SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Votubia® 1 mg dispersible tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains 1 mg everolimus.

Excipient with known effect

Each dispersible tablet contains 0.98 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Dispersible tablet.

White to slightly yellowish, round, flat tablets of approximately 7.1 mm in diameter, with a bevelled edge and no score, engraved with “D1” on one side and “NVR” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Refractory seizures associated with tuberous sclerosis complex (TSC)

Votubia is indicated as adjunctive treatment of patients aged 2 years and older whose refractory partial-onset seizures, with or without secondary generalisation, are associated with TSC.

Subependymal giant cell astrocytoma (SEGA) associated with TSC

Votubia is indicated for the treatment of adult and paediatric patients with SEGA associated with TSC who require therapeutic intervention but are not amenable to surgery.

The evidence is based on analysis of change in SEGA volume. Further clinical benefit, such as improvement in disease-related symptoms, has not been demonstrated.

4.2 Posology and method of administration

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

Posology

Careful titration may be required to obtain the optimal therapeutic effect. Doses that will be tolerated and effective vary between patients. Concomitant antiepileptic therapy may affect the metabolism of everolimus and may contribute to this variance (see section 4.5).

Dosing is individualised based on Body Surface Area (BSA) using the Dubois formula, where weight (W) is in kilograms and height (H) is in centimetres:

$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$

Starting dose and target trough concentrations in SEGA associated with TSC

The recommended starting dose for Votubia for the treatment of patients with SEGA is 4.5 mg/m^2. A higher starting dose of 7 mg/m^2 is recommended for patients 1 to less than 3 years of age based on pharmacokinetic simulations (see section 5.2). Different strengths of Votubia dispersible tablets can be combined to attain the desired dose.

Dosing recommendations for paediatric patients with SEGA are consistent with those for the adult SEGA population, except for patients in the range from 1 year to less than 3 years of age, and those with hepatic impairment (see section “Hepatic impairment” below and section 5.2).

Starting dose and target trough concentrations in TSC with refractory seizures

The recommended starting dose for Votubia for the treatment of patients with seizures is shown in Table 1. Different strengths of Votubia dispersible tablets can be combined to attain the desired dose.

Table 1 Votubia starting dose for patients with TSC and refractory seizures

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

Dosing recommendations for paediatric patients with seizures are consistent with those for the adult population, except for patients in the range from 2 years to less than 6 years of age (see Table 1 above), and those with hepatic impairment (see section "Hepatic impairment" below and section 5.2).

Dose monitoring

Everolimus whole blood trough concentrations should be assessed at least 1 week after commencing treatment. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/ml. The dose may be increased to attain a higher trough concentration within the target range to obtain optimal efficacy, subject to tolerability.

Titration

Individualised dosing should be titrated by increasing the dose by increments of 1 to 4 mg to attain the target trough concentration for optimal clinical response. Efficacy, safety, concomitant therapy, and the current trough concentration should be considered when planning for dose titration. Individualised dose titration can be based on simple proportion:

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

For example, a patient's current dose based on BSA is 4 mg with a steady-state concentration of 4 ng/ml. In order to achieve a target concentration above the lower C_{min} limit of 5 ng/ml, e.g. 8 ng/ml, the new everolimus dose would be 8 mg (an increase of 4 mg from the current daily dose).

Long-term monitoring

For patients with TSC who have SEGA, SEGA volume should be evaluated approximately 3 months after commencing Votubia therapy, with subsequent dose adjustments taking changes in SEGA volume, corresponding trough concentration, and tolerability into consideration.

For patients with TSC who have SEGA and patients with TSC and refractory seizures, once a stable dose is attained, trough concentrations should be monitored every 3 to 6 months in patients with changing BSA, or every 6 to 12 months in patients with stable BSA, for the duration of treatment.

Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

If a dose is missed, the patient should not take an additional dose, but take the usual prescribed next dose.

Dose adjustments due to adverse reactions

Management of severe and/or intolerable suspected adverse reactions may require dose reduction and/or temporary interruption of Votubia therapy. For adverse reactions of Grade 1, dose adjustment is usually not required. If dose reduction is required, the recommended dose is approximately 50% lower than the daily dose previously administered. For dose reductions below the lowest available strength, alternate day dosing should be considered.

Table 2 summarises dose adjustment recommendations for specific adverse reactions (see also section 4.4).

Table 2 Votubia dose adjustment recommendations

Adverse reaction	**Severity**[1]	**Votubia dose adjustment**
Non-infectious pneumonitis	Grade 2	Consider interruption of therapy until symptoms improve to Grade ≤1.
		Re-initiate Votubia at approximately 50% lower than the daily dose previously administered.
		Discontinue treatment if failure to recover within 4 weeks.
	Grade 3	Interrupt Votubia until symptoms resolve to Grade ≤1.
		Consider re-initiating Votubia at approximately 50% lower than the daily dose previously administered. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue Votubia.
Stomatitis	Grade 2	Temporary dose interruption until recovery to Grade ≤1.
		Re-initiate Votubia at same dose.
		If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤1. Re-initiate Votubia at approximately 50% lower than the daily dose previously administered.

	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Re-initiate Votubia at approximately 50% lower than the daily dose previously administered.
	Grade 4	Discontinue Votubia.
Other non-haematological toxicities (excluding metabolic events)	Grade 2	If toxicity is tolerable, no dose adjustment required. If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤1. Re-initiate Votubia at same dose. If toxicity recurs at Grade 2, interrupt Votubia until recovery to Grade ≤1. Re-initiate Votubia at approximately 50% lower than the daily dose previously administered.
	Grade 3	Temporary dose interruption until recovery to Grade ≤1. Consider re-initiating Votubia at approximately 50% lower than the daily dose previously administered. If toxicity recurs at Grade 3, consider discontinuation.
	Grade 4	Discontinue Votubia.
Metabolic events (e.g. hyperglycaemia, dyslipidaemia)	Grade 2	No dose adjustment required.
	Grade 3	Temporary dose interruption. Re-initiate Votubia at approximately 50% lower than the daily dose previously administered.
	Grade 4	Discontinue Votubia.
Thrombocytopenia	Grade 2 (<75, ≥50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate Votubia at same dose.
	Grade 3 & 4 (<50x10^9/l)	Temporary dose interruption until recovery to Grade ≤1 (≥75x10^9/l). Re-initiate Votubia at approximately 50% lower than the daily dose previously administered.
Neutropenia	Grade 2 (≥1x10^9/l)	No dose adjustment required.
	Grade 3 (<1, ≥0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate Votubia at same dose.
	Grade 4 (<0.5x10^9/l)	Temporary dose interruption until recovery to Grade ≤2 (≥1x10^9/l). Re-initiate Votubia at approximately 50% lower than the daily dose previously administered.
Febrile neutropenia	Grade 3	Temporary dose interruption until recovery to Grade ≤2 (≥1.25x10^9/l) and no fever. Re-initiate Votubia at approximately 50% lower than the daily dose previously administered.
	Grade 4	Discontinue Votubia.

[1] Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0

Therapeutic drug monitoring

Therapeutic drug monitoring of everolimus blood concentrations, using a validated assay, is **required**. Trough concentrations should be assessed at least 1 week after the initial dose, after any change in dose or pharmaceutical form, after initiation of or change in co-administration of CYP3A4 inhibitors (see sections 4.4 and 4.5) or after any change in hepatic status (Child-Pugh) (see "Hepatic impairment" below and section 5.2). Trough concentrations should be assessed 2 to 4 weeks after initiation of or change in co-administration of CYP3A4 inducers (see sections 4.4 and 4.5) since the natural degradation time of the induced enzymes has to be taken into account. When possible, the same assay and laboratory for therapeutic drug monitoring should be used throughout the treatment.

Switching pharmaceutical forms

Votubia is available in two pharmaceutical forms: tablets and dispersible tablets. Votubia tablets and Votubia dispersible tablets are **not** to be used interchangeably. The two pharmaceutical forms must not be combined to achieve the desired dose. The same pharmaceutical form must be used consistently, as appropriate for the indication being treated.

When switching pharmaceutical forms, the dose should be adjusted to the closest milligram strength of the new pharmaceutical form and the everolimus trough concentration should be assessed at least 1 week later (see section "Therapeutic drug monitoring" above).

Special populations

Elderly

No dose adjustment is required (see section 5.2).

Renal impairment

No dose adjustment is required (see section 5.2).

Hepatic impairment

Patients <18 years of age:

Votubia is not recommended for patients <18 years of age with SEGA or refractory seizures and hepatic impairment.

Patients ≥18 years of age:

- Mild hepatic impairment (Child-Pugh A): 75% of the recommended starting dose calculated based on BSA (rounded to the nearest strength)
- Moderate hepatic impairment (Child-Pugh B): 50% of the recommended starting dose calculated based on BSA (rounded to the nearest strength)

- Severe hepatic impairment (Child-Pugh C): Votubia is only recommended if the desired benefit outweighs the risk. In this case, 25% of the dose calculated based on BSA (rounded to the nearest strength) must not be exceeded.

Everolimus whole blood trough concentrations should be assessed at least 1 week after any change in hepatic status (Child-Pugh).

Paediatric population

The safety, efficacy and pharmacokinetic profile of Votubia in children below the age of 1 year with TSC who have SEGA have not been established. No data are available (see sections 5.1 and 5.2).

The safety, efficacy and pharmacokinetic profile of Votubia has not been established in children below the age of 2 years with TSC and refractory seizures. Currently available data are described in section 5.2, but no recommendation on a posology can be made.

Clinical study results did not show an impact of Votubia on growth and pubertal development.

Method of administration

Votubia must be administered orally once daily at the same time every day, consistently either with or without food (see section 5.2).

Votubia dispersible tablets are to be taken as a suspension only and must not be swallowed whole, chewed, or crushed. The suspension can be prepared either in an oral syringe or in a small glass. Care should be taken to ensure the entire dose is ingested.

The suspension must be administered immediately after preparation. If not administered within 30 minutes of preparation when using an oral syringe or 60 minutes when using a small glass, the suspension must be discarded and a new suspension must be prepared (see section 6.3). Only water should be used as the vehicle.

For further details on handling, see section 6.6.

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, the clinical condition of the patient should be monitored closely. Monitoring of everolimus through concentrations and dose adjustments of Votubia may be required (see section 4.5).

Concomitant treatment with ***potent*** CYP3A4/PgP 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 SEGA or 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 SEGA or 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 3Effects 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 at least 1 week after the addition of a moderate CYP3A4 or PgP inhibitor. If the moderate inhibitor is discontinued, consider a washout period of at least 2 to 3 days (average elimination time for most commonly used moderate inhibitors) before the Votubia dose is returned to the dose used prior to initiation of the co-administration. The everolimus trough
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)	
Cannabidiol (PgP inhibitor)	AUC ↑2.5-fold C_{max} ↑2.5-fold	
Fluconazole	Not studied. Increased exposure expected.	
Diltiazem		
Dronedarone	Not studied. Increased exposure expected.	
Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	

		concentration should be assessed at least 1 week later (see sections 4.2 and 4.4).
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. SEGA patients receiving concomitant potent CYP3A4 inducers may require an increased Votubia dose to achieve the same exposure as patients not taking potent inducers. Dosing should be titrated to attain trough concentrations of 5 to 15 ng/ml as described below. 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. If concentrations are below 5 ng/ml, the daily dose may be increased by increments of 1 to 4 mg, checking the trough level and assessing tolerability before increasing the dose.
Dexamethasone	Not studied. Decreased exposure expected.	
Antiepileptics (e.g. carbamazepine, phenobarbital, phenytoin)	Not studied. Decreased exposure expected.	
Efavirenz, nevirapine	Not studied. Decreased exposure expected.	

		The addition of another concomitant strong CYP3A4 inducer may not require additional dose adjustment. Assess the everolimus trough level 2 weeks after initiating the additional inducer. Adjust the dose by increments of 1 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 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 2 to 4 weeks later since the natural degradation time of the induced enzymes has to be taken into account (see sections 4.2 and 4.4).
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 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).

- EXIST-2 (CRAD001M2302): This was a randomised, double-blind, controlled, phase III trial of everolimus (n=79) versus placebo (n=39) in patients with either TSC plus renal angiomyolipoma (n=113) or sporadic lymphangioleiomyomatosis (LAM) plus renal angiomyolipoma (n=5). The median duration of blinded study treatment was 48.1 weeks (range 2 to 115) for patients receiving Votubia and 45.0 weeks (range 9 to 115) for those receiving placebo. The cumulative median duration of exposure to Votubia (112 patients who took at least one dose of everolimus) was 46.9 months (range 0.5 to 63.9).
- EXIST-1 (CRAD001M2301): This was a randomised, double-blind, controlled, phase III trial of everolimus (n=78) versus placebo (n=39) in patients with TSC who have SEGA, irrespective of age. The median duration of blinded study treatment was 52.2 weeks (range 24 to 89) for patients receiving Votubia and 46.6 weeks (range 14 to 88) for those receiving placebo. The cumulative median duration of exposure to Votubia (111 patients who took at least one dose of everolimus) was 47.1 months (range 1.9 to 58.3).
- CRAD001C2485: This was a prospective, open-label, single-arm phase II study of everolimus in patients with SEGA (n=28). The median duration of exposure was 67.8 months (range 4.7 to 83.2).

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 the above 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 studies 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 II study, 22 of the 28 SEGA patients studied were below the age of 18 years and in the pivotal phase III study, 101 of the 117 SEGA patients studied were below the age of 18 years. 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. 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 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.

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, protein kinase inhibitors, ATC code: L01EG02

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 TSC syndrome, inactivating mutations in the TSC1 or the TSC2 gene lead to hamartoma formation throughout the body.

Clinical efficacy and safety

Renal angiomyolipoma associated with TSC
EXIST-2 (study CRAD001M2302), a randomised, controlled phase III study was conducted to evaluate the efficacy and safety of Votubia in patients with TSC plus renal angiomyolipoma. Presence of at least one angiomyolipoma ≥3 cm in longest diameter using CT/MRI (based on local radiology assessment) was required for entry.

The primary efficacy endpoint was angiomyolipoma response rate based on independent central radiology review. The analysis was stratified by use of enzyme-inducing antiepileptics at randomisation (yes/no).

Key secondary endpoints included time to angiomyolipoma progression and skin lesion response rate.

A total of 118 patients were randomised, 79 to Votubia 10 mg daily and 39 to placebo. Median age was 31 years (range: 18 to 61 years; 46.6% were <30 years at enrolment), 33.9% were male, and 89.0% were Caucasian. Of the enrolled patients, 83.1% had angiomyolipomas ≥4 cm (28.8% ≥8 cm), 78.0% had bilateral angiomyolipomas, and 39.0% had undergone prior renal embolisation/nephrectomy; 96.6% had skin lesions at baseline and 44.1% had target SEGAs (at least one SEGA ≥1 cm in longest diameter).

Results showed that the primary objective related to best overall angiomyolipoma response was met with best overall response rates of 41.8% (95% CI: 30.8, 53.4) for the Votubia arm compared with 0% (95% CI: 0.0, 9.0) for the placebo arm (p<0.0001) (Table 4).

Patients initially treated with placebo were allowed to cross over to everolimus at the time of angiomyolipoma progression and upon recognition that treatment with everolimus was superior to treatment with placebo. At the time of the final analysis (4 years following the last patient randomisation), the median duration of exposure to everolimus was 204.1 weeks (range 2 to 278). The angiomyolipoma best overall response rate had increased to 58.0% (95% CI: 48.3, 67.3), with a rate of stable disease of 30.4% (Table 4).

Among patients treated with everolimus during the study, no cases of angiomyolipoma-related nephrectomy and only one case of renal embolisation were reported.

Table 4EXIST-2 - Angiomyolipoma response

	Primary analysis[3]			**Final analysis[4]**
	Votubia n=79	**Placebo n=39**	**p-value**	**Votubia n=112**
Primary analysis				
Angiomyolipoma response rate[1,2] – %	41.8	0	<0.0001	58.0
95% CI	30.8, 53.4	0.0, 9.0		48.3, 67.3
Best overall angiomyolipoma response – %				
Response	41.8	0		58.0
Stable disease	40.5	79.5		30.4
Progression	1.3	5.1		0.9
Not evaluable	16.5	15.4		10.7

[1] According to independent central radiology review

[2] Angiomyolipoma responses were confirmed with a repeat scan. Response was defined as: ≥50% reduction in the sum of angiomyolipoma volume relative to baseline, plus absence of new angiomyolipoma ≥1.0 cm in longest diameter, plus no increase in renal volume >20% from nadir, plus absence of grade ≥2 angiomyolipoma-related bleeding.

[3] Primary analysis for double blind period

[4] Final analysis includes patients who crossed over from the placebo group; median duration of exposure to everolimus of 204.1 weeks

Consistent treatment effects on angiomyolipoma response rate were observed across all subgroups evaluated (i.e. enzyme-inducing antiepileptic use versus enzyme-inducing

antiepileptic non-use, sex, age and race) at the primary efficacy analysis.

In the final analysis, reduction in angiomyolipoma volume improved with longer term treatment with Votubia. At weeks 12, 96 and 192, ≥ 30% reductions in volume were observed in 75.0%, 80.6%, and 85.2% of the treated patients, respectively. Similarly, at the same timepoints, ≥50% reductions in volume were observed in 44.2%, 63.3%, and 68.9% of the treated patients, respectively.

Median time to angiomyolipoma progression was 11.4 months in the placebo arm and was not reached in the everolimus arm (HR 0.08; 95% CI: 0.02, 0.37; p<0.0001). Progressions were observed in 3.8% of patients in the everolimus arm compared with 20.5% in the placebo arm. Estimated progression-free rates at 6 months were 98.4% for the everolimus arm and 83.4% for the placebo arm. At the final analysis, median time to angiomyolipoma progression was not reached. Angiomyolipoma progressions were observed in 14.3% of the patients. The estimated angiomyolipoma progression-free rates at 24 months and 48 months were 91.6% and 83.1%, respectively.

At the primary analysis, skin lesion response rates of 26.0% (95% CI: 16.6, 37.2) for the Votubia arm and 0% (95% CI: 0.0, 9.5) for the placebo arm were observed (p=0.0002). At the final analysis, the skin lesion response rate had increased to 68.2% (95% CI: 58.5, 76.9), with one patient reporting a confirmed complete clinical skin lesion response and no patients experiencing progressive disease as their best response.

In an exploratory analysis of patients with TSC with angiomyolipoma who also had SEGA, the SEGA response rate (proportion of patients with ≥50% reduction from baseline in target lesion volumes in the absence of progression) was 10.3% in the everolimus arm in the primary analysis (versus no responses reported in the 13 patients randomised to placebo with a SEGA lesion at baseline) and increased to 48.0% in the final analysis.

Post-hoc sub-group analysis of EXIST-2 (study CRAD001M2302) carried out at time of primary analysis demonstrated that angiomyolipoma response rate is reduced below the threshold of 5 ng/ml (Table 5).

Table 5 EXIST-2 - Angiomyolipoma response rates by time-averaged C_{min} category, at primary analysis

Time-averaged C_{min} category	Number of patients	Response rate	95% confidence interval
≤5 ng/ml	20	0.300	0.099, 0.501
>5 ng/ml	42	0.524	0.373, 0.675
Difference[1]		-0.224	-0.475, 0.027

[1] Difference is "≤5 ng/ml" minus ">5 ng/ml"

SEGA associated with TSC

Phase III study in SEGA patients

EXIST-1 (Study CRAD001M2301), a randomised, double-blind, multicentre phase III study of Votubia versus placebo, was conducted in patients with SEGA, irrespective of age. Patients were randomised in a 2:1 ratio to receive either Votubia or matching placebo. Presence of at least one SEGA lesion ≥1.0 cm in longest diameter using MRI (based on local radiology assessment) was required for entry. In addition, serial radiological evidence of SEGA growth, presence of a new SEGA

lesion ≥1 cm in longest diameter, or new or worsening hydrocephalus was required for entry.

The primary efficacy endpoint was SEGA response rate based on independent central radiology review. The analysis was stratified by use of enzyme-inducing antiepileptics at randomisation (yes/no).

Key secondary endpoints in hierarchal order of testing included the absolute change in frequency of total seizure events per 24-hour EEG from baseline to week 24, time to SEGA progression, and skin lesion response rate.

A total of 117 patients were randomised, 78 to Votubia and 39 to placebo. The two treatment arms were generally well balanced with respect to demographic and baseline disease characteristics and history of prior anti-SEGA therapies. In the total population, 57.3% of patients were male and 93.2% were Caucasian. The median age for the total population was 9.5 years (age range for the Votubia arm: 1.0 to 23.9; age range for the placebo arm: 0.8 to 26.6), 69.2% of the patients were aged 3 to <18 years and 17.1% were <3 years at enrolment.

Of the enrolled patients, 79.5% had bilateral SEGAs, 42.7% had ≥2 target SEGA lesions, 25.6% had inferior growth, 9.4% had evidence of deep parenchymal invasion, 6.8% had radiographic evidence of hydrocephalus, and 6.8% had undergone prior SEGA-related surgery. 94.0% had skin lesions at baseline and 37.6% had target renal angiomyolipoma lesions (at least one angiomyolipoma ≥1 cm in longest diameter).

The median duration of blinded study treatment was 9.6 months (range: 5.5 to 18.1) for patients receiving Votubia and 8.3 months (range: 3.2 to 18.3) for those receiving placebo.

Results showed that Votubia was superior to placebo for the primary endpoint of best overall SEGA response ($p<0.0001$). Response rates were 34.6% (95% CI: 24.2, 46.2) for the Votubia arm compared with 0% (95% CI: 0.0, 9.0) for the placebo arm (Table 6). In addition, all 8 patients on the Votubia arm who had radiographic evidence of hydrocephalus at baseline had a decrease in ventricular volume.

Patients initially treated with placebo were allowed to cross over to everolimus at the time of SEGA progression and upon recognition that treatment with everolimus was superior to treatment with placebo. All patients receiving at least one dose of everolimus were followed until medicinal product discontinuation or study completion. At the time of the final analysis, the median duration of exposure among all such patients was 204.9 weeks (range: 8.1 to 253.7). The best overall SEGA response rate had increased to 57.7% (95% CI: 47.9, 67.0) at the final analysis.

No patient required surgical intervention for SEGA during the entire course of the study.

Table 6EXIST-1 – SEGA response

	Primary analysis[3]			Final analysis[4]
	Votubia N=78	**Placebo N=39**	**p-value**	**Votubia N=111**
SEGA response rate[1,2] - (%)	34.6	0	<0.0001	57.7
95% CI	24.2, 46.2	0.0, 9.0		47.9, 67.0
Best overall SEGA response - (%)				
Response	34.6	0		57.7
Stable disease	62.8	92.3		39.6
Progression	0	7.7		0
Not evaluable	2.6	0		2.7

[1] according to independent central radiology review

[2] SEGA responses were confirmed with a repeat scan. Response was defined as: ≥50% reduction in the sum of SEGA volume relative to baseline, plus no unequivocal worsening of non-target SEGA lesions, plus absence of new SEGA ≥1 cm in longest diameter, plus no new or worsening hydrocephalus

[3] Primary analysis for double blind period

[4] Final analysis includes patients who crossed over from the placebo group; median duration of exposure to everolimus of 204.9 weeks

Consistent treatment effects were observed across all subgroups evaluated (i.e. enzyme-inducing antiepileptic use versus enzyme-inducing antiepileptic non-use, sex and age) at the primary analysis.

During the double-blind period, reduction of SEGA volume was evident within the initial 12 weeks of Votubia treatment: 29.7% (22/74) of patients had ≥50% reductions in volume and 73.0% (54/74) had ≥30% reductions in volume. Sustained reductions were evident at week 24, 41.9% (31/74) of patients had ≥50% reductions and 78.4% (58/74) of patients had ≥30% reductions in SEGA volume.

In the everolimus treated population (N=111) of the study, including patients who crossed over from the placebo group, tumour response, starting as early as after 12 weeks on everolimus, was sustained at later time points. The proportion of patients achieving at least 50% reductions in SEGA volume was 45.9% (45/98) and 62.1% (41/66) at weeks 96 and 192 after start of everolimus treatment. Similarly, the proportion of patients achieving at least 30% reductions in SEGA volume was 71.4% (70/98) and 77.3% (51/66) at weeks 96 and 192 after start of everolimus treatment.

Analysis of the first key secondary endpoint, change in seizure frequency, was inconclusive; thus, despite the fact that positive results were observed for the two subsequent secondary endpoints (time to SEGA progression and skin lesion response rate), they could not be declared formally statistically significant.

Median time to SEGA progression based on central radiology review was not reached in either treatment arm. Progressions were only observed in the placebo arm (15.4%; p=0.0002). Estimated progression-free rates at 6 months were 100% for the Votubia arm and 85.7% for the placebo arm. The long-term follow-up of patients randomised to everolimus and patients randomised to placebo who thereafter crossed over to everolimus demonstrated durable responses.

At the time of the primary analysis, Votubia demonstrated clinically meaningful improvements in skin lesion response (p=0.0004), with response rates of 41.7% (95% CI: 30.2, 53.9) for the Votubia arm and 10.5% (95% CI: 2.9, 24.8) for the placebo

arm. At the final analysis, the skin lesion response rate increased to 58.1% (95% CI: 48.1, 67.7).

Phase II study in patients with SEGA
A prospective, open-label, single-arm phase II study (Study CRAD001C2485) was conducted to evaluate the safety and efficacy of Votubia in patients with SEGA. Radiological evidence of serial SEGA growth was required for entry.

Change in SEGA volume during the core 6-month treatment phase, as assessed via an independent central radiology review, was the primary efficacy endpoint. After the core treatment phase, patients could be enrolled into an extension phase where SEGA volume was assessed every 6 months.

In total, 28 patients received treatment with Votubia; median age was 11 years (range 3 to 34), 61% male, 86% Caucasian. Thirteen patients (46%) had a secondary smaller SEGA, including 12 in the contralateral ventricle.

Primary SEGA volume was reduced at month 6 compared to baseline ($p<0.001$ [see Table 7]). No patient developed new lesions, worsening hydrocephalus or increased intracranial pressure, and none required surgical resection or other therapy for SEGA.

Table 7 Change in primary SEGA volume over time

SEGA volume (cm^3)	**Independent central review**						
	Baseline n=28	**Month 6 n=27**	**Month 12 n=26**	**Month 24 n=24**	**Month 36 n=23**	**Month 48 n=24**	**Month 60 n=23**
Primary tumour volume							
Mean (standard deviation)	2.45 (2.813)	1.33 (1.497)	1.26 (1.526)	1.19 (1.042)	1.26 (1.298)	1.16 (0.961)	1.24 (0.959)
Median	1.74	0.93	0.84	0.94	1.12	1.02	1.17
Range	0.49 - 14.23	0.31 - 7.98	0.29 - 8.18	0.20 - 4.63	0.22 - 6.52	0.18 - 4.19	0.21 - 4.39
Reduction from baseline							
Mean (standard deviation)		1.19 (1.433)	1.07 (1.276)	1.25 (1.994)	1.41 (1.814)	1.43 (2.267)	1.44 (2.230)
Median		0.83	0.85	0.71	0.71	0.83	0.50
Range		0.06 - 6.25	0.02 - 6.05	-0.55 - 9.60	0.15 - 7.71	0.00 - 10.96	-0.74 - 9.84
Percentage reduction from baseline, n (%)							
≥50%		9 (33.3)	9 (34.6)	12 (50.0)	10 (43.5)	14 (58.3)	12 (52.2)
≥30%		21 (77.8)	20 (76.9)	19 (79.2)	18 (78.3)	19 (79.2)	14 (60.9)
>0%		27 (100.0)	26 (100.0)	23 (95.8)	23 (100.0)	23 (95.8)	21 (91.3)
No change		0	0	0	0	1 (4.2)	0
Increase		0	0	1 (4.2)	0	0	2 (8.7)

The robustness and consistency of the primary analysis were supported by the:
- change in primary SEGA volume as per local investigator assessment ($p<0.001$), with

75.0% and 39.3% of patients experiencing reductions of ≥30% and ≥50%, respectively
- change in total SEGA volume as per independent central review ($p<0.001$) or local investigator assessment ($p<0.001$).

One patient met the pre-specified criteria for treatment success (>75% reduction in SEGA volume) and was temporarily taken off trial therapy; however, SEGA re-growth was evident at the next assessment at 4.5 months and treatment was restarted.

Long-term follow-up to a median duration of 67.8 months (range: 4.7 to 83.2) demonstrated sustained efficacy.

Other studies
Stomatitis is the most commonly reported adverse reaction in patients treated with Votubia (see sections 4.4 and 4.8). In a post-marketing single-arm study in postmenopausal women with advanced breast cancer (N=92), topical treatment with dexamethasone 0.5 mg/5 ml alcohol-free oral solution was administered as a mouthwash (4 times daily for the initial 8 weeks of treatment) to patients at the time of initiating treatment with Afinitor (everolimus, 10 mg/day) plus exemestane (25 mg/day) to reduce the incidence and severity of stomatitis. The incidence of Grade ≥2 stomatitis at 8 weeks was 2.4% (n=2/85 evaluable patients) which was lower than historically reported. The incidence of Grade 1 stomatitis was 18.8% (n=16/85) and no cases of Grade 3 or 4 stomatitis were reported. The overall safety profile in this study was consistent with that established for everolimus in the oncology and TSC settings, with the exception of a slightly increased frequency of oral candidiasis which was reported in 2.2% (n=2/92) of patients.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Votubia in all subsets of the paediatric population in angiomyolipoma (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Votubia in one or more subsets of the paediatric population in refractory epilepsy associated with TSC (see section 4.2 for information on paediatric use).

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. $AUC_{0\text{-}inf}$) 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 SEGA, everolimus C_{min} was approximately dose-proportional within the dose range from 1.35 mg/m^2 to 14.4 mg/m^2.

In patients with SEGA, the geometric mean C_{min} values normalised to mg/m^2 dose in patients aged <10 years and 10-18 years were lower by 54% and 40%, respectively, than those observed in adults (>18 years of age), suggesting that everolimus clearance was higher in younger patients. Limited data in patients <3 years of age (n=13) indicate that BSA-normalised clearance is about two-fold higher in patients with low BSA (BSA of 0.556 m^2) than in adults. Therefore it is assumed that steady-state could be reached earlier in patients <3 years of age (see section 4.2 for dosing recommendations).

The pharmacokinetics of everolimus have not been studied in patients younger than 1 year of age. It is reported, however, that CYP3A4 activity is reduced at birth and increases during the first year of life, which could affect the clearance in this patient population.

A population pharmacokinetic analysis including 111 patients with SEGA who ranged from 1.0 to 27.4 years (including 18 patients 1 to less than 3 years of age with BSA 0.42 m^2 to 0.74 m^2) showed that BSA-normalised clearance is in general higher in younger patients. Population pharmacokinetic model simulations showed that a starting dose of 7 mg/m^2 would be necessary to attain C_{min} within the 5 to 15 ng/ml range in patients younger than 3 years of age. A higher starting dose of 7 mg/m^2 is therefore recommended for patients 1 to less than 3 years of age with SEGA (see section 4.2).

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 BSA) was higher in younger patients.

In patients with TSC and refractory seizures Votubia concentrations were investigated in 9 patients in the age between 1 and<2 years. Doses of 6 mg/m2 (absolute doses range 1-5 mg) were administered and resulted in minimal concentrations between 2 and 10 ng/ml (median of 5 ng/ml; total of >50 measurements). No data are available in patients with TSC-seizures below the age of 1 year.

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 Normalised (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 ≥ 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

Butylated hydroxytoluene (E321)
Magnesium stearate
Lactose monohydrate
Hypromellose
Crospovidone type A
Mannitol
Cellulose microcrystalline
Silica colloidal anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

The stability of the ready to use suspension has been demonstrated for 30 minutes when using an oral syringe or 60 minutes when using a small glass. The suspension must be administered immediately after preparation. If not administered within 30 minutes of preparation when using an oral syringe or 60 minutes when using a small glass, the suspension must be discarded and a new suspension must be prepared.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

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

Packs containing 30 x 1 dispersible tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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 MARKETING AUTHORISATION HOLDER

Novartis Pharmaceuticals UK Limited,

2nd Floor, The WestWorks Building, White City Place,

195 Wood Lane,

London,

W12 7FQ

United Kingdom

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10 DATE OF REVISION OF THE TEXT

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