

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

The medicine is dispensed with a doctor's prescription only

Cabometyx[®] 20 mg

Cabometyx[®] 40 mg

Cabometyx[®] 60 mg

Film-coated tablets

Name and quantity of active ingredients

Cabometyx 20 mg

Each tablet contains 20 mg cabozantinib (as (S)-malate)

Cabometyx 40 mg

Each tablet contains 40 mg cabozantinib (as (S)-malate)

Cabometyx 60 mg

Each tablet contains 60 mg cabozantinib (as (S)-malate)

Inactive ingredients and allergens in this medicine - See section 6 "**Additional information**". See also "**Important information about some of the medicine's ingredients**" in section 2.

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 the 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?

Kidney cancer (renal cell carcinoma)

Cabometyx is indicated as monotherapy for an advanced kidney cancer called advanced renal cell carcinoma:

- as first-line treatment of adult patients who are at moderate or high risk according to the IMDC classification.
- in adult patients who have been previously treated with VEGF (vascular endothelial growth factor) inhibitors.

Cabometyx, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults.

Liver cancer (hepatocellular carcinoma)

Cabometyx is used as a single treatment to treat a type of liver cancer called carcinoma in adults with impaired liver function (Child-Pugh Class A) who have been previously treated with sorafenib.

Therapeutic group: inhibitor of the enzyme protein kinase.

Cabometyx blocks the action of proteins called receptor tyrosine kinases (RTKs), which are involved in the growth of cells and the development of new blood vessels that supply them with nutrients. These proteins can be present in large amounts in cancer cells, and by blocking their action Cabometyx can slow down the rate at which the tumor grows and help to cut off the blood supply that the cancer needs.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredient (cabozantinib) or to any of the other ingredients that this medicine contains (see section 6 "**Additional information**").

Special warnings relating to the use of this medicine

Before starting treatment with Cabometyx, tell your doctor or pharmacist if:

- you suffer from high blood pressure
- have or have had an aneurysm (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall
- you suffer from diarrhea
- you have recently suffered from significant bleeding
- you have had surgery within the last month (or if surgical procedures are planned), including dental surgery
- you suffer from inflammatory bowel disease (such as Crohn's disease or ulcerative colitis, diverticulitis or appendicitis)
- you have recently suffered from a blood clot in your leg, stroke or heart attack
- you have thyroid problems. Tell your doctor if you get tired more easily, generally feel colder than other people, or your voice deepens whilst taking this medicine. If your thyroid gland is not producing enough thyroid hormone, you may be treated with thyroid hormone replacement
- you suffer from a liver or kidney disease

Tests and follow-up

Your thyroid function should be checked before you take Cabometyx and regularly while you are taking it.

Tell your doctor if any of these apply to you.

You may need treatment for them, or your doctor may decide to change your dose of Cabometyx or stop treatment altogether. See also section 4 "**Side effects**".

You must tell your dentist that you are taking Cabometyx. It is important for you to practice good mouth care during treatment with Cabometyx.

Children and adolescents

Cabometyx is not intended for children and adolescents. The effects of Cabometyx on people under 18 years old are not known.

Interactions with other medicines

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

- medicines that treat fungal infections, such as itraconazole, ketoconazole, and posaconazole
- medicines used to treat bacterial infections (antibiotics) such as erythromycin, clarithromycin, and rifampicin
- medicines to treat allergy such as fexofenadine
- medicines to treat angina pectoris (chest pain owing to inadequate supply to the heart) such as ranolazine
- medicines used to treat epilepsy or convulsions such as phenytoin, carbamazepine, and phenobarbital
- herbal preparations containing St. John's Wort (*Hypericum perforatum*), sometimes used for treating depression or depression-related conditions such as anxiety
- medicines used to thin the blood, such as warfarin and dabigatran etexilate
- medicines to treat high blood pressure or other heart conditions, such as aliskiren, ambrisentan, digoxin, talinolol, and tolvaptan
- medicines for diabetes, such as saxagliptin and sitagliptin
- medicines used to treat gout, such as colchicine
- medicines used to treat HIV or AIDS, such as efavirenz, ritonavir, maraviroc and emtricitabine
- medicines used to prevent rejection of transplanted organs (cyclosporine), and cyclosporine-based regimens in rheumatoid arthritis and psoriasis

Using this medicine and food

Do not take Cabometyx with food. Do not eat anything for at least two hours before taking Cabometyx and for one hour after taking the medicine. Avoid consuming grapefruit-containing products for as long as you are using this medicine, because they may increase the levels of Cabometyx in your blood.

Pregnancy, breastfeeding, and fertility

Avoid becoming pregnant while being treated with Cabometyx. If you could become pregnant or if you are being treated and your partner could become pregnant, use adequate contraception during treatment and for at least 4 months after treatment has finished. Consult with your doctor about which methods of contraception are appropriate while you are taking Cabometyx (see also under "**Interactions with other medicines**").

Tell your doctor if you, or your partner, become pregnant or plan to become pregnant while you are being treated with Cabometyx.

You have to talk to your doctor before taking Cabometyx if you or your partner are considering or planning to become pregnant after your treatment has finished or if you finished your treatment and your partner is considering or planning to become pregnant. There is a possibility that your fertility could be affected by treatment with Cabometyx.

Women taking Cabometyx should not breastfeed during treatment and for at least 4 months after treatment has finished, because Cabometyx and/or its metabolites may pass into breast milk and be harmful to your infant.

If you take Cabometyx while you are using oral contraceptives, the oral contraceptives may be ineffective. You must also use a barrier contraceptive (such as a condom or diaphragm) while you are taking Cabometyx and for at least 4 months after treatment has finished.

Driving and using machines

Use caution when driving or using machines. Keep in mind that treatment with Cabometyx may make you feel tired or weak and can affect your ability to drive or use machines.

Important information about some of this medicine's ingredients

Cabometyx contains lactose.

Cabometyx contains lactose (a type of sugar).

If you have been told by your doctor that you have an intolerance to some sugars, talk to your doctor before taking this medicine.

Cabometyx contains sodium.

This medicine contains less than 23 mg sodium per tablet, 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. The recommended dose is usually 60 mg once a day. However, your doctor will decide on the right dose for you.

When Cabometyx is given in combination with nivolumab for the treatment of advanced kidney cancer, the recommended dose of Cabometyx is 40 mg once a day.

Continue taking this medicine until your doctor decides to stop your treatment. If you get serious side effects, your doctor may decide to change your dose or stop treatment earlier than originally planned. Your doctor will tell you if you need your dose adjusted.

How to take this medicine:

Swallow the tablet whole with a full glass of water.

There is no information about crushing or splitting the tablet.

Do not exceed the recommended dose.

If you have accidentally taken a higher dose

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

If you forget to take the medicine

If there are still 12 hours or more before your next dose is due, take the missed dose as soon as possible.

If your next dose is due in less than 12 hours, do not take the dose that you have missed. Take your next dose at the normal time.

If you stop using this medicine

Stopping your treatment may stop the effect of the medicine. Do not stop using Cabometyx unless you have discussed this with your doctor.

When Cabometyx is given in combination with nivolumab, you will first be given nivolumab followed by Cabometyx.

Please refer to the package leaflet of nivolumab in order to understand the use of this medicine. If you have any further questions on the use of this medicine, ask your doctor.

Do not take medicines in the dark! Check the label and dose each 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

Like all medicines, using Cabometyx may cause side effects in some people. Do not be alarmed by this list of side effects; you may not experience any of them. If you experience side effects, your doctor may tell you to take Cabometyx at a lower dose. Your doctor may also prescribe other medicines to help control your side effects.

Tell your doctor immediately if you notice any of the following side effects – you may need urgent medical treatment:

- Symptoms including pain in the abdomen, nausea, vomiting, constipation or fever. These may be signs of a gastrointestinal perforation – a hole that develops in your stomach or intestine that could be life-threatening.
- Severe or uncontrollable bleeding with symptoms such as vomiting blood, black stools, bloody urine, headache, coughing up blood.
- Swelling, pain in your hands and feet or shortness of breath.
- A wound that does not heal.
- Convulsions, headaches, confusion or finding it difficult to concentrate. These may be signs of a condition called posterior reversible encephalopathy syndrome (PRES). This condition is rare (it affects less than 1 in 1,000 users).
- Feeling drowsy, confused or loss of consciousness. This may be due to liver problems.
- Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of teeth. These could be signs of bone damage in the jaw (osteonecrosis).

Additional side effects with Cabometyx as monotherapy

Very common side effects (may affect more than one in ten users)

- Stomach upset including diarrhea, nausea, vomiting, constipation, indigestion, and abdominal pain
- Blisters, pain of the hands or feet, rash or redness of the skin
- Decreased appetite, weight loss, altered sense of taste
- Fatigue, weakness, headache, dizziness
- Hypertension (high blood pressure)
- Anemia (low levels of red blood cells)
- Low level of platelets
- Redness, swelling or pain in the mouth or throat, difficulty in speaking, hoarseness, cough
- Changes in the blood tests used to monitor general health and function of your organs (including the liver and kidneys), low levels of electrolytes (like magnesium, or potassium)
- Shortness of breath
- Reduced thyroid activity; symptoms may include tiredness, weight gain, constipation, feeling cold and dry skin
- Swelling in the legs and arms
- Pain in the arms, hands, legs or feet
- Low level of albumin in blood
- Inflammation of mucous membranes
- Perforation in the digestive system
- Bleeding

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

- Abscess (collection of pus, with swelling and inflammation)
- Dehydration
- Difficulty swallowing
- Ringing in your ears (tinnitus)
- Blood clots in your blood vessels and lungs
- Low levels of white blood cells
- Increase or decrease in blood sugar levels
- Decrease in levels of calcium, sodium and phosphorus in the blood
- Increase in level of potassium in the blood
- Increase in the level of bilirubin in the blood (which may result in jaundice/yellow skin or eyes)
- Increase in amylase levels in the blood
- Increase in lipase levels in the blood
- Increase in cholesterol or triglyceride levels in the blood
- Numbness, tingling, burning sensation or pain in the limbs
- A painful tear or abnormal connection of the tissues in your body (fistula)
- Gastro-esophageal reflux disease (bringing up stomach acid)
- Hemorrhoids
- Dry mouth and pain in the mouth
- Feeling drowsy, confused or loss of consciousness due to liver problems
- Dry skin, severe itching of skin, acne
- Thickening of the skin outer layer
- Alopecia (hair loss and thinning), hair color change
- Pain in joints, muscle spasms
- Protein in urine (seen in tests)
- Burning or stinging sensation of the tongue
- Increased amounts of creatinine in your blood
- Increased amounts of the enzymes ALT and GGT

Uncommon side effects (may affect 1 in 100 users)

- Convulsions
- Severe high blood pressure
- Inflammation of the pancreas
- Reduced flow of bile from the liver
- Bone damage in the jaw
- Complications in wound healing

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

- Stroke
- Heart attack
- An enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections)

The following side effects have been reported **with Cabometyx in combination with nivolumab**:

Very common side effects (may affect more than 1 in 10 users)

- Infections of the upper respiratory tract
- Reduced thyroid activity; symptoms can include tiredness, weight gain, constipation, feeling cold and dry skin

- Increased thyroid activity; symptoms can include rapid heart rate, sweating and weight loss
- Decreased appetite, altered sense of taste
- Headache, dizziness
- High blood pressure
- Difficulty in speaking, hoarseness (dysphonia), cough and shortness of breath
- Stomach upset, including diarrhea, nausea, vomiting, indigestion, abdominal pain and constipation
- Redness, swelling or pain in the mouth or throat (stomatitis)
- Skin rash sometimes with blisters, itching, pain of the hands or soles of the feet, rash or redness of the skin
- Pain in joints (arthralgia), muscle spasm, muscle weakness and aching muscles
- Protein in the urine (seen in test)
- Feeling tired or weak, fever and edema (swelling)

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

- Serious lung infection (pneumonia)
- Increase in some white blood cells called eosinophils
- Allergic reaction (including anaphylactic reaction)
- Decreased secretion of hormones produced by the adrenal glands (glands situated above the kidneys)
- Dehydration
- Inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs)
- Ringing in ears (tinnitus)
- Dry eyes and blurred vision
- Changes in the rate or rhythm of the heartbeat, fast heart rate
- Blood clots in the blood vessels
- Inflammation of the lungs (characterized by coughing and difficulty breathing), blood clots in the lung, fluid around the lungs
- Nose bleeding
- Inflammation of the colon (colitis), dry mouth, pain in the mouth, inflammation of the stomach (gastritis) and hemorrhoids
- Inflammation of the liver (hepatitis)
- Dry skin and severe itching of skin
- Alopecia (hair thinning and loss), hair color change
- Inflammation of the joints (arthritis)
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain

Uncommon side effects (may affect 1 in 100 users)

- Allergic reactions related to the infusion of the medicine nivolumab
- Inflammation of the pituitary gland situated at the base of the brain (hypophysitis), swelling of the thyroid gland (thyroiditis)
- A temporary inflammation of the nerves that causes pain, weakness and paralysis in the extremities (Guillain Barré syndrome); muscle weakness and tiredness without atrophy (myasthenic syndrome)
- Inflammation of the brain
- Inflammation of the eye (which causes pain and redness)
- Inflammation of the heart muscle
- Inflammation of the pancreas (pancreatitis), intestinal perforation, burning or painful sensation in the tongue
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis)
- Hives (itchy rash)

- Muscle tenderness or weakness, not caused by exercise (myopathy), bone damage in the jaw, painful tear or abnormal connection of the tissues in your body (fistula)
- Inflammation of the kidney

Changes in test results:

Cabometyx in combination with nivolumab may cause changes in the results of tests carried out by your doctor. These include:

- Abnormal liver function tests (increased amounts of the liver enzymes aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase in your blood, higher blood levels of the waste product bilirubin)
- Abnormal kidney function tests (increased amounts of creatinine in your blood)
- High (hyperglycemia) or low (hypoglycemia) sugar levels in the blood
- A decreased number of red blood cells (which carry oxygen), white blood cells (which are important in fighting infection) or platelets (cells which help the blood to clot)
- An increased level of the enzyme that breaks down fats and of the enzyme that breaks down starch
- Decrease in levels of amount of phosphate
- Increased or decreased amount of calcium or potassium
- Increased or decreased blood levels of magnesium or sodium
- Decrease in body weight
- Increase in triglyceride levels in the blood
- Increase in cholesterol levels in the blood

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.

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 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) stated on the bottle label and carton. The expiry date refers to the last day of that month.

Store in the original package. Do not remove the 3 desiccant (drying agent) packs from the bottle.

Storage conditions

Store below 25°C.

Do not throw away medicines into the sink or domestic trash. Ask your pharmacist how to throw away medicines that you no longer use. These measures will help protect the environment.

6. Additional information

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

Tablet contents:

Microcrystalline cellulose, lactose anhydrous, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide (anhydrous)

Film-coating:

Opadry® yellow components: hypromellose (HPMC) 2910, titanium dioxide (E171), triacetin, iron oxide yellow

What the medicine looks like and contents of the packCabometyx 20 mg

Round, yellow film-coated tablets with no score, marked with "XL" on one side and "20" on the other side.

Cabometyx 40 mg

Triangle shaped, yellow film-coated tablets with no score, and marked with "XL" on one side and "40" on the other side

Cabometyx 60 mg

Oval, yellow film-coated tablets with no score, and marked with "XL" on one side and "60" on the other side.

Cabometyx tablets are packaged in a plastic bottle with a child-resistant cap. Each bottle contains 30 film-coated tablets and 3 silica gel desiccant packs. Keep the desiccant packs in the bottle and do not swallow them.

Registration holder name and address

Medison Pharma Ltd., 10 Hashiloah St., POB 7090, Petach Tikva

Manufacturer name and address

Ipsen Pharma, 65 quai Georges Gorse, 92100 Boulogne Billancourt, France

Revised in July 2022 according to MOH guidelines.

Registration number of the medicine in the Ministry of Health National Drug Registry

Cabometyx 20 mg: 160-99-35263-00

Cabometyx 40 mg: 161-01-35264-00

Cabometyx 60 mg: 161-02-35265-00