recently taken other medicines, including nonprescription medicines and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:

Medicines which in combination with Sunitinib Taro increase its concentration in the blood:

ketoconazole, itraconazole (used to treat fungal infections), erythromycin, clarithromycin (antibiotics), ritonavir (used to treat HIV).

Medicines which in combination with Sunitinib Taro lower its concentration in the blood:

dexamethasone (a corticosteroid used to treat various conditions such as allergies/breathing disorders or skin diseases), phenytoin, carbamazepine, phenobarbital (used to treat epilepsy and other neurological diseases), rifampin (an antibiotic), the herb Hypericum (St. John's wort) (used to treat depression and anxiety).

Warfarin (to treat hypercoagulation) – your blood clotting measures must be monitored medically.

Cholesterol-lowering medicines in the statin class and medicines in the bisphosphonate class (such as alendronate) administered intravenously before or during treatment with Sunitinib Taro.

Using this medicine and food

The medicine can be taken with or without food. Swallow the medicine with a small amount of water. Do not drink grapefruit juice or eat grapefruit during treatment with the medicine. Consumption of grapefruit may change the concentration of the medicine in your body.

Pregnancy and breastfeeding

If you are pregnant or breastfeeding, think you may be pregnant, or are planning to get pregnant, consult your doctor before taking this medicine.

If you might get pregnant, you should use effective methods of contraception during treatment with Sunitinib Taro.

If you are breastfeeding, tell your doctor. Do not breastfeed during treatment with Sunitinib Taro.

Driving and using machines

Use of this medicine may impair alertness and cause dizziness and sleepiness; therefore, caution should be exercised when driving a car, operating dangerous machinery and when engaging in any activity that requires alertness.

Important information about some of this medicine's ingredients

This medicine contains less than 1 mmol (23 mg) sodium per capsule, that is to say essentially 'sodium-free'.

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.

It is recommended to take the medicine at the same time every day.

Do not exceed the recommended dose.

There is no information about opening capsules and releasing their content.

If you have taken an overdose or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine at the scheduled time, skip the dose and take the next dose the following day at the scheduled time, but under no circumstances should you take a double 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 every time 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

As with any medicine, using Sunitinib Taro may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

You must immediately contact your doctor if you experience any of the following serious side effects (see also section 2 under 'Special warnings regarding use of the medicine'):

Heart problems. Tell your doctor if you feel very tired, are short of breath, or have swollen feet and ankles. These may be symptoms of heart problems that may include heart failure and heart muscle problems (cardiomyopathy).

Lung or breathing problems. Tell your doctor if you develop cough, chest pain, sudden onset of shortness of breath, or are coughing up blood. These may be symptoms of a condition called pulmonary embolism that occurs when blood clots travel to your lungs.

Kidney disorders. Tell your doctor if you experience altered frequency or absence of urination which may be symptoms of kidney failure.

Bleeding. Tell your doctor if you have any of the following symptoms or serious bleeding during treatment with Sunitinib Taro: painful and swollen stomach; vomiting blood; black,

sticky stools; bloody urine; headache or change in your mental status; coughing up blood or bloody sputum from the lungs or airway.

Tumor destruction leading to a hole in the intestine. Tell your doctor if you have severe abdominal pain, fever, nausea, vomiting, blood in your stool, or changes in bowel habits.

Additional side effects

Very common side effects - affect more than 1 in 10 users:

Diarrhea, constipation, abdominal pain/swelling, nausea, loss/decrease of appetite, dizziness, fever, inflammation and/or sores and/or dryness of the mouth, digestive disturbances, vomiting, mouth irritation or pain, taste changes, severe allergic rash, skin discoloration/yellowing of the skin, pigmentation of the skin, hair color change, extreme fatigue, weakness, headache, insomnia, back pain, joint pain, limb pain, cough, decreased thyroid activity, reduction in the level of platelets, red and/or white blood cells, swelling caused by fluid under the skin or around the eyes, nose bleed, shortness of breath, high blood pressure, rash on the palms of the hands and soles of the feet, rash, dryness of skin.

Common side effects - affect up to 1 in 10 users:

Blood clots in the blood vessels, deficiency in blood supply to the heart muscle due to narrowing or obstruction of the coronary arteries, chest pain, reduction in the amount of blood pumped by the heart on each beat, fluid retention including around the lungs, flu-like feeling, infections, complication of a severe infection (infection in the blood) that can lead to tissue damage, organ failure and death. Decreased blood sugar level - (see section 2 under 'Special warnings regarding use of the medicine'), depression, hemorrhoids, pain in the rectum, gingival bleeding, difficulty or inability to swallow, pain and/or burning sensation on the tongue, inflammation of the esophagus and mucosa, gas in the stomach or intestine, weight loss, muscle and bone pain, muscular weakness, muscular fatigue, sudden muscle contraction (spasm), nasal dryness, congested nose, excessive tearing, abnormal sensation in the skin, flaking and inflammation of the skin, blisters on the skin, itching, acne, dehydration, hot flashes, abnormally colored urine, nail discoloration, hair loss, high levels of uric acid in the blood, loss of protein in the urine (can lead to swelling), abnormal blood test results, including liver and pancreatic enzyme levels, abnormal sensation in the extremities, increased/decreased sensitivity, particularly to touch, heartburn, chills.

Uncommon side effects - affect up to 1 in 100 users:

Life-threatening infection of the soft tissues, including the ano-genital regions (see section 2 under 'Special warnings regarding use of the medicine'). Stroke, heart attack caused by a decreased or interrupted blood supply to the heart, changes in the electrical activity or heart rhythm disorder, fluid around the heart (pericardial effusion), liver failure, abdominal pains due to inflammation of the pancreas. Tumor destruction leading to perforation of the intestine, inflammation (redness and swelling) of the gallbladder (with or without gallstones), abnormal passage between body cavities or the skin. Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or a feeling that a tooth is loose, may be signs and symptoms of bone damage in the jaw (see section 2 under 'Special warnings regarding use of the medicine'). Overproduction of thyroid hormones, which increase the amount of energy the body uses at rest, problems with wound healing after surgery, increased blood level of enzyme (creatine phosphokinase) from muscle, severe reaction to allergens including allergic rhinitis (hay fever), skin rash, itchy skin, hives, swelling of body parts and trouble breathing. Inflammation of the colon (colitis, ischemic colitis).

Rare side effects - affect up to 1 in 1,000 users:

Severe reactions of the skin and/or mucous membranes (Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme), painful skin ulceration (pyoderma gangrenosum), muscle breakdown (rhabdomyolysis), which can lead to kidney problems. Tumor lysis syndrome: metabolic complications that can occur during treatment of cancer, due to breakdown of cancerous cells. Effects that are included in this group are nausea, shortness of breath, irregular heart rate, muscle cramps, seizures, tiredness and cloudy urine associated with changes in blood test results (high levels of potassium, uric acid and phosphate and low levels of calcium in the blood) that can lead to changes in kidney function and kidney failure, hepatitis - inflammation of the liver, abnormal changes in the brain that can cause a collection of symptoms such as: headaches, confusion, seizures, and loss of sight. Inflammation of the thyroid gland, damage in the small blood vessels, an effect called TMA (thrombotic microangiopathy).

Side effects of unknown frequency (frequency cannot be estimated from the available information):

An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysm and artery dissection), lack of energy, confusion, sleepiness, unconsciousness/coma – these symptoms may be signs of brain toxicity caused by high blood levels of ammonia (hyperammonemic encephalopathy).

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.

You can report side effects to the Ministry of Health by following the 'Reporting Side Effects of Drug Treatment' link on the Ministry of Health home page (www.health.gov.il), which opens an online form for reporting side effects, or 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 your doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions

- Store the medicine below 25°C.

6. Additional information

In addition to the active ingredient, this medicine also contains:

Sunitinib 12.5 mg:

Cellulose, microcrystalline, mannitol, croscarmellose sodium, povidone, magnesium stearate, hard gelatin capsule shell: red iron oxide, titanium dioxide, gelatin, and printing white ink (containing shellac, titanium dioxide, propylene glycol).

Sunitinib 25 mg:

Cellulose, microcrystalline, mannitol, croscarmellose sodium, povidone, magnesium stearate, hard gelatin capsule shell: black iron oxide, red iron oxide, yellow iron oxide, titanium dioxide, gelatin, and printing white ink (containing shellac, titanium dioxide, propylene glycol).

Sunitinib 37.5 mg:

Cellulose, microcrystalline, mannitol, croscarmellose sodium, povidone, magnesium stearate, hard gelatin capsule shell: yellow iron oxide, titanium dioxide, gelatin, and printing black ink (containing shellac, black iron oxide, propylene glycol, ammonium hydroxide).

Sunitinib 50 mg:

Cellulose, microcrystalline, mannitol, croscarmellose sodium, povidone, magnesium stearate, hard gelatin capsule shell: black iron oxide, red iron oxide, yellow iron oxide, titanium dioxide, gelatin, and printing white ink (containing shellac, titanium dioxide, propylene glycol).

What the medicine looks like and contents of the pack:

Sunitinib Taro 12.5 mg: an orange capsule with “12.5 mg” imprinted in white ink and that contains yellow-orange granules.

Sunitinib Taro 25 mg: a capsule, the cap of which is caramel-colored and the body of which is orange and imprinted with “25 mg” in white ink and that contains yellow-orange granules.

Sunitinib Taro 37.5 mg: a yellow capsule with "37.5 mg" imprinted in black ink and that contains yellow-orange granules.

Sunitinib Taro 50 mg: a caramel-colored capsule with “50 mg” imprinted in white ink, and that contains yellow-orange granules.

The medicine is marketed in blister packs containing 28 capsules.

Registration holder’s name and address: Taro International Ltd., 14 Hakitor St., Haifa Bay 2624761

Manufacturer's name and address:

Pharmacare Premium Ltd.

HHF003 Hal Far Industrial Estate, Birzebbugia, BBG 3000, Malta

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Registration number of the medicine in the Ministry of Health’s National Drug Registry:

Sunitinib Taro 12.5 mg: 167-94-36017-00

Sunitinib Taro 25 mg: 167-95-36030-00

Sunitinib Taro 37.5 mg: 167-96-36031-00

Sunitinib Taro 50 mg: 167-97-36032-00