

Patient leaflet in accordance with the Regulations (Preparations) - 1996

This medicine is dispensed with a doctor's prescription only

Votubia 2 mg dispersible tablets

Each dispersible tablet contains 2 mg everolimus.

Votubia 3 mg dispersible tablets

Each dispersible tablet contains 3 mg everolimus.

Inactive ingredients and allergens: See section 2 '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 this medicine. If you have any further questions, consult your doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

1. What is this medicine intended for?

Votubia is used as adjunctive treatment to treat children aged 2 years and above and adults with seizures associated with a genetic disorder called tuberous sclerosis complex (TSC), and which are not controlled by other antiepileptic medicines. Votubia is given together with other medicines for epilepsy.

Therapeutic group: protein kinase inhibitors

2. Before using this medicine

Votubia will only be prescribed by a doctor with experience in treating patients with seizures and with access to blood tests which will measure how much Votubia is in your blood.

Follow all the doctor's instructions carefully. They may differ from the general information contained in this leaflet.

If you have any questions about Votubia or why it has been prescribed for you, ask your doctor.

Do not use this medicine if:

- **you are allergic** (hypersensitive) to everolimus, to related substances such as sirolimus or temsirolimus, or to any of the other ingredients in this medicine listed in section 6 'Additional information' in this leaflet.

If you had allergic reactions before, please ask your doctor for advice.

Special warnings about using this medicine

Before taking Votubia, tell the doctor if:

- you have any problems with your liver or if you have ever had any disease which may have affected your liver.

If this is the case, your doctor may need to prescribe a different dose of Votubia or stop treatment, either for a short time or permanently.

- you have diabetes (high level of sugar in your blood). Votubia may increase blood sugar levels and worsen diabetes mellitus. This may result in the need for insulin and/or oral diabetes treatment. Tell your doctor if you experience any excessive thirst or increased frequency of urination.

- you need to receive a vaccine while taking Votubia as vaccination may be less effective. For children with seizures, it is important to have a discussion with the doctor about the childhood vaccination program before treatment with Votubia.

- you have high cholesterol. Votubia may elevate cholesterol and/or other blood fats.

- you have had recent major surgery, or if you still have an unhealed wound following surgery.

Votubia may increase the risk of problems with wound healing.

- you have an infection. It may be necessary to treat your infection before starting Votubia.

- you have previously had hepatitis B, because this may occur again during treatment with Votubia (see section 4 'Side effects').

- you have a tendency to bleed or a history of bleeding or if you are using other medicines that may affect your platelet function or increase the risk of bleeding. Pay attention to signs of bleeding while you are taking Votubia.
- you have received or are about to receive radiation therapy (radiotherapy).

Votubia may also:

- cause mouth sores (oral ulcerations).
- weaken your immune system. Therefore, you may be at risk of getting an infection while you are taking Votubia. If you have fever or other signs of an infection, consult your doctor. Some infections may be severe and may have fatal consequences in adults and children.
- impact your kidney function. Therefore, your doctor will monitor your kidney function while you are taking Votubia.

- cause shortness of breath, cough and fever (see section 4 'Side effects').

- cause complications of radiation therapy. Severe complications

of radiation therapy (such as shortness of breath, nausea, diarrhoea, skin rashes and soreness in mouth, gums and throat), including fatal cases, have been observed in some patients who were taking everolimus at the same time as radiation therapy or who were taking everolimus shortly after they had radiation therapy. In addition, so called radiation recall syndrome comprising skin redness or lung inflammation at the site of previous radiation therapy has been reported in patients who had radiation therapy in the past. Tell your doctor if you are planning to have radiation therapy in the near future, or if you have had radiation therapy before.

Tell your doctor immediately if you experience these symptoms.

Children and adolescents

Votubia is not to be used in children below the age of 2 years with tuberous sclerosis complex (TSC) and seizures.

Tests and follow-up

You will have blood tests before and periodically during treatment with Votubia. These will check the amount of blood cells (white blood cells, red blood cells and platelets) in your body to see if Votubia is having an unwanted effect on these cells. Blood tests will also be carried out to monitor your kidney function (levels of creatinine, blood urea nitrogen or urinary protein), liver function (level of transaminases in your blood) and your blood sugar and lipid levels. This is because these can also be affected by Votubia.

Regular blood tests are also necessary to measure how much Votubia is in your blood since this will help your doctor decide how much Votubia you need to take.

Other medicines and Votubia

Votubia may affect the way some other medicines work. If you are taking other medicines at the same time as Votubia, your doctor may need to change the dose of Votubia or the other medicines.

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

- The following medicines may increase the risk of side effects with Votubia:

- ketoconazole, itraconazole, voriconazole, or fluconazole and other antifungals used to treat fungal infections.
- clarithromycin, telithromycin or erythromycin, antibiotics used to treat bacterial infections.

- ritonavir, and other medicines used to treat human immunodeficiency virus (HIV) infection/AIDS.
- verapamil or diltiazem, used to treat heart conditions or high blood pressure.

- dronedarone, a medicine used to help regulate your heart beat.

- ciclosporin, a medicine used to stop the body from rejecting organ transplants.

- imatinib, used to inhibit the growth of abnormal cells.
- angiotensin-converting enzyme (ACE) inhibitors (such as ramipril) used to treat high blood pressure or other cardiovascular problems. The combination may increase the risk of angioedema (swelling of tongue or airways possibly with difficulty breathing).

- nefazodone, a medicine used to treat depression.

- The following medicines may reduce the effectiveness of Votubia:

- rifampicin, used to treat tuberculosis (TB).
- efavirenz or nevirapine, used to treat HIV infection/AIDS.
- St. John's wort (also known as *Hypericum perforatum*), a herbal medicine used to treat depression and other conditions.

- dexamethasone, a corticosteroid used to treat a wide variety of conditions including inflammatory or immune problems.
- phenytoin, carbamazepine or phenobarbital and other anti-epileptics used to stop seizures or fits.

- medicines that may affect your platelet function or increase the risk of bleeding.

- certain medicines taken by mouth that have a narrow therapeutic range such as pimozide, terfenadine, astemizole, quinidine, alkaloid ergot derivatives or carbamazepine. Combining these medicines with Votubia may increase the chance of getting side effects from them.

Avoid these medicines during your treatment with Votubia. If you are taking any of them, your doctor may switch you to a different medicine, or may change your dose of Votubia.

If you are taking an anti-seizure medicine, a change in the dose of the anti-seizure medicine (increase or decrease) may make a change in the Votubia dose necessary. Your doctor will decide this. If the dose of your anti-seizure medicine changes, please inform your doctor.

If you are following a specific diet to reduce the frequency of your seizures, please inform your doctor before taking Votubia.

Using this medicine and food

Do not eat grapefruit or drink grapefruit juice while you are on Votubia. It may increase the amount of Votubia in the blood, possibly to a harmful level.

You can take this medicine with or without food but you need to do this in the same way each day.

Pregnancy, breastfeeding, and fertility

Pregnancy could harm an unborn baby so it is not recommended during pregnancy. Tell your doctor if you are pregnant or think that you may be pregnant.

Women who could potentially become pregnant must use highly effective contraception during treatment, and for 8 weeks after ending treatment. If, despite these measures, you think you may have become pregnant, ask your doctor for advice **before** taking any more Votubia.

Breastfeeding

Votubia could harm a breastfed baby. Do not breastfeed during treatment and for 2 weeks after the last dose of Votubia. Tell your doctor if you are breastfeeding.

Fertility

Votubia may affect male and female fertility. Talk to your doctor if you wish to have children.

Driving and using machines

If you feel unusually tired (fatigue is a common side effect), take special care when driving or using machines. Caution children against riding a bicycle, playing near a road, and similar activities.

Important information about some of this medicine's ingredients

Votubia contains lactose (milk sugar). If you have been told by your doctor that you have intolerance to certain sugars, contact your doctor before taking this medicine.

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.

Your doctor will determine the dose of Votubia you need to take depending on:

- your age
- your body size
- the health of your liver
- other medicines you are taking

Do not exceed the recommended dose.

You will have blood tests during treatment with Votubia. This is to measure the amount of Votubia in your blood and find the best daily dose for you.

If you experience certain side effects (see section 4 'Side effects') while you are taking Votubia, your doctor may lower your dose or stop treatment, either for a short time or permanently.

How to take this medicine

- Take Votubia dispersible tablets once a day.
- Take them at the same time every day.
- You can take them either with or without food, but you need to do this in the same way each day.

Take Votubia dispersible tablets as an oral suspension only.

Do not chew or crush the dispersible tablets. Do not swallow them whole. You must mix the dispersible tablets with water to create a cloudy liquid (known as an oral suspension).

How to prepare and take the oral suspension

Prepare the oral suspension by mixing the dispersible tablets with water either in an oral syringe or in a small glass. You must drink the suspension immediately after preparing it. If you do not drink it within 60 minutes, throw it away and prepare a new suspension. Please read the detailed instructions at the end of this leaflet to find out how to do this. Ask your doctor or pharmacist if you are not sure.

Special information for caregivers

Caregivers are advised to avoid contact with suspensions of Votubia dispersible tablets. Wash hands thoroughly before and after preparation of the suspension.

If you accidentally take a higher dose

If you have taken an overdose, or if a child or other person has accidentally swallowed the medicine, immediately see a doctor or go to a hospital emergency room and take the medicine package and this leaflet with you, so that the doctor knows what has been taken. Urgent treatment may be necessary.

If you forget to take the medicine

If you forget to take this medicine at the scheduled time, take the next dose at the usual time. Do not take a double dose to make up for the forgotten 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

Like with all medicines, using Votubia may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Stop taking Votubia and seek medical help immediately if you or your child experiences any of the following signs of an allergic reaction:

- difficulty breathing or swallowing
- swelling of the face, lips, tongue or throat (signs of angioedema)
- severe itching of the skin, with a red rash or raised bumps

Serious side effects of Votubia include:

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

- Fever, cough, difficulty breathing, wheezing (signs of inflammation of the lung due to infection, also known as pneumonia).

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

- swelling, feeling of heaviness or tightness, pain, limited mobility of body parts (this could occur anywhere in the body and is a potential sign of an abnormal build-up of fluid in soft tissue due to a blockage in the lymphatic system, also known as lymphoedema)
- rash, itching, hives, difficulty breathing or swallowing, dizziness (signs of serious allergic reaction, also known as hypersensitivity)
- fever, cough, difficulty breathing, wheezing (signs of inflammation of the lung, also known as pneumonitis).

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

- rash of small fluid-filled blisters, appearing on reddened skin (signs of viral infection that can be potentially severe, also known as herpes zoster [shingles])
- fever, chills, rapid breathing and heart rate, rash, and possibly confusion and disorientation (signs of serious infection, also known as sepsis).

Other possible side effects of Votubia include:

Very common side effects (effects that occur in more than 1 in 10 users)

- upper respiratory tract infection
- sore throat and runny nose (nasopharyngitis)
- headache, pressure in the eyes, nose or cheek area (signs of inflammation of the sinuses and nasal passages, also known as sinusitis)
- urinary tract infection
- high level of lipids (fats) in the blood (hypercholesterolaemia)
- decreased appetite
- headache
- cough
- mouth ulcers
- diarrhoea
- vomiting
- acne
- skin rash
- feeling tired
- fever

- menstruation disorders such as absence of periods (amenorrhoea) or irregular periods
- sore throat (pharyngitis)
- headache, dizziness, signs of high blood pressure (hypertension).

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

- middle ear infection
- swollen, bleeding gums (signs of gum inflammation, also known as gingivitis)
- skin inflammation (cellulitis)
- high level of lipids (fats) in the blood (hyperlipidaemia, raised triglycerides)
- low level of phosphate in the blood (hypophosphataemia)
- high level of sugar in the blood (hyperglycaemia)
- tiredness, breathlessness, dizziness, pale skin (signs of low level of red blood cells [anaemia])
- fever, sore throat or mouth ulcers due to infections (signs of low level of white blood cells [leucopenia, lymphopenia, neutropenia])
- spontaneous bleeding or bruising (signs of low level of platelets [thrombocytopenia])
- mouth pain
- nose bleeds (epistaxis)
- stomach upset like nausea
- abdominal pain
- severe pain in the lower abdomen and pelvic area that may be sharp, with menstrual irregularities (ovarian cyst)
- excess amount of gas in the bowels (flatulence)
- constipation
- abdominal pain, nausea, vomiting, diarrhoea, swelling and

bloating of the abdomen (signs of inflammation of the stomach lining, also known as gastritis or gastroenteritis viral)

- dry skin, itching (pruritus)
- an inflammatory condition of the skin characterised by redness, itching, and oozing liquid-filled cysts which become scaly, crusted, or hardened (dermatitis acneiform)
- loss of hair (alopecia)
- protein in the urine
- menstruation disorders such as heavy periods (menorrhagia) or vaginal bleeding
- trouble sleeping (insomnia)
- Irritability
- aggression
- high level of an enzyme called blood lactate dehydrogenase that gives information about the health of certain organs
- high level of the hormone that triggers ovulation (blood luteinising hormone increased)
- weight loss.

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

- muscle spasms, fever, red-brown urine which may be symptoms of a muscle disorder (rhabdomyolysis)
- cough with phlegm, chest pain, fever (signs of inflammation of airways, also known as bronchitis viral)
- disturbed taste (dysgeusia)
- menstruation disorders such as delayed periods
- higher level of female reproductive hormone (blood follicle stimulating hormone [FSH] increased).

Side effects whose frequency is not known (frequency has not been established yet)

Reaction at the site of previous radiation therapy, e.g. skin redness or lung inflammation (so called radiation recall syndrome); worsening of radiation treatment side effects.

If these side effects get severe please tell your doctor and/or pharmacist. Most of the side effects are mild to moderate and will generally disappear if your treatment is interrupted for a few days.

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.

Hepatitis B reactivation has been observed in some patients taking everolimus. Tell your doctor if you experience symptoms of hepatitis B during treatment with everolimus. The first symptoms may include fever, skin rash, joint pain and inflammation. Other symptoms may include fatigue, loss of appetite, nausea, jaundice (yellowing of the skin), and pain in the upper right abdomen. Pale stools or dark urine may also be signs of hepatitis.

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 the 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) which is stated on the package and blister tray.

- The expiry date refers to the last day of that month.
- Do not store above 30°C. Store in the original package in order to protect from light and moisture.

- Open the blister just before taking Votubia dispersible tablets.
- The stability of the ready to use suspension has been demonstrated for 60 minutes if using a small cup or a syringe for oral administration. After preparation, the suspension must be taken straight away. If you do not use it within 60 minutes of preparation, throw it away and prepare a new suspension.
- Do not use this medicine if the pack is damaged or shows signs of tampering.

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 to protect the environment.

6. Additional information

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

mannitol, cellulose microcrystalline, crospovidone, hypromellose, magnesium stearate, silica colloidal anhydrous, lactose monohydrate and butylated hydroxytoluene.

Each tablet of Votubia 2 mg contains 1.96 mg lactose monohydrate. Each tablet of Votubia 3 mg contains 2.94 mg lactose monohydrate.

What the medicine looks like and contents of the pack:

The dispersible tablets are white to slightly yellowish, round, and flat with a bevelled edge and no score.

Votubia 2 mg: The dispersible tablets are engraved with "D2" on

one side and "NVR" on the other. Votubia 3 mg: The dispersible tablets are engraved with "D3" on one side and "NVR" on the other.

Each pack of Votubia 2 mg contains 30 dispersible tablets in blister trays.

Each pack of Votubia 3 mg contains 30 dispersible tablets in blister trays.

Not all pack sizes may be marketed.

Registration holder and importer:

Novartis Israel Ltd., P.O.B 7126, Tel Aviv.

Revised in August 2021 according to MOH guidelines.

Registration number of the medicine in the Ministry of Health's National Drug Registry:
Votubia 2 mg 164-73-35765
Votubia 3 mg 164-74-35766

Directions for use

Read and follow these instructions carefully so that you know how to correctly prepare the medicine. This will look like a cloudy liquid (an oral suspension).

Use an oral syringe or a small glass for preparing and taking the Votubia suspension only – do not use it for anything else.

Important information:

Take Votubia dispersible tablets as an oral suspension only.

These instructions are for taking a dose between 2 mg and 10 mg.

- The most you can take at one time using the oral syringe or small glass is 10 mg, using a maximum of 5 dispersible tablets.
- If you need to take a higher dose or need to use more than 5 dispersible tablets, split the dose and repeat the steps using the same oral syringe or small glass.

- Ask your doctor or pharmacist about how to split the dose if you are not sure.

Caregivers should try to avoid skin contact with the oral suspension. Keep the medicine out of the reach of children.

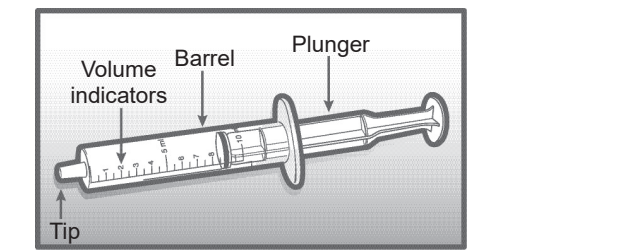
Only use water (drinkable tap water or non-sparkling bottled water) to prepare the oral suspension. Do not use juice or any other liquids.

The patient must drink the suspension immediately after it is prepared. If the patient does not drink it within 60 minutes, throw it away and prepare a new suspension.

Instructions for caregivers preparing the suspension using an oral syringe:

You will need:

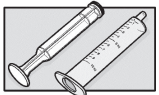
- the blister with Votubia dispersible tablets
- scissors to open the blister
- 10 ml oral syringe with 1 ml increments (for single use): see figure below
- 2 clean glasses
- approximately 30 ml of water



Getting ready

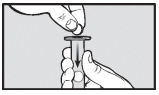
1. Wash and dry your hands.

2. Take the 10 ml oral syringe and pull out the plunger, removing it completely from the barrel of the syringe.



Adding the dispersible tablets

3. Use scissors to open the blister along the dotted line. Remove the dispersible tablets from the blister. Place them into the barrel of the oral syringe straight away.



4. Re-insert the plunger into the barrel of the oral syringe. Push the plunger in until it touches the dispersible tablets.



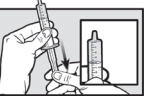
Adding water

5. Fill a small glass with water (drinkable tap water or non-sparkling bottled water). Put the tip of the syringe into the water. Draw up about 5 ml of water by slowly pulling the plunger out until it is at the 5 ml mark on the syringe.

Note: The amount of water in the oral syringe does not need to be exact but all the tablets should be covered with water. If any tablets get stuck in the (dry) upper part of the oral syringe, gently tap the oral syringe until they fall down into the water.

Mixing the medicine

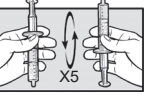
6. Hold the oral syringe with the tip pointing up. Pull the plunger slowly down to draw in air until it is at the 9 ml mark on the syringe.



7. Put the filled oral syringe in the clean, empty glass with the tip pointing up. Wait for 3 minutes - until the dispersible tablets have completely broken apart.



8. Mix the medicine by slowly turning the oral syringe upside down and back again five times just before using the dose. Do not shake it. Use the oral suspension immediately. If you do not use it within 60 minutes, throw it away and prepare a new suspension.



Removing air

9. Hold the