

Package leaflet: Information for the user

Votubia® 2.5 mg tablets

Votubia® 5 mg tablets

Votubia® 10 mg tablets

everolimus

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What **Votubia** is and what it is used for
2. What you need to know before you take **Votubia**
3. How to take **Votubia**
4. Possible side effects
5. How to store **Votubia**
6. Contents of the pack and other information

1. What **Votubia** is and what it is used for

Votubia is an anti-tumour medicine which can block certain cells in the body from growing. It contains an active substance called everolimus which may reduce the size of kidney tumours called renal angiomyolipomas and brain tumours called subependymal giant cell astrocytomas (SEGA). These tumours are caused by a genetic disorder called tuberous sclerosis complex (TSC).

Votubia tablets are used to treat:

- TSC with angiomyolipoma of the kidney in adults who do not require immediate surgery.
- SEGA associated with TSC in adults and children for whom surgery is not appropriate.

2. What you need to know before you take **Votubia**

If you are being treated for TSC with angiomyolipoma of the kidney, **Votubia** will only be prescribed for you by a doctor with experience in treating patients with TSC.

If you are being treated for SEGA associated with TSC, **Votubia** will only be prescribed by a doctor with experience in treating patients with SEGA 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 take **Votubia**

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

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

Warnings and precautions

Talk to your doctor before taking Votubia:

- 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.
- if 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 antidiabetic agent therapy. Tell your doctor if you experience any excessive thirst or increased frequency of urination.
- if you need to receive a vaccine while taking Votubia as vaccination may be less effective. For children with SEGA, it is important to have a discussion with the doctor about the childhood vaccination program before treatment with Votubia.
- if you have high cholesterol. Votubia may elevate cholesterol and/or other blood fats.
- if 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.
- if you have an infection. It may be necessary to treat your infection before starting Votubia.
- if you have previously had hepatitis B, because this may occur again during treatment with Votubia (see section 4 ‘Possible side effects’).
- if you have received or are about to receive radiation therapy.

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 with 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 ‘Possible side effects’).
- cause complications of radiation therapy. Severe complications of radiotherapy (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.

You will have blood tests before and periodically during treatment. 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 check your kidney function (levels of creatinine, blood urea nitrogen or urinary protein), liver function (level of transaminases) and your blood sugar and lipid levels. This is because these can also be affected by Votubia.

If you receive Votubia for the treatment of SEGA associated with TSC, 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.

Children and adolescents

Votubia can be used in children and adolescents SEGA associated with TSC.

Votubia is not to be used in children or adolescents with TSC who have angiomyolipoma of the kidney in the absence of SEGA, as it has not been studied in such patients.

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.

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

The following 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 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.
- cannabidiol (uses amongst others include treatment of seizures).

The following 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 (*Hypericum perforatum*), a herbal product 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.

All medicines listed above should be avoided 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.

Votubia with food and drink

Avoid grapefruit and grapefruit juice while you are on Votubia. It may increase the amount of Votubia in the blood, possibly to a harmful level.

Pregnancy, breast-feeding and fertility

Pregnancy

Votubia could harm an unborn baby and 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 up to 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.

Breast-feeding

Votubia could harm a breast-fed baby. You should not breast-feed during treatment and for 2 weeks after the last dose of Votubia. Tell your doctor if you are breast-feeding.

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.

Votubia contains lactose

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

3. How to take Votubia

Always take this medicine exactly as your doctor or pharmacist has told you. Votubia exists as tablets and dispersible tablets. Consistently take only the tablets or only the dispersible tablets, and never a combination of both. Check with your doctor or pharmacist if you are not sure.

How much Votubia to take

If you receive Votubia for the treatment of TSC with angiomyolipoma of the kidney, the usual dose is 10 mg, to be taken once daily.

A higher or lower dose may be recommended by your doctor based on your individual treatment needs, for example if you have problems with your liver or if you are taking certain other medicines in addition to Votubia.

If you receive Votubia for the treatment of TSC with SEGA, 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.

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) 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 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.

Swallow the tablets whole with a glass of water. Do not chew or crush the tablets. If you are taking Votubia tablets for the treatment of TSC with SEGA and if you are unable to swallow the tablets, you can stir them into a glass of water:

- Put the required number of tablets into a glass of water (approximately 30 ml).
- Gently stir the contents of the glass until the tablets break apart (approximately 7 minutes) and then drink the contents immediately.
- Refill the glass with the same amount of water (approximately 30 ml), gently stir the remaining content and drink the whole amount to make sure that you get the full dose of Votubia tablets.
- If necessary, drink additional water to wash out any residues in your mouth.

Special information for caregivers

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

If you take more Votubia than you should

- If you have taken too much Votubia, or if someone else accidentally takes your tablets, see a doctor or go to a hospital immediately. Urgent treatment may be necessary.
- Take the carton and this leaflet, so that the doctor knows what has been taken.

If you forget to take Votubia

If you miss a dose, take your next dose as scheduled. Do not take a double dose to make up for the forgotten tablets.

If you stop taking Votubia

Do not stop taking Votubia tablets unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets 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** (*may affect more than 1 in 10 people*)

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

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

- 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 (*may affect up to 1 in 100 people*)

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

If you experience any of these side effects, tell your doctor immediately as this might have life-threatening consequences.

Other possible side effects of Votubia include:**Very common side effects** (*may affect more than 1 in 10 people*)

- 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
- Being sick (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 (*may affect up to 1 in 10 people*)

- 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, also known as anaemia)
- Fever, sore throat or mouth ulcers due to infections (signs of low level of white blood cells, also known as leucopenia, lymphopenia, neutropenia)
- Spontaneous bleeding or bruising (signs of low level of platelets, also known as thrombocytopenia)
- Mouth pain
- Nose bleeds (epistaxis)
- Stomach upset like feeling sick (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 (*may affect up to 1 in 100 people*)

- 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 increased)

Not known (*frequency cannot be estimated from the available data*)

- 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.

The following side effects have been reported in patients taking everolimus for the treatment of conditions other than TSC:

- Kidney disorders: altered frequency or absence of urination may be symptoms of kidney failure and have been observed in some patients receiving everolimus. Other symptoms may include altered kidney function test (increase in creatinine).
- Symptoms of heart failure such as breathlessness, difficulty breathing when lying down, swelling of the feet or legs
- Blockage or obstruction of a blood vessel (vein) in the leg (deep vein thrombosis). Symptoms may include swelling and/or pain in one of your legs, usually in the calf, redness or warm skin in the affected area
- Problems with wound healing
- High levels of sugar in the blood (hyperglycaemia)

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.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Votubia

- 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 carton and blister foil. The expiry date refers to the last day of that month.
- Do not store above 25°C.
- Store in the original package in order to protect from light and moisture.
- Open the blister just before taking the Votubia tablets.
- 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. Contents of the pack and other information

What Votubia tablets contain

- The active substance is everolimus.
Each Votubia 2.5 mg tablet contains 2.5 mg of everolimus.
Each Votubia 5 mg tablet contains 5 mg of everolimus.
Each Votubia 10 mg tablet contains 10 mg of everolimus.
- The other ingredients are butylated hydroxytoluene (E321), magnesium stearate, lactose monohydrate, hypromellose, crospovidone type A and lactose anhydrous (see section 2 “Votubia contains lactose”).

What Votubia tablets looks like and contents of the pack

Votubia 2.5 mg tablets are white to slightly yellowish, elongated tablets. They are engraved with “LCL” on one side and “NVR” on the other.

Votubia 5 mg tablets are white to slightly yellowish, elongated tablets. They are engraved with “5” on one side and “NVR” on the other.

Votubia 10 mg tablets are white to slightly yellowish, elongated tablets. They are engraved with “UHE” on one side and “NVR” on the other.

Votubia 2.5 mg tablets are available in packs containing 10 x 1, 30 x 1 or 100 x 1 tablets in perforated unit-dose blisters of 10 x 1 tablets each.

Votubia 5 mg tablets are available in packs containing 30 x 1 or 100 x 1 tablets in perforated unit-dose blisters of 10 x 1 tablets each.

Votubia 10 mg tablets are available in packs containing 10 x 1, 30 x 1 or 100 x 1 tablets in perforated unit-dose blisters of 10 x 1 tablets each.

Not all pack sizes or strengths may be marketed in your country.

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