

CABOMETYX™ Film-coated Tablets

Cabozantinib (20mg, 40mg, 60mg)

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What CABOMETYX is used for

CABOMETYX is a cancer medicine that contains the active substance cabozantinib.

It is used in adults to treat:

- advanced stages of a type of kidney cancer called renal cell carcinoma
- liver cancer when a specific anticancer medicine (sorafenib) is no longer stopping the disease from progressing.

CABOMETYX is also used to treat locally advanced or metastatic differentiated thyroid cancer, a type of cancer in the thyroid gland, in adults when radioactive iodine and anticancer medicine treatments are no longer stopping the disease from progressing.

CABOMETYX may be given in combination with nivolumab for advanced kidney cancer. It is important that you also read the package leaflet of nivolumab. If you have any questions about these medicines, please ask your doctor.

How CABOMETYX works

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. These proteins can be present in high amounts in cancer cells, and by blocking their action this medicine can slow down the rate at which the tumour grows and help to cut off the blood supply that the cancer needs.

Before you use CABOMETYX

- When you must not use it

if you are allergic to cabozantinib or any of the other ingredients of this medicine (listed under Ingredients).

Pregnancy and lactation

Avoid becoming pregnant while being treated with CABOMETYX. If you or your partner could become pregnant, use adequate contraception during treatment and for at least 4 months after treatment has finished. Talk to your doctor about which methods of contraception are appropriate while you are taking this medicine.

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

Talk to your doctor BEFORE taking this medicine if you or your partner are considering or planning to have a baby after your treatment has finished. There is a possibility your fertility could be affected by treatment with this medicine.

Women taking this medicine should not breast-feed during treatment and for at least 4 months after treatment has finished, as cabozantinib and/or its metabolites may be excreted in breast milk and be harmful to your child.

If you take medicine whilst using oral contraceptives, the oral contraceptives may be ineffective. You should also use a barrier contraceptive (e.g. condom or diaphragm) whilst taking this medicine and for at least 4 months after treatment has finished.

• Before you start to use it

Talk to your doctor or pharmacist before taking CABOMETYX if you:

- have 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
- have diarrhoea
- have a recent history of significant bleeding
- have had surgery within the last month (or if surgical procedures are planned), including dental surgery

- have inflammatory bowel disease (for example, Crohn's disease or ulcerative colitis, diverticulitis, or appendicitis)
- have a recent history of blood clot in the leg, stroke, or heart attack
- have heart failure (can include symptoms like shortness of breath, feeling tired, fainting, swollen ankles and legs)
- have thyroid problems. Your thyroid function should be checked before you take this medicine and regularly while you are taking it. 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.
- have liver or kidney disease.

Tell your doctor if any of these affect you.

You may need treatment for them, or your doctor may decide to change your dose of CABOMETYX or stop treatment altogether. See also Side Effects.

Children and adolescents

CABOMETYX is not recommended for children or adolescents. The effects of this medicine in people younger than 18 years old are not known.

• Taking other medicines

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This is because CABOMETYX can affect the way some other medicines work. Also, some medicines can affect the way CABOMETYX works. This could mean that your doctor needs to change the dose(s) that you take. You should tell your doctor about every medicine, but in particular if 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

- * Allergy medicines 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 fits 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, dabigatran etexilate, 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 transplant rejection (cyclosporin) and cyclosporin-based regimens in rheumatoid arthritis and psoriasis

How to use CABOMETYX

• How much to use

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

• When to use it

CABOMETYX should be taken once a day. The usual dose is 60 mg, however your doctor will decide on the right dose for you.

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

• How long to use it

You should continue to take 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.

• If you forget to use it

If there are still 12 hours or more before your next dose is due, then take the missed dose as soon as you remember. Take the next dose at the normal time.

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

• If you stop using CABOMETYX

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

When this medicine 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.

• If you use too much (overdose)

If you have taken more CABOMETYX than you have been instructed to, talk to a doctor or go to the hospital with the tablets and this leaflet straight away.

While you are using it

• Things you must do

Take your medicine exactly as your doctor has told you.

Tell all the doctors, dentists and pharmacists treating you that you are taking CABOMETYX.

Tell your doctor immediately if you become pregnant while taking this medication.

• Things you must not do

CABOMETYX should **not** be taken with food. You should not eat anything for at least 2 hours before and for 1 hour after taking the medicine. Swallow the tablet with a full glass of water. Do not crush the tablets.

Avoid consuming grapefruit-containing products for as long as you are using this

medicine, as they may increase the levels of CABOMETYX in your blood.

• Things to be careful of

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.

CABOMETYX contains lactose

This medicine 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 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

Side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get 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 straight away if you notice any of the following side effects – you may need urgent medical treatment:

- Symptoms including pain in the abdomen, nausea (feeling sick), 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.
- Fits, headaches, confusion, or finding it difficult to concentrate. These may be signs of a condition called posterior reversible encephalopathy syndrome (PRES). PRES is rare (it affects less than 1 in 1000 people).

- 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 a tooth. These could be signs of bone damage in the jaw (osteonecrosis).

Other side effects include:

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

- Stomach upset, including diarrhoea, nausea, vomiting, constipation, indigestion, abdominal pain
- Blisters, pain of the hands or soles of the feet, rash or redness of the skin
- Decreased appetite, weight loss, altered sense of taste
- Fatigue, weakness, headache, dizziness
- Hypertension (high blood pressure)
- Anaemia (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 blood tests used to monitor general health and function of your organs (including the liver, and kidney), low levels of electrolytes (like magnesium, or potassium)
- Shortness of breath
- Reduced thyroid activity; symptoms can include tiredness, weight gain, constipation, feeling cold and dry skin
- Swelling in your legs and arms
- Pain in the arms, hands, legs or feet
- Low level of albumin in blood

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

- Abscess (collection of pus, with swelling and inflammation)
- Dehydration
- Difficulty in swallowing
- Ringing in ears (tinnitus)
- Blood clots in the blood vessels and lungs
- Low level of white blood cells
- Increased or decreased blood glucose level

- Decrease in levels of calcium, sodium and phosphate 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
- Inflammation of the pancreas
- A painful tear or abnormal connection of the tissues in your body (fistula)
- Gastro-oesophageal reflux disease (bringing up stomach acid)
- Haemorrhoids (piles)
- 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 colour change
- Pain in joints, muscle spasms
- Protein in urine (seen in tests)
- A burning or stinging sensation of the tongue
- Wound complications
- Lung infection (pneumonia)

Uncommon side effects (may affect 1 in 100 people)

- Stroke
- Fits
- Severe high blood pressure
- Decrease in bile flow from the liver
- Bone damage in the jaw
- Heart failure (can include symptoms like shortness of breath, feeling tired, fainting, swollen ankles and legs)
- Clot/embolus that travelled through your arteries and become stuck
- Collapsed lung with air trapped in the space between the lung and chest, often causing shortness of breath (pneumothorax)

Not known (proportion of people affected not known)

- Heart attack
- An enlargement and weakening of a blood vessel wall or a tear in a blood

vessel wall (aneurysms and artery dissections)

- Inflammation of the blood vessels in the skin (cutaneous vasculitis)

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

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

- 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 (hypertension)
- Difficulty in speaking, hoarseness (dysphonia), cough and shortness of breath
- Stomach upset, including diarrhoea, 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 oedema (swelling)
- 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 (hyperglycaemia) or low (hypoglycaemia) sugar levels in the blood
- Anemia (low levels of red blood cells which carry oxygen), low levels of white blood cells (which are

important in fighting infection), low levels of platelets (cells which help the blood to clot)

- An increased level of the enzyme that breaks down fats (lipase) and of the enzyme that breaks down starch (amylase)
- Decreased amount of phosphate
- Increased or decreased amount of potassium
- Decreased or increased blood levels of calcium, magnesium, or sodium
- Decrease in body weight

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

- Serious lung infection (pneumonia)
- Increase in some white blood cells called eosinophils
- Allergic reaction (including anaphylactic reaction)
- Decreased secretion of hormones produced by 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 rhythm or rate of the heartbeat, fast heart rate
- Blood clots in the blood vessels
- Inflammation of the lungs (pneumonitis, characterised 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 haemorrhoids (piles)
- Inflammation of the liver (hepatitis)
- Dry skin and severe itching of skin
- Alopecia (hair loss and thinning), hair colour change
- Inflammation of the joints (arthritis)
- Kidney failure (including abrupt loss of kidney function)
- Pain, chest pain
- Increase in triglyceride levels in the blood
- Increase in cholesterol levels in the blood

Uncommon side effects (may affect 1 in 100 people)

- 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
- Clot/embolus that travelled through your arteries through your arteries and become stuck
- Inflammation of the pancreas (pancreatitis), intestinal perforation, burning or painful sensation in the tongue (glossodynia)
- Skin disease with thickened patches of red skin, often with silvery scales (psoriasis)
- Hives (itchy rash)
- Muscle tenderness of 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
- Collapsed lung with air trapped in the space between the lung and chest, often causing shortness of breath (pneumothorax)

Not known (proportion of people affected not known)

- Inflammation of the blood vessels in the skin (cutaneous vasculitis)
- Progressive destruction and loss of intrahepatic bile ducts and jaundice

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 (hyperglycaemia) or low (hypoglycaemia) 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
- Increased blood levels of magnesium
- Decrease in body weight
- Increase in triglyceride levels in the blood
- Increase in cholesterol levels in the blood

You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website npra.gov.my [Consumers → Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)].

Storage and Disposal of CABOMETYX

Storage

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister, bottle label and carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

- Disposal

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines

you no longer use. These measures will help protect the environment.

Product Description

- What it looks like
- CABOMETYX 20 mg film-coated tablets are yellow, round with no score, and identified with “XL” on one side and “20” on the other side.
- CABOMETYX 40 mg film-coated tablets are yellow, triangle shaped with no score, and identified with “XL” on one side and “40” on the other side.
- CABOMETYX 60 mg film-coated tablets are yellow, oval shaped with no score, and identified with “XL” on one side and “60” on the other side.

CABOMETYX is available in packs containing one plastic bottle with 30 film-coated tablets. The bottle contains three silica gel desiccant canisters. Keep the canisters in the bottle and do not swallow the desiccant canisters.

- Ingredients

Active ingredient(s)

The active substance is cabozantinib (S)-malate.

CABOMETYX 20 mg film-coated tablets: Each tablet contains cabozantinib (S)-malate equivalent to 20 mg of cabozantinib.

CABOMETYX 40 mg film-coated tablets: Each tablet contains cabozantinib (S)-malate equivalent to 40 mg of cabozantinib.

CABOMETYX 60 mg film-coated tablets: Each tablet contains cabozantinib (S)-malate equivalent to 60 mg of cabozantinib.

Inactive ingredients

Tablet contents: microcrystalline cellulose, lactose anhydrous, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide anhydrous, magnesium stearate. (see section ‘While you are using it’ for lactose content)

Film coating: hypromellose, titanium dioxide (E171), triacetin, iron oxide yellow (E172)

- MAL number(s):

CABOMETYX 20mg film-coated tablets

MAL21046002ACRZ

CABOMETYX 40mg film-coated tablets

MAL21046003ACRZ

CABOMETYX 60mg film-coated tablets

MAL21046004ACRZ

Manufacturer

Patheon Inc
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Product Registration Holder

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