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EPAR summary for the public

Votubia

everolimus

This is a summary of the European public assessment report (EPAR) for Votubia. It explains how the Agency assessed the medicine to recommend its authorisation in the EU and its conditions of use. It is not intended to provide practical advice on how to use Votubia.

What is Votubia and what is it used for?

Votubia is a medicine used to treat the following benign (non-cancerous) tumours caused by the genetic disease tuberous sclerosis:

- subependymal giant cell astrocytoma (SEGA), a benign tumour of the brain, where it is used in adults and children whose brain tumour cannot be surgically removed;
- renal angiomyolipoma, a benign tumour of the kidneys, where it is used in adults who are at risk of complications but who do not require immediate surgery.

The medicine is also used as an add-on treatment in patients from 2 years of age with seizures (fits) related to tuberous sclerosis that have not responded to other treatments. Votubia is used for partial-onset seizures (seizures that start in one part of the brain), which may or may not spread to affect the whole brain (secondary generalisation).

Votubia contains the active substance everolimus.

Because the number of patients with tuberous sclerosis is low, the disease is considered 'rare', and Votubia was designated an 'orphan medicine' (a medicine used in rare diseases) on 4 August 2010.

How is Votubia used?

Votubia treatment should be started by a doctor experienced in treating tuberous sclerosis and in monitoring levels of medicine in the blood. It is available as tablets (2.5, 5 and 10 mg) and as dispersible tablets (2, 3 and 5 mg) and is taken by mouth once a day at the same time every day, consistently either with or without food.

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For SEGA, and for use as add-on treatment of seizures, the starting dose depends on the body surface area (calculated using the patient's height and weight) and the patient's age, but the doctor will adjust the dose based on the patient's blood levels of the medicine and how well the patient tolerates the medicine.

In patients with renal angiomyolipoma, the recommended dose is 10 mg once a day. If patients experience severe side effects the doctor may need to reduce the dose or interrupt treatment temporarily.

Starting doses may need to be reduced, or treatment avoided, in patients with reduced liver function, depending on how severe this is and on the patient's age and the condition they are being treated for. When used together with other medicines, e.g. as an add-on treatment for seizures, the dosage may also be affected by the other medicines being taken. For further details see the summary of product characteristics (also part of the EPAR).

How does Votubia work?

The active substance in Votubia, everolimus, is an anti-tumour medicine that acts by blocking an enzyme called 'mammalian target of rapamycin' (mTOR), which has increased activity in tumour cells of patients with SEGA or renal angiomyolipoma. In the body, everolimus first attaches to a protein called FKBP-12 that is found inside cells to make a 'complex'. This complex then blocks mTOR. Since mTOR is involved in the control of cell division and the growth of blood vessels, Votubia prevents the division of tumour cells and reduces their blood supply. mTOR is also thought to play a role in the seizures that occur in patients with tuberous sclerosis but it is not fully understood how the medicine acts to prevent them.

What benefits of Votubia have been shown in studies?

Votubia has been shown to be effective at treating patients with SEGA and renal angiomyolipoma by shrinking the volume of the tumours. It has also shown to be effective at reducing partial-onset seizures associated with tuberous sclerosis.

- In **SEGA** caused by tuberous sclerosis, Votubia has been studied in two main studies: the first study involved 28 adults and children aged three years and above. The main measure of effectiveness was based on how much the patient's main brain tumour shrank after six months of treatment: the main brain tumour shrank by half in approximately 30% of patients and by about a third in around 70% of patients. The second study involved 117 patients (including 20 children aged below 3 years) and compared Votubia with placebo (a dummy treatment). The main measure of effectiveness was the proportion of patients who responded to treatment and whose brain tumour shrank by at least half after six months of treatment. This occurred in 35% of patients (27 out of 78 patients) treated with Votubia, compared with none of the 39 patients who received placebo.
- In **renal angiomyolipoma** caused by tuberous sclerosis, Votubia has been compared with placebo in one study involving 118 adults. The main measure of effectiveness was the proportion of patients who responded to treatment and whose kidney tumour shrank by at least half, which was seen in 42% of patients (33 out of 79) treated with Votubia, compared with none of the 39 patients who received placebo.
- The benefits of Votubia as an **add-on treatment of partial onset seizures related to tuberous sclerosis** that have not been sufficiently controlled by other treatments have been

shown in one main study. It involved 366 adults and children 2 years of age and over. Two different dosage regimens of add-on treatment with Votubia (tailored to give lower or higher levels in the blood) were compared with placebo. Before treatment, patients had 16 to 17 seizures per week on average and response was considered to be shown by a reduction in seizures of at least 50%. This response was seen in 28% (33 of 117 patients) in the lower blood level group and 40% (52 of 130 patients) in the higher blood level group, compared with 15% (18 of 119) of patients taking placebo. Overall, the patients given Votubia had a 29 and 40% reduction respectively in the number of seizures during treatment, compared with a 15% reduction in those given placebo.

What are the risks associated with Votubia?

The most common side effects with Votubia (seen in more than 1 in 10 patients) are acne, stomatitis (inflammation of the lining of the mouth), upper respiratory tract infections (colds), nasopharyngitis (inflammation of the nose and throat), sinusitis (inflammation of the sinuses), cough, pneumonia (infection of the lung), urinary tract infection, increased blood levels of cholesterol, irregular menstruation (periods), amenorrhoea (absence of periods), headache, diarrhoea, vomiting, rash, tiredness, fever and decreased appetite. For the full list of all side effects reported with Votubia, see the package leaflet.

Votubia must not be used in people who are hypersensitive (allergic) to everolimus, to related medicines such as sirolimus and temsirolimus or to any of the other ingredients.

Why is Votubia approved?

The Agency's Committee for Medicinal Products for Human Use (CHMP) noted that Votubia has been shown to reduce the size of the brain tumours in adults and children with tuberous sclerosis and that this is expected to reduce the signs and symptoms of SEGA such as seizures, hydrocephalus (accumulation of fluid in the brain), and increased pressure within the brain. Although surgery remains the standard treatment for this condition, Votubia is expected to benefit patients whose tumour cannot be operated on. Votubia has also been shown to reduce the size of kidney tumours in patients with renal angiomyolipoma and has been shown to be beneficial as an add-on treatment in the management of partial-onset seizures related to tuberous sclerosis that have not sufficiently responded to other therapy. The side effects of the medicine were considered to be manageable and were generally mild or moderate. The CHMP therefore concluded that the benefits of Votubia outweigh its risks and recommended that it be given marketing authorisation.

Votubia was originally given 'conditional approval' because there was more evidence to come about the medicine, in particular its long-term effects. As the company has supplied the additional information necessary, the authorisation has been switched from conditional to full approval.

What measures are being taken to ensure the safe and effective use of Votubia?

Recommendations and precautions to be followed by healthcare professionals and patients for the safe and effective use of Votubia have also been included in the summary of product characteristics and the package leaflet.

Other information about Votubia

The European Commission granted a conditional marketing authorisation valid throughout the European Union for Votubia on 2 September 2011. This was switched to a full marketing authorisation on 16 November 2015.

The full EPAR for Votubia can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports. For more information about treatment with Votubia, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

The summary of the opinion of the Committee for Orphan Medicinal Products for Votubia can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designations.

This summary was last updated in 01-2017.