Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

Votubia 2 mg
Votubia 3 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Votubia 2 mg dispersible tablets

Each dispersible tablet contains 2 mg everolimus.

Excipient with known effect
Each dispersible tablet contains 1.96 mg lactose monohydrate.

Votubia 3 mg dispersible tablets

Each dispersible tablet contains 3 mg everolimus.

Excipient with known effect
Each dispersible tablet contains 2.94 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersible tablet.

Votubia 2 mg dispersible tablets
White to slightly yellowish, round, flat, with beveled edges, unscored tablet, with smooth surface, debossed with "D2" on one side and "NVR" on the other side

Votubia 3 mg dispersible tablets

White to slightly yellowish, round, flat, with beveled edges, unscored tablet, with smooth surface, debossed with"D3" on one side and "NVR" on the other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Votubia is indicated as adjunctive treatment of patients aged 2 years and older whose refractory epileptic seizures are associated with tuberous sclerosis complex (TSC)

4.2 Posology and method of administration

Dosage/Administration

Treatment with Votubia should be initiated by a physician experienced in therapeutic drug monitoring and the treatment of patients with tuberous sclerosis complex (TSC).

Votubia should be taken orally once daily at the same time every day, either consistently with or consistently without food.

The patient should not make up for a missed dose, but should take the next prescribed dose as usual.

Treatment should continue as long as a clinical benefit is observed or until unacceptable toxicity occurs.Votubia dispersible tablets are recommended only for the treatment of TSC patients with refractory epileptic seizures who are undergoing therapeutic drug monitoring.

Votubia dispersible tablets disintegrate quickly in water, forming a suspension that can be prepared in an oral syringe or in a small drinking glass. The suspension may only be prepared with water. The suspension should be administered immediately following preparation. If the suspension cannot be used within 60 minutes of preparation, it must be discarded.

Dosing

Careful titration, with monitoring of everolimus blood concentration using a validated test, is required in order to obtain the optimal therapeutic effect. If possible, the same test method and the same laboratory should be used for therapeutic drug monitoring over the whole course of treatment.

Concomitant anticonvulsant therapy may affect the metabolism of everolimus (see section 4.5).

Dosing is individualised based on body surface area (BSA, in m^2).

Starting dose and target trough concentration:

The recommended starting daily dose of Votubia dispersible tablets is shown in Table 1. The starting dose should be rounded to the nearest available strength of Votubia dispersible tablets. Different strengths can be combined to attain the desired dose. Dosing should be titrated to attain a trough concentration of 5 to 15 ng/ml.

Table 1 Votubia starting dose in TSC with refractory epileptic seizures

Age	Starting dose without co-administration of CYP3A4/P-gp inducers	Starting dose with co-administration of CYP3A4/P-gp inducers
<6 years	6 mg/m^2	9 mg/m^2
≥6 years	5 mg/m^2	8 mg/m^2

Dose monitoring, titration and long-term dose monitoring

Dose monitoring: The everolimus blood trough concentration should be measured approximately 1 to 2 weeks after the initial dose, after any change in dose or pharmaceutical form, after initiation of or change in concomitant treatment with CYP3A4/P-gp inhibitors, after any change in hepatic status (Child-Pugh) and approximately 2 weeks after initiation of or change in concomitant treatment with CYP3A4/P-gp inducers.

Titration: Individualised dosing should be titrated by increasing the dose by increments of 2 to 4 mg to attain the target trough concentration for optimal clinical response. Efficacy, safety, concomitant medication and the current trough concentration should be considered when planning dose titration. Individualised dose titration can be based on a simple proportion equation:

New everolimus dose = current dose × (target concentration/current concentration)

The trough concentration should be assessed 1 to 2 weeks after a change in dose.

Long-term dose monitoring:

Once a stable target dose is attained, the trough concentration should be checked in patients with a changing body surface area every 3 to 6 months and in patients with an unchanged body surface area every 6 to 12 months for the duration of treatment.

Dose modifications

Adverse effects:

Severe and/or intolerable adverse drug reactions (ADRs) may require temporary interruption of treatment, with or without dose reduction, or discontinuation of treatment with Votubia. If dose reduction is required, a dose approximately 50% lower than the daily dose previously administered is recommended.

If dose reductions cannot be implemented using the lowest dosage strength, alternate-day dosing should be considered (see section 4.4)

Dose reduction, interruption or discontinuation of treatment, as well as any measures to manage adverse effects, should be based on the clinical judgement of the treating physician and an individual benefit-risk assessment.

- For grade 1 adverse reactions, no dose adjustment is normally required.
- For grade 2 adverse reactions, temporary interruption of treatment until the ADR improves to grade ≤1 may be necessary. In most cases treatment may subsequently be resumed at the same dose. In the case of pneumonitis, Votubia treatment should be resumed at a lower dose.
- For grade 3 adverse reactions, temporary interruption of treatment until the ADR improves to grade ≤1 is necessary. Votubia treatment may subsequently be resumed at a lower dose.
- For grade 4 adverse reactions, treatment with Votubia should be discontinued, except in the case of thrombocytopenia and neutropenia.

Moderate CYP3A4/P-gp inhibitors

In combination with moderate CYP3A4 or P-gp inhibitors, the Votubia dose should generally be reduced by 50%.

The everolimus trough concentration should be assessed approximately 1 to 2 weeks after co-administration of a moderate CYP3A4/P-gp inhibitor. If the moderate inhibitor is discontinued, the Votubia dose should be returned to that used before initiation of the moderate CYP3A4/P-gp inhibitor, and the trough concentration should be re-assessed approximately 2 weeks later (see section 4.4 and section 4.5.

Strong CYP3A4 inducers

Co-administration of Votubia and a strong inducer of its metabolism should be avoided if possible (see section 4.5). However, enzyme-inducing antiepileptic drugs may become necessary in these patients.

- *Patients with epileptic seizures receiving concomitant strong CYP3A4 inducers* (e.g. enzyme-inducing antiepileptics such as carbamazepine, phenobarbital and phenytoin) at the start of treatment with Votubia require an increased everolimus starting dose to attain trough concentrations of 5 to 15 ng/ml (see dosage recommendations in Table 1). The dose should be

further adjusted by increments of 2 to 4 mg as necessary to maintain the target trough concentration.

- *For TSC patients with epileptic seizures not receiving concomitant strong CYP3A4 inducers at the start of treatment with Votubia*, the addition of a strong inducer may require an increased everolimus dose. The daily dose should be doubled, and tolerability assessed. The everolimus trough concentration should be assessed approximately two weeks after doubling the dose, and the dose further adjusted by increments of 2 to 4 mg as necessary to maintain the target trough concentration.
- *The addition of another strong CYP3A4 inducer* may not require additional dose adjustment. The everolimus trough concentration should be assessed approximately two weeks after starting treatment with the additional inducer, and the dose further adjusted by increments of 2 to 4 mg as necessary to maintain the target trough concentration.
- *Discontinuation of one of multiple co-administered strong CYP3A4 inducers* may not require additional dose adjustment. The everolimus trough level should be determined approximately two weeks after discontinuation of one of multiple strong CYP3A4 inducers. *If discontinuing all strong CYP3A4 inducers*, a washout phase of at least 3 to 5 days (reasonable time for significant enzyme de-induction) should be considered before returning to the Votubia dose used before initiation of the strong CYP3A4 inducers. The everolimus trough concentration should be assessed approximately two weeks later (see section 4.4 and section 4.5)

Special dosage instructions

Paediatric patients

Votubia has not been studied in paediatric patients <2 years of age with TSC and refractory epileptic seizures.

Dosage recommendations for paediatric patients with TSC and refractory epileptic seizures are consistent with those for the corresponding adult patient population, with the exception of the starting dose in patients <6 years of age or patients with hepatic impairment.

Treatment with Votubia is not recommended in patients <18 years of age with hepatic impairment and TSC with epileptic seizures.

Elderly patients

No dose adjustment is required (see section 5.2).

Patients with renal impairment

No dose adjustment is required (however, please see section 4.4 and section 5.2).

Patients with hepatic impairment

Dose adjustments for patients with hepatic impairment should be made based on the indication (due to the different dosage recommendations) and hepatic function (Child-Pugh).

Recommended starting dose for patients >18 years of age with hepatic impairment

- Mild hepatic impairment (Child-Pugh A) – 75% of the dose calculated based on BSA (rounded to the nearest available strength)
- Moderate hepatic impairment (Child-Pugh B) – 50% of the dose calculated based on BSA (rounded to the nearest available strength)
- Severe hepatic impairment (Child-Pugh C) – not recommended. In the event of a positive benefit-risk assessment, 25% of the dose, calculated based on BSA and rounded to the nearest available strength, must not be exceeded.

Everolimus whole blood trough concentrations should be assessed approximately 1 to 2 weeks after commencing treatment or after any change in hepatic status (Child-Pugh). Dosing should be titrated to attain trough concentrations of 5 to 15 ng/ml (see "Dose monitoring"). A dose adjustment should be made if a patient's hepatic status (Child-Pugh) changes during treatment (see section 5.2).

4.3 Contraindications

Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including everolimus. Non-infectious pneumonitis (including interstitial lung disease) was described very commonly in patients taking everolimus in the advanced renal cell carcinoma (RCC) setting (see section 4.8). Some cases were severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) should be ruled out in the differential diagnosis of non-infectious pneumonitis (see section "Infections" below). Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Votubia therapy without dose adjustments. If symptoms are moderate, consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Votubia may be reinitiated at a daily dose approximately 50% lower than the dose previously administered.

For cases where symptoms of non-infectious pneumonitis are severe, Votubia therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Votubia may be reinitiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances.

For patients who require use of corticosteroids for treatment of non-infectious pneumonitis, prophylaxis for pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) may be considered.

Infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens (see section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections such as aspergillosis, candidiasis or pneumocystis jirovecii (carinii) pneumonia (PJP, PCP) and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to sepsis [including septic shock], respiratory or hepatic failure) and occasionally fatal in adult and paediatric patients (see section 4.8).

Physicians and patients should be aware of the increased risk of infection with Votubia. Pre-existing infections should be treated appropriately and should have resolved fully before starting treatment with Votubia. While taking Votubia, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of Votubia.

If a diagnosis of invasive systemic fungal infection is made, Votubia treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

Cases of pneumocystis jirovecii (carinii) pneumonia (PJP, PCP), some with fatal outcome, have been reported in patients who received everolimus. PJP/PCP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP/PCP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see section 4.3).

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

Stomatitis

Stomatitis, including mouth ulcerations and oral mucositis, is the most commonly reported adverse reaction in patients treated with Votubia (see section 4.8). Stomatitis mostly occurs within the first 8 weeks of treatment. A single-arm study in postmenopausal breast cancer patients treated with Afinitor (everolimus) plus exemestane suggested that an alcohol-free corticosteroid oral solution, administered as a mouthwash during the initial 8 weeks of treatment, may decrease the incidence and severity of stomatitis (see section 5.1). Management of stomatitis may therefore include prophylactic (in adults) and/or therapeutic use of topical treatments, such as an alcohol-free corticosteroid oral solution as a mouthwash. However products containing alcohol, hydrogen peroxide, iodine and thyme derivatives should be avoided as they may exacerbate the condition. Monitoring for and treatment of fungal infection is recommended, especially in patients being treated with steroid-based medicinal products. Antifungal agents should not be used unless fungal infection has been diagnosed (see section 4.5).

Haemorrhage

Serious cases of haemorrhage, some with a fatal outcome, have been reported in patients treated with everolimus in the oncology setting. No serious cases of renal haemorrhage were reported in the TSC setting.

Caution is advised in patients taking Votubia, particularly during concomitant use with active substances known to affect platelet function or that can increase the risk of haemorrhage as well as in patients with a history of bleeding disorders. Healthcare professionals and patients should be vigilant for signs and symptoms of bleeding throughout the treatment period, especially if risk factors for haemorrhage are combined.

Renal failure events

Cases of renal failure (including acute renal failure), some with a fatal outcome, have been observed in patients treated with Votubia (see section 4.8). Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function.

Laboratory tests and monitoring

Renal function
Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients treated with Votubia (see section 4.8). Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein or serum creatinine, is recommended prior to the start of Votubia therapy and periodically thereafter.

Blood glucose
Hyperglycaemia has been reported in patients taking Votubia (see section 4.8). Monitoring of fasting serum glucose is recommended prior to the start of Votubia therapy and periodically thereafter. More frequent monitoring is recommended when Votubia is co-administered with other medicinal products that may induce hyperglycaemia. When possible optimal glycaemic control should be achieved before starting a patient on Votubia.

Blood lipids
Dyslipidaemia (including hypercholesterolaemia and hypertriglyceridaemia) has been reported in patients taking Votubia. Monitoring of blood cholesterol and triglycerides prior to the start of Votubia therapy and periodically thereafter, as well as management with appropriate medical therapy, is also recommended.

Haematological parameters
Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported in patients treated with Votubia (see section 4.8). Monitoring of complete blood count is recommended prior to the start of Votubia therapy and periodically thereafter.

Interactions

Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a ***moderate*** CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Votubia may be required (see section 4.5).

Concomitant treatment with ***potent*** CYP3A4 inhibitors result in dramatically increased blood concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Votubia and ***potent*** inhibitors is not recommended.

Caution should be exercised when Votubia is taken in combination with orally administered CYP3A4 substrates with a narrow therapeutic index due to the potential for drug interactions. If Votubia is

taken with orally administered CYP3A4 substrates with a narrow therapeutic index (e.g. pimozide, terfenadine, astemizole, cisapride, quinidine, ergot alkaloid derivatives or carbamazepine), the patient should be monitored for undesirable effects described in the product information of the orally administered CYP3A4 substrate (see section 4.5).

Hepatic impairment

Votubia is not recommended for use in patients:

- **≥18 years of age with refractory seizures** and concomitant severe hepatic impairment (Child-Pugh C) unless the potential benefit outweighs the risk (see sections 4.2 and 5.2).
- **<18 years of age with refractory seizures** and concomitant hepatic impairment (Child-Pugh A, B and C) (see sections 4.2 and 5.2).

Vaccinations

The use of live vaccines should be avoided during treatment with Votubia (see section 4.5). For paediatric patients who do not require immediate treatment, completion of the recommended childhood series of live virus vaccinations is advised prior to the start of therapy according to local treatment guidelines.

Wound healing complications

Impaired wound healing is a class effect of rapamycin derivatives, including Votubia. Caution should therefore be exercised with the use of Votubia in the peri-surgical period.

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Radiation therapy complications

Serious and severe radiation reactions (such as radiation oesophagitis, radiation pneumonitis and radiation skin injury), including fatal cases, have been reported when everolimus was taken during, or shortly after, radiation therapy. Caution should therefore be exercised for the potentiation of radiotherapy toxicity in patients taking everolimus in close temporal relationship with radiation therapy.

Additionally, radiation recall syndrome (RRS) has been reported in patients taking everolimus who had received radiation therapy in the past. In the event of RRS, interrupting or stopping everolimus treatment should be considered

4.5 Interaction with other medicinal products and other forms of interaction

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and PgP are listed in Table 3 below.

CYP3A4 and PgP inhibitors increasing everolimus concentrations

Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells.

CYP3A4 and PgP inducers decreasing everolimus concentrations

Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells.

Table 2 Effects of other active substances on everolimus

Active substance by interaction	**Interaction – Change in Everolimus AUC/C_{max} Geometric mean ratio (observed range)**	**Recommendations concerning co-administration**
***Potent* CYP3A4/PgP inhibitors**		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) C_{max} ↑4.1-fold (range 2.6-7.0)	Concomitant treatment of Votubia and potent inhibitors is not recommended.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentration is expected.	
Telithromycin, clarithromycin		
Nefazodone		
Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
***Moderate* CYP3A4/PgP inhibitors**		
Erythromycin	AUC ↑4.4-fold (range 2.0-12.6) C_{max} ↑2.0-fold (range 0.9-3.5)	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, reduce the daily dose by approximately 50%. Further dose reduction may be required to manage adverse reactions (see sections 4.2 and 4.4). Everolimus trough concentrations should be assessed approximately 1 to 2 weeks after the addition of a moderate CYP3A4 or PgP inhibitor. If the moderate inhibitor is discontinued, the Votubia dose should be returned to the dose used prior to initiation of the co-administration. The everolimus trough concentration should be assessed approximately 2 weeks later (see sections 4.2 and 4.4).
Imatinib	AUC ↑ 3.7-fold C_{max} ↑ 2.2-fold	
Verapamil	AUC ↑3.5-fold (range 2.2-6.3) C_{max} ↑2.3-fold (range1.3-3.8)	
Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) C_{max} ↑1.8-fold (range 1.3-2.6)	
Fluconazole	Not studied. Increased exposure expected.	
Diltiazem		
Dronedarone	Not studied. Increased exposure expected.	
Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	
Grapefruit juice or other food affecting CYP3A4/PgP	Not studied. Increased exposure expected (the effect varies widely).	Combination should be avoided.
***Potent and moderate* CYP3A4 inducers**		
Rifampicin	AUC ↓63% (range 0-80%) C_{max} ↓58% (range 10-70%)	Avoid the use of concomitant potent CYP3A4 inducers.

Dexamethasone	Not studied. Decreased exposure expected.	Patients with seizures receiving concomitant strong CYP3A4 inducers (e.g., enzyme inducing antiepileptics carbamazepine, phenobarbital, and phenytoin) at the start of treatment with everolimus require an increased starting dose to attain trough concentrations of 5 to 15 ng/ml (see Table 1). For patients not receiving concomitant strong inducers at the start of everolimus treatment, the co-administration may require an increased Votubia dose. The daily dose should be doubled, and tolerability assessed. The everolimus trough concentration should be assessed approximately two weeks after doubling the dose, and the dose further adjusted by increments of 2 to 4 mg as necessary to maintain the target trough concentration The addition of another concomitant strong CYP3A4 inducer may not require additional dose adjustment. Assess the everolimus trough level approximately 2 weeks after initiating the additional inducer. Adjust the dose by increments of 2 to 4 mg as necessary to maintain the target trough concentration. Discontinuation of one of multiple strong CYP3A4 inducers may not require additional dose adjustment. Assess the everolimus trough level approximately 2 weeks after discontinuation of one of multiple strong CYP3A4 inducers. If all potent inducers are discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction) before the Votubia dose is returned to the dose used prior to initiation of the co-administration. The everolimus trough concentrations should be assessed approximately 2 weeks later since the natural degradation time of the induced enzymes has to be taken into account (see sections 4.2 and 4.4).
Antiepileptics (e.g. carbamazepine, phenobarbital, phenytoin)	Not studied. Decreased exposure expected.	
Efavirenz, nevirapine	Not studied. Decreased exposure expected.	
St John's Wort (*Hypericum perforatum*)	Not studied. Large decrease in exposure expected.	Preparations containing St John's Wort should not be used during treatment with everolimus

Agents whose plasma concentration may be altered by everolimus

Based on *in vitro* results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and PgP in the gut cannot be excluded. An interaction study in healthy subjects demonstrated that co-administration of an oral dose of midazolam, a sensitive CYP3A substrate probe, with everolimus resulted in a 25% increase in midazolam C_{max} and a 30% increase in midazolam $AUC_{(0\text{-}inf)}$. The effect is likely to be due to inhibition of intestinal CYP3A4 by everolimus. Hence everolimus may affect the bioavailability of orally co-administered CYP3A4 substrates. However, a clinically relevant effect on the exposure of systemically administered CYP3A4 substrates is not expected (see section 4.4).

In EXIST-3 (Study CRAD001M2304), everolimus increased pre-dose concentrations of the antiepileptics carbamazepine, clobazam, and the clobazam metabolite N-desmethylclobazam by about 10%. The increase in the pre-dose concentrations of these antiepileptics may not be clinically significant but dose adjustments for antiepileptics with a narrow therapeutic index, e.g carbamazepine, may be considered. Everolimus had no impact on pre-dose concentrations of antiepileptics that are substrates of CYP3A4 (clonazepam, diazepam, felbamate and zonisamide).

Concomitant use of angiotensin-converting enzyme (ACE) inhibitors

Patients taking concomitant ACE inhibitor (e.g. ramipril) therapy may be at increased risk for angioedema (see section 4.4).

Concomitant ketogenic diet

The effect of a ketogenic diet may be mediated through mTOR inhibition. In the absence of clinical data, the possibility of an additive effect on adverse events cannot be excluded when everolimus is given in conjunction with a ketogenic diet.

Vaccinations

The immune response to vaccination may be affected and, therefore, vaccination may be less effective during treatment with Votubia. The use of live vaccines should be avoided during treatment with Votubia. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG (Bacillus Calmette-Guérin), yellow fever, varicella, and TY21a typhoid vaccines.

Radiation treatment

Potentiation of radiation treatment toxicity has been reported in patients receiving everolimus (see sections 4.4 and 4.8).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential must use a highly effective method of contraception (e.g. oral, injected, or implanted non-oestrogen-containing hormonal method of birth control, progesterone-based contraceptives, hysterectomy, tubal ligation, complete abstinence, barrier methods, intrauterine device [IUD], and/or female/male sterilisation) while receiving everolimus, and for up to 8 weeks after ending treatment.

Male patients should not be prohibited from attempting to father children.

Pregnancy

There are no adequate data from the use of everolimus in pregnant women. Studies in animals have

shown reproductive toxicity effects including embryotoxicity and foetotoxicity (see section 5.3). The potential risk for humans is unknown.

Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is not known whether everolimus is excreted in human breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk (see section 5.3). Therefore, women taking everolimus should not breast-feed during treatment and for 2 weeks after the last dose.

Fertility

The potential for everolimus to cause infertility in male and female patients is unknown, however secondary amenorrhoea and associated luteinising hormone (LH)/follicle stimulating hormone (FSH) imbalance has been observed in female patients (see also section 5.3 for preclinical observations on the male and female reproductive systems). Based on non-clinical findings, male and female fertility may be compromised by treatment with everolimus (see section 5.3).

4.7 Effects on ability to drive and use machines

Votubia has minor or moderate influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with Votubia.

4.8 Undesirable effects

Summary of the safety profile

Three randomised, double-blind, placebo-controlled pivotal phase III studies, including double-blind and open label treatment periods, and a non-randomised, open-label, single-arm phase II study contribute to the safety profile of Votubia (n=612, including 409 patients <18 years of age; median duration of exposure 36.8 months [range 0.5 to 83.2]).

- EXIST-3 (CRAD001M2304): This was a randomised, double-blind, controlled, phase III trial comparing adjunctive treatment of low and high everolimus exposure (low trough [LT] range of 3-7 ng/ml [n=117] and high trough [HT] range of 9-15 ng/ml [n=130]) versus placebo (n=119), in patients with TSC and refractory partial-onset seizures receiving 1 to 3 antiepileptics. The median duration of the double-blind period was 18 weeks. The cumulative median duration exposure to Votubia (361 patients who took at least one dose of everolimus) was 30.4 months (range 0.5 to 48.8).

The adverse events considered to be associated with the use of Votubia (adverse reactions), based upon the review and medical assessment of all adverse events reported in three studies, are described below.

The most frequent adverse reactions (incidence ≥1/10) from the pooled safety data are (in decreasing order): stomatitis, pyrexia, nasopharyngitis, diarrhoea, upper respiratory tract infection, vomiting, cough, rash, headache, amenorrhoea, acne, pneumonia, urinary tract infection, sinusitis, menstruation irregular, pharyngitis, decreased appetite, fatigue, hypercholesterolaemia, and hypertension.

The most frequent grade 3-4 adverse reactions (incidence ≥1%) were pneumonia, stomatitis, amenorrhoea, neutropenia, pyrexia, menstruation irregular, hypophosphataemia, diarrhoea, and cellulitis. The grades follow CTCAE Version 3.0 and 4.03.

Tabulated list of adverse reactions

Table 4 shows the incidence of adverse reactions based on pooled data of patients receiving everolimus in the three TSC studies (including both the double-blind and open-label extension phase, where applicable). Adverse reactions are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4 Adverse reactions reported in TSC studies

Infections and infestations	
Very common	Nasopharyngitis, upper respiratory tract infection, pneumonia [a], urinary tract infection, sinusitis, pharyngitis
Common	Otitis media, cellulitis, pharyngitis streptococcal, gastroenteritis viral, gingivitis
Uncommon	Herpes zoster, sepsis, bronchitis viral
Blood and lymphatic system disorders	
Common	Anaemia, neutropenia, leucopenia, thrombocytopenia, lymphopenia
Immune system disorders	
Common	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Decreased appetite, hypercholesterolaemia
Common	Hypertriglyceridaemia, hyperlipidaemia, hypophosphataemia, hyperglycaemia
Psychiatric disorders	
Common	Insomnia, aggression, irritability
Nervous system disorders	
Very common	Headache
Uncommon	Dysgeusia
Vascular disorders	
Very common	Hypertension
Common	Lymphoedema
Respiratory, thoracic and mediastinal disorders	
Very common	Cough
Common	Epistaxis, pneumonitis
Gastrointestinal disorders	
Very common	Stomatitis [b], diarrhoea, vomiting
Common	Constipation, nausea, abdominal pain, flatulence, oral pain, gastritis
Skin and subcutaneous tissue disorders	
Very common	Rash [c], acne
Common	Dry skin, acneiform dermatitis, pruritus, alopecia
Uncommon	Angioedema
Musculoskeletal and connective tissue disorders	
Uncommon	Rhabdomyolysis
Renal and urinary disorders	
Common	Proteinuria
Reproductive system and breast disorders	
Very common	Amenorrhoea [d], menstruation irregular [d]
Common	Menorrhagia, ovarian cyst, vaginal haemorrhage
Uncommon	Menstruation delayed [d]
General disorders and administration site conditions	
Very common	Pyrexia, fatigue
Investigations	
Common	Blood lactate dehydrogenase increased, blood luteinising hormone increased,

	weight decreased
Uncommon	Blood follicle stimulating hormone increased
Injury, poisoning and procedural complications	
Not known[e]	Radiation recall syndrome, potentation of radiation reaction

[a] Includes pneumocystis jirovecii (carinii) pneumonia (PJP, PCP)
[b] Includes (very common) stomatitis, mouth ulceration, aphthous ulcer; (common) tongue ulceration, lip ulceration and (uncommon) gingival pain, glossitis
[c] Includes (very common) rash; (common) rash erythematous, erythema, and (uncommon) rash generalised, rash maculo-papular, rash macular
[d] Frequency based upon number of women from 10 to 55 years of age while on treatment in the pooled data
[e] Adverse reaction identified in the post-marketing setting

Description of selected adverse reactions

In clinical studies, everolimus has been associated with serious cases of hepatitis B reactivation, including fatal outcome. Reactivation of infection is an expected reaction during periods of immunosuppression.

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with renal failure events (including fatal outcome), proteinuria and increased serum creatinine. Monitoring of renal function is recommended (see section 4.4).

In clinical studies, everolimus has been associated with haemorrhage events. On rare occasions, fatal outcomes were observed in the oncology setting (see section 4.4). No serious cases of renal haemorrhage were reported in the TSC setting.

In clinical studies and post-marketing spontaneous reports, everolimus has been associated with cases of pneumocystis jirovecii (carinii) pneumonia (PJP, PCP), some with fatal outcome (see section 4.4).

Additional adverse reactions of relevance observed in oncology clinical studies and post-marketing spontaneous reports, were cardiac failure, pulmonary embolism, deep vein thrombosis, impaired wound healing and hyperglycaemia.

In clinical trials and post-marketing spontaneous reports, angioedema has been reported with and without concomitant use of ACE inhibitors (see section 4.4).

Paediatric population

In the pivotal phase III study in patients with TSC and refractory seizures, 299 of the 366 patients studied were below the age of 18 years. Two additional clinical trials were conducted with Votubia for other indications: A phase III study which included 101 paediatric patients and a phase II study which included 22 paediatric patients. The overall type, frequency and severity of adverse reactions observed in children and adolescents have been generally consistent with those observed in adults, with the exception of infections which were reported at a higher frequency and severity in children below the age of 6 years. A total of 49 out of 137 patients (36%) aged <6 years had Grade 3/4 infections, compared to 53 out of 272 patients (19%) aged 6 to <18 years and 27 out of 203 patients (13%) aged ≥18 years. Two fatal cases due to infection were reported in 409 patients aged <18 years receiving everolimus.

Elderly

In the oncology safety pooling, 37% of the patients treated with everolimus were ≥65 years of age. The number of oncology patients with an adverse reaction leading to discontinuation of everolimus was higher in patients ≥65 years of age (20% versus 13%). The most common adverse reactions leading to discontinuation were pneumonitis (including interstitial lung disease), fatigue, dyspnoea,

and stomatitis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability in the adult population.

It is essential to assess everolimus blood levels in cases of suspected overdose. General supportive measures should be initiated in all cases of overdose. Everolimus is not considered dialysable to any relevant degree (less than 10% was removed within 6 hours of haemodialysis).

Paediatric population

A limited number of paediatric patients have been exposed to doses higher than 10 mg/m^2/day. No signs of acute toxicity have been reported in these cases.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, protein kinase inhibitors, ATC code: L01XE10

Mechanism of action

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers. Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. Inhibition of the mTORC1 signalling pathway interferes with the translation and synthesis of proteins by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the cell cycle, angiogenesis and glycolysis. Everolimus can reduce levels of vascular endothelial growth factor (VEGF). In patients with TSC, treatment with everolimus increases VEGF-A and decreases VEGF-D levels. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours *in vitro* and *in vivo*.

Two primary regulators of mTORC1 signalling are the oncogene suppressors tuberin-sclerosis complexes 1 & 2 (TSC1, TSC2). Loss of either TSC1 or TSC2 leads to elevated rheb-GTP levels, a ras family GTPase, which interacts with the mTORC1 complex to cause its activation. mTORC1 activation leads to a downstream kinase signalling cascade, including activation of the S6 kinases. In tuberous sclerosis complex syndrome, inactivating mutations in the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body. Besides pathological changes in brain tissue (such as cortical tubers) which may cause seizures, the mTOR pathway is also implicated in the pathogenesis of epilepsy in TSC. The mTOR regulates protein synthesis and multiple downstream cellular functions that may influence neuronal excitability and epileptogenesis. Overactivation of mTOR results in neuronal dysplasia, aberrant axonogenesis and dendrite formation, increased excitatory synaptic currents, reduced myelination, and disruption of the cortical laminar structure causing abnormalities in neuronal development and function. Preclinical studies in models of mTOR dysregulation in the brain demonstrated that treatment with an mTOR inhibitor such as everolimus could prolong survival,

suppress seizures, prevent the development of new-onset seizures and prevent premature death. In summary, everolimus is highly active in this neuronal model of TSC, with benefit apparently attributable to effects on mTORC1 inhibition. However, the exact mechanism of action in the reduction of seizures associated with TSC is not fully elucidated.

Clinical efficacy and safety

Phase III study in patients with TSC and refractory seizures
EXIST-3 (Study CRAD001M2304), a randomised, double-blind, multicentre, three-arm, parallel-group phase III study of Votubia versus placebo as adjunctive therapy was conducted in TSC patients with refractory partial-onset seizures. In the study, partial-onset seizures were defined as all electroencephalogram (EEG)-confirmed sensory seizures or motor seizures in which a generalised onset had not been demonstrated on a past EEG. Patients were treated with concomitant and stable dose of 1 to 3 antiepileptics prior to study entry. The study consisted of three phases: an 8-week baseline observation phase; an 18-week double-blind, placebo-controlled core treatment phase (composed of titration and maintenance periods), an extension phase of ≥48 weeks in which all patients received Votubia and a post-extension phase of ≤48 weeks in which all patients received Votubia.

The study independently tested two different primary endpoints: 1) response rate defined as at least a 50% reduction from baseline in frequency of partial-onset seizures during the maintenance period of the core phase; and 2) percentage reduction from baseline in frequency of partial-onset seizures during the maintenance period of the core phase.

Secondary endpoints included seizure freedom, proportion of patients with ≥25% seizure frequency reduction from baseline, distribution of reduction from baseline in seizure frequency (≤-25%, >-25% to <25%; ≥25% to <50%; ≥50% to <75%; ≥75% to <100%; 100%), long-term evaluation of seizure frequency and overall quality of life.

A total of 366 patients were randomised in a 1:1.09:1 ratio to Votubia (n=117) low trough (LT) range (3 to 7 ng/ml), Votubia (n=130) high trough (HT) range (9 to 15 ng/ml) or placebo (n=119). The median age for the total population was 10.1 years (range: 2.2-56.3; 28.4% <6 years, 30.9% 6 to <12 years, 22.4% 12 to <18 years and 18.3% >18 years). Median duration of treatment was 18 weeks for all three arms in the core phase and 90 weeks (21 months) when considering both the core and extension phases.

At baseline, 19.4% of patients had focal seizures with retained awareness (sensory previously confirmed on EEG or motor), 45.1% had focal seizures with impaired awareness (predominantly non-motor), 69.1% had focal motor seizures (i.e. focal motor seizures with impaired awareness and/or secondary generalised seizures), and 1.6% had generalised onset seizures (previously confirmed by EEG). The median baseline seizure frequency across the treatment arms was 35, 38, and 42 seizures per 28 days for the Votubia LT, Votubia HT, and placebo groups, respectively. The majority of patients (67%) failed 5 or more antiepileptics prior to the study and 41.0% and 47.8% of patients were taking 2 and ≥3 antiepileptics during the study. The baseline data indicated mild to moderate mental retardation in patients 6-18 years of age (scores of 60-70 on the Adaptive Behavior Composite and Communication, Daily Living Skills, and Socialization Domain Scores).

The efficacy results for the primary endpoint are summarised in Table 5.

Table 5 EXIST-3 – Seizure frequency response rate (primary endpoint)

Statistic	Votubia LT target of 3-7 ng/ml N=117	Votubia HT target of 9-15 ng/ml N=130	Placebo N=119
Responders – n (%)	**33 (28.2)**	**52 (40.0)**	**18 (15.1)**
Response rate 95% CI [a]	20.3, 37.3	31.5, 49.0	9.2, 22.8
Odds ratio (versus placebo) [b]	**2.21**	**3.93**	
95% CI	1.16, 4.20	2.10, 7.32	
p-value (versus placebo) [c]	0.008	<0.001	
Statistically significant per Bonferroni-Holm procedure [d]	Yes	Yes	
Non-responders – n (%)	84 (71.8)	78 (60.0)	101 (84.9)

[a] Exact 95% CI obtained using Clopper-Pearson method

[b] Odds ratio and its 95% CI obtained using logistic regression stratified by age subgroup. Odds ratio >1 favours everolimus arm.

[c] p-values computed from the Cochran-Mantel-Haenszel test stratified by age subgroup

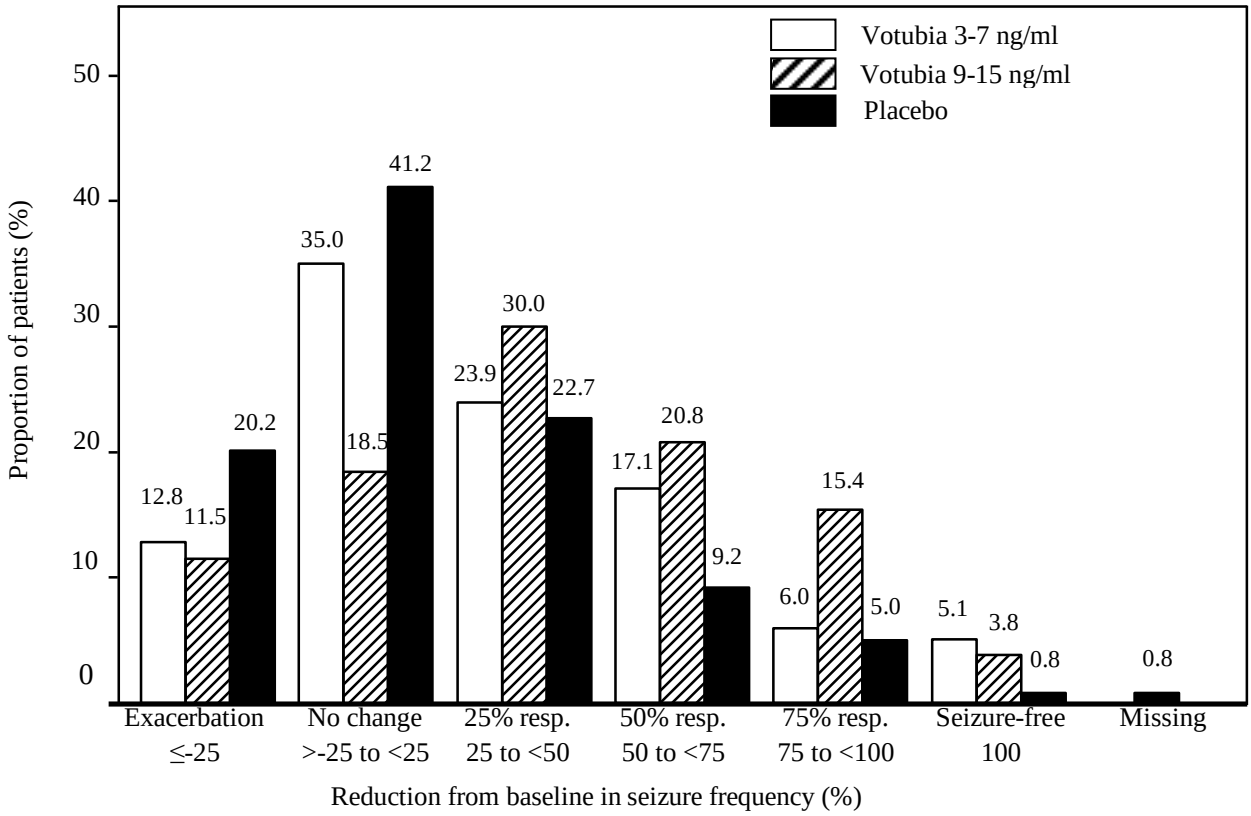
[d] Family-wise error rate of 2.5% one-sided

Consistent results were found for the supportive analysis of the median percentage reduction from baseline in seizure frequency (other primary endpoint): 29.3% (95% CI: 18.8, 41.9) in the Votubia LT arm, 39.6% (95% CI: 35.0, 48.7) in the Votubia HT arm and 14.9% (95% CI: 0.1, 21.7) in the placebo arm. The p-values for superiority versus placebo were 0.003 (LT) and <0.001 (HT).

The seizure-free rate (the proportion of patients who became seizure-free during the maintenance period of the core phase) was 5.1% (95% CI: 1.9, 10.8) and 3.8% (95% CI: 1.3, 8.7) in the Votubia LT and HT arms, respectively, versus 0.8% (95% CI: 0.0, 4.6) of patients in the placebo arm.

Higher proportions of responders were evident for all response categories in the Votubia LT and HT arms relative to placebo (Figure 1). Furthermore, almost twice as many patients in the placebo arm experienced seizure exacerbation relative to the Votubia LT and HT arms.

Figure 1 EXIST-3 – Distribution of reduction from baseline in seizure frequency



A homogeneous and consistent everolimus effect was observed across all subgroups evaluated for the primary efficacy endpoints by: age categories (Table 6), gender, race and ethnicity, seizure types, seizure frequency at baseline, number and name of concomitant antiepileptics, and TSC features (angiomyolipoma, SEGA, cortical tuber status). The effect of everolimus on infantile/epileptic spasms or on seizures associated with Lennox-Gastaut syndrome has not been studied and is not established for generalised-onset seizures and subjects without cortical tubers.

Table 6 EXIST-3 – Seizure frequency response rate by age

	Votubia		**Placebo**
Age category	**LT target of 3-7 ng/ml N=117**	**HT target of 9-15 ng/ml N=130**	**N=119**
<6 years	**n=33**	**n=37**	**n=34**
Response rate (95% CI) [a]	30.3 (15.6, 48.7)	59.5 (42.1, 75.2)	17.6 (6.8, 34.5)
6 to <12 years	**n=37**	**n=39**	**n=37**
Response rate (95% CI) [a]	29.7 (15.9, 47.0)	28.2 (15.0, 44.9)	10.8 (3.0, 25.4)
12 to <18 years	**n=26**	**n=31**	**n=25**
Response rate (95% CI) [a]	23.1 (9.0, 43.6)	32.3 (16.7, 51.4)	16.0 (4.5, 36.1)
≥18 years [b]	**n=21**	**n=23**	**n=23**
Response rate (95% CI) [a]	28.6 (11.3, 52.2)	39.1 (19.7, 61.5)	17.4 (5.0, 38.8)

[a] Exact 95% CI obtained using Clopper-Pearson method
[b] No efficacy data available in elderly patients

At the end of the core phase, overall quality of life in patients aged 2 to <11 years (as measured by the mean change from baseline in overall Quality Of Life score [total score] in the Childhood Epilepsy Questionnaire [QOLCE]) was maintained in each Votubia treatment arm as well as in the placebo arm.

Reduction in seizure frequency was sustained over an evaluation period of approximately 2 years. Based on a sensitivity analysis considering patients who prematurely discontinued everolimus as non-

responders, response rates of 38.4% (95% CI: 33.4, 43.7) and 44.4% (95% CI: 38.2, 50.7) were observed after 1 and 2 years of exposure to everolimus, respectively.

5.2 Pharmacokinetic properties

Absorption

In patients with advanced solid tumours, peak everolimus concentrations (C_{max}) are reached at a median time of 1 hour after daily administration of 5 and 10 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional between 5 and 10 mg. Everolimus is a substrate and moderate inhibitor of PgP.

Food effect
In healthy subjects, high fat meals reduced systemic exposure to Votubia 10 mg tablets (as measured by AUC) by 22% and the peak blood concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max} by 42%.

In healthy subjects taking a single 9 mg dose (3 x 3 mg) of Votubia dispersible tablets in suspension, high fat meals reduced AUC by 11.7% and the peak blood concentration C_{max} by 59.8%. Light fat meals reduced AUC by 29.5% and C_{max} by 50.2%.

Food, however, had no apparent effect on the post absorption phase concentration-time profile 24 hours post-dose of either dosage form.

Relative bioavailability/bioequivalence
In a relative bioavailability study, $AUC_{0\text{-}inf}$ of 5 x 1 mg everolimus tablets when administered as suspension in water was equivalent to 5 x 1 mg everolimus tablets administered as intact tablets, and C_{max} of 5 x 1 mg everolimus tablets in suspension was 72% of 5 x 1 mg intact everolimus tablets.

In a bioequivalence study, $AUC_{0\text{-}inf}$ of the 5 mg dispersible tablet when administered as suspension in water was equivalent to 5 x 1 mg intact everolimus tablets, and C_{max} of the 5 mg dispersible tablet in suspension was 64% of 5 x 1 mg intact everolimus tablets.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/ml, is 17% to 73%. Approximately 20% of the everolimus concentration in whole blood is confined to plasma of cancer patients given Votubia 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment. In patients with advanced solid tumours, V_d was 191 l for the apparent central compartment and 517 l for the apparent peripheral compartment.

Nonclinical studies in rats indicate:
- A rapid uptake of everolimus in the brain followed by a slow efflux.
- The radioactive metabolites of [3H]everolimus do not significantly cross the blood-brain barrier.
- A dose-dependent brain penetration of everolimus, which is consistent with the hypothesis of saturation of an efflux pump present in the brain capillary endothelial cells.
- The co-administration of the PgP inhibitor, cyclosporine, enhances the exposure of everolimus in the brain cortex, which is consistent with the inhibition of PgP at the blood-brain barrier.

There are no clinical data on the distribution of everolimus in the human brain. Non-clinical studies in rats demonstrated distribution into the brain following administration by both the intravenous and oral routes.

Biotransformation

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100 times less activity than everolimus itself. Hence, everolimus is considered to contribute the majority of the overall pharmacological activity.

Elimination

Mean CL/F of everolimus after 10 mg daily dose in patients with advanced solid tumours was 24.5 l/h. The mean elimination half-life of everolimus is approximately 30 hours.

No specific excretion studies have been undertaken in cancer patients; however, data are available from the studies in transplant patients. Following the administration of a single dose of radiolabelled everolimus in conjunction with ciclosporin, 80% of the radioactivity was recovered from the faeces, while 5% was excreted in the urine. The parent substance was not detected in urine or faeces.

Steady-state pharmacokinetics

After administration of everolimus in patients with advanced solid tumours, steady-state $AUC_{0-\tau}$ was dose-proportional over the range of 5 to 10 mg daily dose. Steady-state was achieved within 2 weeks. C_{max} is dose-proportional between 5 and 10 mg. t_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state.

Special populations

Hepatic impairment
The safety, tolerability and pharmacokinetics of Votubia were evaluated in two single oral dose studies of Votubia tablets in 8 and 34 adult subjects with impaired hepatic function relative to subjects with normal hepatic function.

In the first study, the average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh B) was twice that found in 8 subjects with normal hepatic function.

In the second study of 34 subjects with different impaired hepatic function compared to normal subjects, there was a 1.6-fold, 3.3-fold and 3.6-fold increase in exposure (i.e. AUC_{0-inf}) for subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, respectively.

Simulations of multiple dose pharmacokinetics support the dosing recommendations in subjects with hepatic impairment based on their Child-Pugh status.

Based on the results of the two studies, dose adjustment is recommended for patients with hepatic impairment (see sections 4.2 and 4.4).

Renal impairment
In a population pharmacokinetic analysis of 170 patients with advanced solid tumours, no significant influence of creatinine clearance (25-178 ml/min) was detected on CL/F of everolimus. Post-transplant renal impairment (creatinine clearance range 11-107 ml/min) did not affect the pharmacokinetics of everolimus in transplant patients.

Paediatric population

In patients with TSC and refractory seizures receiving Votubia dispersible tablets, a trend was observed toward lower C_{min} normalised to dose (as mg/m^2) in younger patients. Median C_{min} normalised to mg/m^2 dose was lower for the younger age groups, indicating that everolimus clearance (normalised to body surface area) was higher in younger patients.

Elderly
In a population pharmacokinetic evaluation in cancer patients, no significant influence of age (27-85 years) on oral clearance of everolimus was detected.

Ethnicity
Oral clearance (CL/F) is similar in Japanese and Caucasian cancer patients with similar liver functions. Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in black transplant patients.

Pharmacokinetic/pharmacodynamic relationship(s)

In patients with TSC and refractory seizures, a conditional logistic regression analysis based on the core phase of Study CRAD001M2304 to estimate the probability of seizure response versus Time Normalized(TN)-C_{min} stratified by age sub-group, indicated that a 2-fold increase in TN-C_{min} was associated with a 2.172-fold increase (95% CI: 1.339, 3.524) in the odds for a seizure response over the observed TN-C_{min} ranges of 0.97 ng/ml to 16.40 ng/ml. Baseline seizure frequency was a significant factor in the seizure response (with an odds ratio of 0.978 [95% CI: 0.959, 0.998]). This outcome was consistent with the results of a linear regression model predicting the log of absolute seizure frequency during the maintenance period of the core phase, which indicated that for a 2-fold increase in TN-C_{min} there was a statistically significant 28% reduction (95% CI: 12%, 42%) in absolute seizure frequency. Baseline seizure frequency and TN-C_{min} were both significant factors (α=0.05) in predicting the absolute seizure frequency in the linear regression model.

5.3 Preclinical safety data

The non-clinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species; lungs (increased alveolar macrophages) in rats and mice; pancreas (degranulation and vacuolation of exocrine cells in monkeys and minipigs, respectively, and degeneration of islet cells in monkeys), and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs.

Everolimus appeared to spontaneously exacerbate background diseases (chronic myocarditis in rats, coxsackie virus infection of plasma and heart in monkeys, coccidian infestation of the gastrointestinal tract in minipigs, skin lesions in mice and monkeys). These findings were generally observed at systemic exposure levels within the range of therapeutic exposure or above, with the exception of the findings in rats, which occurred below therapeutic exposure due to a high tissue distribution.

In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure and which caused a reduction in male fertility. There was evidence of reversibility.

In animal reproductive studies female fertility was not affected. However, oral doses of everolimus in female rats at $\geq$ 0.1 mg/kg (approximately 4% of the $AUC_{0\text{-}24h}$ in patients receiving the 10 mg daily dose) resulted in increases in pre-implantation loss.

Everolimus crossed the placenta and was toxic to the foetus. In rats, everolimus caused embryo/foetotoxicity at systemic exposure below the therapeutic level. This was manifested as

mortality and reduced foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions.

In juvenile rat toxicity studies, systemic toxicity included decreased body weight gain, food consumption, and delayed attainment of some developmental landmarks, with full or partial recovery after cessation of dosing. With the possible exception of the rat-specific lens finding (where young animals appeared to be more susceptible), it appears that there is no significant difference in the sensitivity of juvenile animals to the adverse reactions of everolimus as compared to adult animals. Toxicity study with juvenile monkeys did not show any relevant toxicity.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 4.3 and 0.2 times the estimated clinical exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

The stability of the ready to use suspension has been demonstrated for 60 minutes. The suspension must be administered immediately after preparation. If not administered within 60 minutes, the suspension must be discarded and a new suspension must be prepared.

6.4 Special precautions for storage

Do not store above 30^{o}C. Protect from ligth and moisture.

6.5 Nature and contents of container

Aluminium/polyamide/aluminium/PVC perforated unit-dose blister containing 10 x 1 dispersible tablets.

<u>Votubia 2 mg dispersible tablets</u>

Packs containing 30 dispersible tablets.

<u>Votubia 3 mg dispersible tablets</u>

Packs containing 30 dispersible tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use and handling

Using an oral syringe
The prescribed dose of Votubia dispersible tablets should be placed in a 10 ml oral dosing syringe graduated in 1 ml increments. A total of 10 mg of Votubia dispersible tablets per syringe using a maximum of 5 dispersible tablets must not be exceeded. If a higher dose or number of tablets is required, an additional syringe must be prepared. The dispersible tablets must not be broken or crushed. Approximately 5 ml of water and 4 ml of air should be drawn into the syringe. The filled syringe should be placed into a container (with the tip pointing up) for 3 minutes, until the Votubia dispersible tablets are in suspension. The syringe should be gently inverted 5 times immediately prior to administration. After administration of the prepared suspension, approximately 5 ml of water and 4 ml of air should be drawn into the same syringe, and the contents should be swirled to suspend remaining particles. The entire contents of the syringe should be administered.

Using a small glass
The prescribed dose of Votubia dispersible tablets should be placed in a small glass (maximum size 100 ml) containing approximately 25 ml of water. A total of 10 mg of Votubia dispersible tablets per glass using a maximum of 5 dispersible tablets must not be exceeded. If a higher dose or number of tablets is required, an additional glass must be prepared. The dispersible tablets must not be broken or crushed. Three minutes must be allowed for suspension to occur. The contents should be gently stirred with a spoon and then administered immediately. After administration of the prepared suspension, 25 ml of water should be added and be stirred with the same spoon to re-suspend any remaining particles. The entire contents of the glass should be administered.

A complete and illustrated set of instructions for use is provided at the end of the package leaflet "Instructions for use".

Important information for caregivers

The extent of absorption of everolimus through topical exposure is not known. Therefore caregivers are advised to avoid contact with the suspension. Hands should be washed thoroughly before and after preparation of the suspension.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. REGISTRATION HOLDER AND IMPORTER:
Novartis Israel Ltd
P.O.B 7126, Tel Aviv, Israel

8. REGISTRATION NUMBERS
Votubia 2 mg 164-73-35765-00
Votubia 3 mg 164-74-35766-00

Revised in August 2021 according to MOH guidelines