

NOVARTIS

PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS’ REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor’s prescription only

Votrient® 200 mg

Each film-coated tablet contains: Pazopanib (as hydrochloride) 200 mg

Votrient® 400 mg

Each film-coated tablet contains: Pazopanib (as hydrochloride) 400 mg

The list of inactive ingredients is detailed in Section 6 “Further Information”. See also in Section 2 “Important information about some of the ingredients of the medicine”.

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others.

It may harm them even if it seems to you that their ailment is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Votrient is used in adults to treat:

- kidney cancer that is advanced or has spread to other organs.

- certain forms of advanced soft tissue sarcoma, which is a type of cancer that affects the supportive tissues of the body. It can occur in muscles, blood vessels, fat tissue or in other tissues that support, surround and protect the organs.

Therapeutic group:

Protein kinase inhibitor.

Votrient works by inhibiting the activity of proteins that are involved in the growth and spread of cancer cells.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:

- **you are sensitive (allergic)** to pazopanib or to any of the additional ingredients contained in the medicine (detailed in Section 6 “Further Information”).

Check with your doctor if you think this applies to you.

Special warnings regarding use of the medicine

Before treatment with Votrient, tell your doctor if:

- you have **heart disease**.
- you have **liver disease**.
- you have had **heart failure or a heart attack**.
- you have had prior **collapse of a lung** (loss of lung volume).
- you have had problems with **bleeding, blood clots or narrowing of the arteries**.
- you have had **stomach or bowel problems** such as *perforation* (hole) or *fistula* (abnormal passage that forms between parts of the intestine).
- you have **thyroid problems**.
- you have **problems with your kidney function**.
- you have or have had an **aneurysm** (enlargement and weakening of a blood vessel wall) or a tear in a blood vessel wall.
- Tell your doctor** if any of these apply to you. Your doctor will decide whether Votrient is suitable for you. You may need **extra tests** to check that your kidneys, heart and liver are working properly.

High blood pressure and Votrient

Votrient can raise your blood pressure. Your blood pressure will be checked before you take Votrient and while you are taking it. If you have high blood pressure, you will be treated with medicines to reduce it.

- **Tell your doctor** if you have high blood pressure.

If you are about to undergo surgery

Your doctor will stop the treatment with Votrient at least 7 days before your operation as it may affect wound healing. Your treatment will be restarted when the wound has adequately healed.

Conditions you need to look out for

Votrient can make some conditions worse or cause serious side effects. You must look out for certain symptoms while you are taking Votrient to reduce the risk of any problems. See **Section 4**.

Children and adolescents

The medicine is not intended for 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 food supplements, tell the doctor or pharmacist.

Some medicines may affect the way Votrient works or increase the likelihood that you will have side effects.

Votrient can also affect the way some other medicines work. In particular, **inform the doctor or pharmacist** if you are taking:

- clarithromycin, ketoconazole, itraconazole, rifampin, telithromycin, voriconazole (used to **treat infection**).
- atazanavir, indinavir, nelfinavir, ritonavir, saquinavir (used to **treat HIV**).
- nefazodone (used to **treat depression**).
- simvastatin and possibly other statins (used to **treat high cholesterol levels**).
- medicines that **reduce stomach acid**. The medicines that you are taking to reduce your stomach acid (e.g., proton pump inhibitor, H₂ histamine receptor antagonists or antacids) may affect the way Votrient is taken. Please consult with your doctor.

Using the medicine with food and drink
Do not take Votrient with food, since food affects the way the medicine is absorbed. Take Votrient at least two hours after a meal or one hour before a meal. For example, you can take it two hours after breakfast or one hour before lunch.

Do not drink grapefruit juice during treatment with Votrient as this may increase the chance of side effects.

Pregnancy, breast-feeding and fertility
Votrient is not recommended if you are pregnant. The effect of Votrient during pregnancy is not known.

- **Tell your doctor if you are pregnant** or are planning to get pregnant.
- **Use a reliable method of contraception** while you’re taking Votrient, and for at least 2 weeks after the last dose.
- **If you do become pregnant during treatment** with Votrient, refer to your doctor.

Do not breast-feed while taking Votrient. It is not known whether the ingredients in Votrient pass into breast milk. Talk to your doctor about this.

Male patients (including those who underwent a vasectomy), whose female partners are pregnant or are able to become pregnant (including those using other contraceptives) should use condoms during sexual relations while using Votrient, and for at least another 2 weeks after the last dose.

Fertility may be affected by treatment with Votrient. Talk to your doctor about this.

Driving and using machines

Votrient can have side effects that may affect your ability to drive or use machines.

- Avoid driving or using machines if you feel dizzy, tired or weak, or if your energy levels are low.

Important information about some of the ingredients of the medicine

This medicine contains less than 1 mmol sodium (23 mg) per unit dose, i.e., is essentially ‘sodium-free’.

3. HOW SHOULD YOU USE THE MEDICINE?
Always use Votrient according to the doctor’s instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of Votrient. The dosage and treatment regimen will be determined by the doctor only.

How much to take

The usual dose is generally two Votrient 400 mg tablets (800 mg pazopanib) taken once a day. This is the maximum dose per day. Your doctor may need to reduce your dose if side effects occur.

Do not exceed the recommended dose.

When to take

Take Votrient at about the same time each day. See also in Section 2 “Using the medicine with food and drink”.

Mode of administration

Swallow the tablets whole with water, one after the other. Do not break or crush the tablets as it affects the way the medicine is absorbed and may increase the chance of side effects.

If you accidentally take a higher dosage, consult with the doctor or pharmacist. If you took an overdose, or if a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forget to take Votrient

Do not take a double dose to compensate for a forgotten dose. Take your next dose at the usual time.

Adhere to the treatment regimen recommended by the doctor.

Do not stop Votrient without advice

Take Votrient for as long as your doctor recommends. Don’t stop unless your doctor advises you to.

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, use of Votrient may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Possible serious side effects

Swelling of the brain (reversible posterior leukoencephalopathy syndrome)

Votrient can, on rare occasions, cause swelling of the brain, which may be life-threatening.

Symptoms include:

- loss of ability to speak
- change in vision
- seizures (fits)
- confusion
- high blood pressure

Stop taking Votrient and seek medical help immediately if you develop any of these symptoms, or if you develop a headache accompanied by any of these symptoms.

Hypertensive crisis (sudden and severe rise in blood pressure)

Votrient can, in certain cases, cause a sudden and severe rise in blood pressure. This effect is known as a hypertensive crisis. The doctor will monitor your blood pressure while you are taking the medicine. Signs and symptoms of a hypertensive crisis may include:

- severe chest pain
- severe headache
- blurred vision
- confusion
- nausea
- vomiting
- severe anxiety
- shortness of breath
- seizures (fits)
- fainting

Stop taking Votrient and seek medical help immediately if you develop hypertensive crisis.

Heart conditions

The risks of heart problems may be higher for people with an existing heart problem, or who are taking other medicines. You will be checked for any heart problems while you are taking Votrient.

Cardiac dysfunction/heart failure, heart attack
Votrient can affect the effectiveness of your heartbeat or can increase the likelihood of a heart attack.

Signs and symptoms include:

- irregular or fast heartbeat
- rapid fluttering of the heart
- fainting
- chest pain or pressure
- pain in the arms, back, neck or jaw
- shortness of breath
- swelling in the leg

Seek medical help immediately if you develop any of these symptoms.

Changes in heart rhythm (prolongation of the QT interval)

Votrient can affect the heart rhythm, which in some people can develop into a serious heart condition known as torsade de pointes. This can result in a very fast heartbeat, causing a sudden loss of consciousness.

Tell your doctor if you notice any **unusual changes in your heart rate**, such as beating too fast or too slow.

Stroke

Votrient can increase your likelihood of having a stroke. Signs and symptoms of stroke may include:

- weakness or numbness on one side of the body
- difficulty talking
- headache
- dizziness

Seek medical help immediately if you develop any of these symptoms.

Bleeding

Votrient can cause severe bleeding in the digestive system (such as stomach, esophagus, rectum or intestine), or the lungs, kidneys, mouth, vagina and brain, although this is uncommon. Symptoms include:

- bloody or black stools
- blood in the urine
- stomach pain
- coughing or vomiting up blood

Seek medical help immediately if you develop any of these symptoms.

Perforation in the digestive system and fistula

Votrient can cause a tear (perforation) in your stomach or intestinal wall or the development of an abnormal connection between two parts of your digestive tract (a fistula). Signs and symptoms may include:

- severe stomach pain
- nausea and/or vomiting
- fever

- development of a hole (perforation) in the stomach, small or large intestine, from which bloody or foul-smelling pus is released

Seek medical help immediately if you develop any of these symptoms.

Liver problems

Votrient can cause liver problems which may develop into serious conditions such as liver dysfunction and liver failure, which may be fatal. The doctor will check your liver enzymes while you are taking the medicine. Signs that your liver is not working properly may include:

- yellowing of the skin or the whites of the eyes (jaundice)
- dark urine
- tiredness
- nausea
- vomiting
- loss of appetite
- pain on the right side of the stomach (abdomen)
- bruising easily

Seek medical help immediately if you develop any of these symptoms.

Blood clots

Deep vein thrombosis (DVT) and pulmonary embolism

Votrient may cause blood clots in the veins, especially in the legs (deep vein thrombosis or DVT), which may travel to your lungs (pulmonary embolism). Signs and symptoms may include:

- sharp chest pain
- shortness of breath
- rapid breathing
- leg pain
- swelling of the arms and hands or legs and feet

Seek medical help immediately if you develop any of these symptoms.

Blood clots accompanied by a reduction in red blood cells and cells involved in clotting (thrombotic microangiopathy, TMA)

Votrient may cause formation of blood clots in the small blood vessels in the kidneys and brain, accompanied by a decrease in red blood cells and cells involved in clotting. Signs and symptoms may include:

- bruising easily
- high blood pressure
- fever
- confusion
- drowsiness
- seizures (fits)
- decrease in urine output

Seek medical help immediately if you develop any of these symptoms.

Tumor lysis syndrome

Votrient can cause a fast breakdown of cancer cells resulting in tumor lysis syndrome, which in some people may be fatal. Symptoms may include irregular heartbeat, seizures (fits), confusion, muscle cramps or spasms, or decrease in urine output.

Seek medical help immediately if you develop any of these symptoms.

Infections

Infections occurring while you take Votrient may become serious. Symptoms of infections may include:

- fever
- flu-like symptoms such as cough, tiredness and body aches that do not go away
- shortness of breath and/or wheezing
- pain upon urinating
- cuts, scrapes or wounds that are red, warm, swollen or painful

Seek medical help immediately if you develop any of these symptoms.

Lung inflammation

Votrient can, on rare occasions, cause lung inflammation (interstitial lung disease, pneumonitis), which in some people can be fatal. Symptoms include shortness of breath or persistent cough. You will be checked for any lung problems while you are taking Votrient.

Seek medical help immediately if you develop any of these symptoms.

Thyroid problems

Votrient can lower the amount of thyroid hormone produced in your body. This condition can result in weight gain and tiredness. Your thyroid hormone levels will be checked while you are taking Votrient.

Tell your doctor if you notice significant weight gain or tiredness.

Blurry or impaired vision

Votrient can cause a separation or tear of the inner lining of the back part of the eye (retinal detachment or tear). This can be manifested by blurry or impaired vision.

Tell your doctor if you notice any change in your vision.

Possible side effects (including serious side effects under the relevant frequency category).

Very common side effects (effects that occur in **more than 1 user in 10**):

- high blood pressure
- diarrhea
- nausea or vomiting
- stomach pain
- loss of appetite
- weight loss

- taste disturbance or loss of taste
- sore mouth
- headache
- pain resulting from a tumor
- lack of energy, feeling weak or tired
- changes in hair color
- unusual hair loss or thinning
- loss of skin pigment
- skin rash, possibly involving peeling of the skin

- redness and swelling of the palms of the hands or soles of the feet

Tell your doctor or pharmacist if any of these side effects become troublesome.

Very common side effects that may show up in your blood or urine tests:

- increased levels of liver enzymes
- decrease in albumin in the blood
- protein in the urine
- decreased number of platelets (cells that help blood to clot)
- decreased number of white blood cells

Common side effects (effects that occur in **1-10 in 100 users**):

- indigestion, bloating, flatulence
- nosebleed
- dry mouth or mouth ulcers
- infections
- abnormal drowsiness
- sleeping difficulties
- chest pain, shortness of breath, leg pain and swelling of the legs/feet. These could be signs of a blood clot in your body (thromboembolism). If the clot breaks off, it may travel to your lungs and this may be life-threatening or even fatal.
- the heart becomes less effective at pumping blood through your body (decreased heart function)
- slow heartbeat
- bleeding in the mouth, rectum or lung
- dizziness
- blurred vision
- hot flushes
- swelling caused by fluid in the face, hands, ankles, feet or eyelids
- tingling, weakness or numbness of the hands, arms, legs or feet
- skin disorders, redness, itching, dry skin
- nail disorders

- burning, prickling, itching or tingling skin sensation
- sensation of coldness, accompanied by shivering
- excessive sweating
- dehydration
- muscle, joint, tendon or chest pain, muscle spasms
- hoarseness
- shortness of breath
- cough
- bloody cough
- hiccups
- lung collapse (loss of lung volume) and entrapment of air in the space between the lung and chest, often causing shortness of breath (pneumothorax)

Tell your doctor or pharmacist if any of these effects become troublesome.

Common side effects that may show up in your blood or urine tests:

- under-active thyroid gland
- abnormal liver function
- increase in bilirubin levels (a substance produced by the liver)
- increase in lipase levels (an enzyme involved in digestion)
- increase in creatinine levels (a substance produced in muscles)
- changes in the levels of other different chemicals/enzymes in the blood. Your doctor will inform you about the results of the blood tests

Uncommon side effects (effects that occur in **1-10 in 1000 users**):

- stroke
- temporary fall in blood supply to the brain (transient ischemic attack)
- interruption of blood supply to part of the heart or heart attack (myocardial infarction)
- partial interruption in blood supply to part of the heart (myocardial ischemia)

- blood clots accompanied by a decrease in red blood cells and cells involved in clotting (thrombotic microangiopathy, TMA). These may harm organs such as the brain and kidneys.

- increase in the number of red blood cells
- sudden shortness of breath, especially when accompanied with sharp pain in the chest and/ or rapid breathing (pulmonary embolism)
- severe bleeding in the digestive system (such as stomach, esophagus or intestine), or the kidneys, vagina and brain
- heart rhythm disturbance (prolongation of the QT interval)

- hole (perforation) in stomach or intestine
- abnormal passages that form between parts of the intestine (fistula)
- heavy or irregular menstrual periods
- sudden sharp increase in blood pressure (hypertensive crisis)
- inflammation of the pancreas (pancreatitis)
- liver inflamed, not functioning or damaged
- yellowing of the skin or whites of the eyes (jaundice)

- inflammation of the lining of the abdominal cavity (peritonitis)

- runny nose
- rashes which may be itchy or inflamed (flat or raised spots or blisters)
- frequent bowel movements

- increased sensitivity of the skin to sunlight

- decreased sensation or sensitivity, especially in the skin

- skin wound which does not heal (skin ulcer)

Rare side effects (effects that occur in **1-10 in 10000 users**):

- inflammation of the lung (pneumonitis)
- an enlargement and weakening of a blood vessel wall or a tear in a blood vessel wall (aneurysms and artery dissections)

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

- tumor lysis syndrome resulting from a fast breakdown of cancer cells
- hepatic failure

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult with the doctor.

Side effects can be reported to the Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” found on the Ministry of Health homepage (www.health.gov.il), that directs you to the online form for reporting side effects, or by entering the link:

https://sideeffects.health.gov.il

5. HOW TO STORE THE MEDICINE?

Avoid poisoning! This medicine and any other medicine should be kept in a closed place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting without explicit instruction from the doctor.

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

There are no special storage conditions; it is recommended to store at a room temperature. Can be used for 3 months after first opening.

6. FURTHER INFORMATION

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

Tablet core:

Votrient 200 mg, Votrient 400 mg
Microcrystalline cellulose, Sodium starch glycolate (type A), Povidone K30, Magnesium stearate

Tablet coating:

Votrient 200 mg, Votrient 400 mg
Hyppromellose (E464), Titanium dioxide (E171), Macrogol/PEG 400, Polysorbate 80 (E433)

Votrient 200 mg

Iron oxide red (E172)

What the medicine looks like and the contents of the package

Votrient 200 mg - pink, film coated, capsule shaped tablets, marked with “GS JT” on one side.

The tablets are packaged in a bottle containing 30 tablets.

Votrient 400 mg - white, film coated, capsule shaped tablets, marked with “GS UHL” on one side.

The tablets are packaged in a bottle containing 30 tablets.

Registration Holder and Importer and its address: Novartis Israel Ltd., P.O.B 7126, Tel Aviv.

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

Votrient 200 mg: 145 09 33192

Votrient 400 mg: 145 10 33194

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