The European Society for Paediatric Oncology (SIOP Europe)

Clos Chapelle-aux-Champs 30, Bte 1.30.30, B-1200
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Application for the Inclusion of Everolimus on the WHO Essential Medicines List for Children (EMLc) 2021

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1. Summary statement of the proposal for inclusion of Everolimus

Everolimus is indicated in patients ≥3 year of age, diagnosed with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC) who need therapeutic intervention but are not eligible for surgery. TSC is a genetic disorder, inherited autosomal dominant and characterized by the development of hamartomas in different organs. SEGA are non-infiltrative, slow-growing tumours, classified under low grade glioma (LGG) and correspond to grade I brain lesions by the World Health Organization. The TuberOus SClerosis (TOSCA) registry provided epidemiological data on SEGA in patients with TSC. Between 2012 and 2016 the registry enrolled 2,216 TSC patients from 170 sites across 31 countries. SEGA were reported in 25% (n=554) of these patients. The median age at SEGA diagnosis was 8 years (range <1-51) with 26.6% diagnosed before the age of 2 years, 81.9% before the age of 18 years and only 18.1% diagnosed after the age of 18 years (1). The typical location of SEGA is near the ventricles (subependymal) and the foramen of Monroi. This location near the foramen of Monro and their tendency to grow can lead to obstructive hydrocephalus with consecutive substantial morbidity and mortality. In the TOSCA registry 42.1% of SEGA patients were symptomatic, showing signs of increased intracranial pressure, increased seizure frequency, behavioral disturbances, and regression/loss of cognitive skills (1). At this point it is also important to mention, that not all patients with SEGA need treatment at initial diagnosis. Depending on the initial size of the SEGA, follow-up imaging are performed and treatment is initiated in case of tumour growth with the risk to develop hydrocephalus or other secondary complications.

TSC is caused by a mutation in the TSC1 and/or TSC2 gene. These genes are normally involved in the regulation of cell growth and division by controlling the activity of a protein called “mammalian

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target of rapamycin" (mTOR). Mutations in the TSC1 and/or TSC2 gen lead to an activation of the mammalian target of rapamycin complex 1 (mTORC1), resulting in an uncontrolled cell growth. Everoliums directly inhibits the mTOR pathway and acts as targeted drug (2, 3). As a consequence the uncontrolled division of cells harboring the TSC mutation becomes inhibited and the number or size of tumors reduces. The alternative treatment options to Everolimus are surgery and the symptomatic treatment of secondary complications, such as ventriculo-peritoneal shunts. Due to the location of the SEGA, surgery is not always feasible, may results in partial resection of the tumor needing second surgery, or may still require additional treatment, such as ventriculo-pertitoneal shunt (4, 5). Therefore, Everolimus is a very important alternative if surgery is not feasible, due to various reasons.

In summary, the target population of Everolimus are patients ≥3 year of age with a SEGA associated to TSC. Everolimus directly targets and inhibits the mTORC1 protein complex, which leads to a reduction in number and size of SEGA and is therefore an essential non-invasive treatment option. This applications intends to add Everolimus to the complementary cEML.

2. Relevant WHO technical department and focal point

This application has been pre-discussed with Bernadette Cappello, Lorenzo Moja, Albert Figueras, Elizabeth de Vries and Andrea Bondi and was additionally reviewed by Bernadette Cappello.

3. Name of the organisation(s) consulted and/or supporting the project

European Society for Paediatric Oncology (SIOPE)

SIOPE Brain Tumor Group (SIOPE BTG)

4. International Nonproprietary Name (INN)

INN: Everolimus

ATC: L01EG02

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5. Dose form(s) and strength(s) proposed for inclusion

Everolimus is available as a generic compound from multiple companies. It is available in two formulations, as tablets and as dissolvable tablets. The second formulation allows dissolving in water and thus the easy administration to infants, children or other patients with difficulties swallowing tables. The available doses of dissolvable tablets cover the doses needed in the treatment of infants and children.

- Votubia: 2.5mg, 5mg, and 10mg tablets
- Votubia Disp Tabl: 2mg and 3mg
- Afinitor: 2.5mg, 5mg, 7.5mg, and 10mg tablets
- Afinitor Disperz: 2mg, 3mg, and 5mg tablets

6. Whether listing is requested as an individual medicine or as representative of a pharmaceutical class

Everolimus is requested to be listed as an individual medicine

7. Treatment details (requirements for diagnosis, treatment and monitoring)

SEGAs are diagnosed by magnet resonance imaging (MRI). On imaging, they are classically located subependymal and periventricular with protrusion into the ventricles and near the foramen of Monroi. The MRI signal is heterogeneous with marked contrast enhancement and calcified components can appear hypointense. For the diagnosis of SEGAs clinics have to be able to perform MRI and neuroradiologists trained in pediatric neuroradiology are required. If SEGA are detected on imaging, genetic counseling of the patient and family is needed, if this has not taken place already.

Indication to start treatment:

Everolimus is indicated in the treatment of SEGAs that require therapeutic intervention but for which surgery is not appropriate.

Dosing:

After a defined starting dose, Everolimus has subsequently to be adjusted individually to attain a blood concentration of 5-15ng/ml. Younger age at treatment (<6 years) and concomitant treatment with drugs that induce CYP3A4 require higher starting doses.

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Table 1: Starting dose of Everolimus for different clinical situations *(information from FDA (6))*

Indication	**Starting dose**
TSC-associated SEGA	4.5mg/m^2 orally once daily
TSC-associated partial-onset seizure	5mg/m^2 orally once daily
TSC with refractory epilepsy and no CYP3A4/PgP inductor and age <6 years	6mg/m^2 orally once daily
TSC with refractory epilepsy and no CYP3A4/PgP inductor and age ≥6 years	5mg/m^2 orally once daily
TSC with refractory epilepsy and CYP3A4/PgP inductor and age <6 years	9mg/m^2 orally once daily
TSC with refractory epilepsy and CYP3A4/PgP inductor and age ≥6 years	8mg/m^2 orally once daily

Therapeutic Drug Monitoring and Dose Titration for Everolimus:

- Monitor Everolimus whole blood trough concentrations (**Table 2**: recommended time points)
- Titrate the dose to attain trough concentrations of 5 ng/mL to 15 ng/mL
- Dose adjustment in case of too low or high concentration should use the following equation:

  New dose* = current dose x (target concentration divided by current concentration)

  *Recommendations for dose increase vary: 1) increase dissolvable tablets for 2mg every two weeks or 2.5mg for tables; 2) the maximum dose increment at any titration must not exceed 5 mg.

  - Increase dose if concentration <3mg/ml or 5ng/ml respectively
  - Keep the dose if concentration 10-15ng/ml and tolerated by the patients
  - Reduce if concentration >15ng/ml
- Use the same assay and laboratory for therapeutic drug monitoring throughout treatment, is possible.
- Tablets and dissolvable tablets should not be combined to reach the dose needed

In addition, to drug modifications based on drug monitoring or adverse events, treatment of SEGA is also guided by follow-up MRI and response to treatment.

Table 2: Recommended time points to monitor Everolimus whole blood trough concentrations *(Information from FDA (6))*

Event	**Time point of monitoring**
Initiation of Everolimus	1-2 weeks
Modification of Everolimus	1-2 weeks
Switch between tablet and dissolvable tablets	1-2 weeks
Initiation or discontinuation of P-gp and moderate CYP3A inhibitor	2 weeks
Initiation or discontinuation of P-gp and strong CYP3A inducer	2 weeks
Change in hepatic function	2 weeks
Stable dose with changing body surface area	Every 3-6 months
Stable dose with stable body surface area	Every 6-12 months

8. Information supporting the public health relevance

Tuberous sclerosis complex (TSC) is an autosomal dominant inherited neurocutaneous disorder characterized by multisystem hamartomas, associated with neuropsychiatric features. With a prevalence of approximately 1/6'000, TSC belongs to orphan diseases with nearly 1 million people are affected worldwide (7, 8). Brain involvement is very frequent with cortico-/subcortical tubers, subependymal nodules, and SEGAs. In the TOSCA registry, SEGAs were reported in 25% of TSC patients. The median age at SEGA diagnosis was 8 years (range <1-51) with 26.6 diagnosed before the age of 2 years, 81.9% before the age of 18 years and only 18.1% diagnosed after the age of 18 years (1). Additional clinical features of TSC include skin involvement (hypomelanotic macules, angiofibromas, ungual fibromas), early-onset epilepsy, neuropsychiatric features (intellectual disability, attention-deficit/hyperactivity disorder, autism spectrum disorders), renal angiomyolipomas, lymphangioleiomyomatosis (LAM), multifocal micronodular pneumocyte hyperplasia (MMPH) and pulmonary cysts, cardiac rhabdomyomas, dental enamel pitting, intraoral fibromas and skeletal dysplasia.

SEGAs are slow-growing glioneuronal tumors, they belong to the low grade glioma, and are graded according to WHO as Grade I tumors. They typically arise near the foramen of Monroi and represent a significant medical risk for these patients. The proximity of SEGA to the foramen of Monroi can lead to obstructive hydrocephalus with consecutive substantial morbidity, including increased

intracranial pressure, new neurological deficits or deterioration of seizure control. In a systematic review, seven studies reported cause of mortality in patients with TSC and included 3376 patients (9). A total of 294 patients died with a mean mortality over all studies of 8.7%. Of these 294 patients, 11 (3.7%) died directly due to a structural brain manifestation of TSC. It was not reported how many patients have been diagnosed with a SEGA and how many death due to structural brain manifestations have been SEGA-related.

Surgery was the only treatment option of SEGA for many years. Depending on the location, not all SEGA can be removed (e.g. in the region of the hypothalamus or pineal gland, parenchymal invasion) or some can be removed only partially and subsequent surgeries are needed in case of tumor regrowth. Even when surgery is successful, it always bears the risk of peri- and postoperative complications such as meningitis, hematoma and subsequent infection, or cerebrospinal fluid leakage. If macroscopically complete resection can be achieved, the surgery can be considered curative in most cases.

Everolimus is a selective mTOR inhibitor and targets directly the protein complex (mTORC1), which is de-regulated due to the underlying mutation in TSC1 or TSC2 gen. Several studies could confirm that the administration of Everolimus caused a relevant reduction in number and size of SEGA in children and adults without unexpected and unmanageable acute toxicities (summaries for studies in section 9 and 10). Therefore, Everolimus has a high impact and is the only treatment option for children and adults diagnosed with SEGA which cannot be treated with surgery only.

Beside the indication of SEGA, Everolimus is approved in the treatment of the following diseases in adults and TSC_associated Partial_onset Seizure also in children:

- Hormone Receptor-Positive, HER2-Negative Breast Cancer
- Neuroendocrine Tumors (NET)
- Renal Cell Carcinoma (RCC)
- TSC-associated Renal Angiomyolipoma
- TSC-asociated Partial-Onset Seizure

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At this point, it is important to highlight that TSC, as the underlying condition of SEGA, is a chronic and life-long condition. Also SEGA behave as a chronic disease, which is a characteristic of most low grade glioma. If a SEGA can completely be removed surgically, there is a low risk of regrowth at the same site. However, since the underlying disease remains, many more SEGAs may develop at other sites.

9. Review of benefits, harms and toxicity of treatment with Everolimus

Everolimus was first approved in 2009 for treatment of advanced kidney cancer. Later it has been approved for treatment in a variety of cancers, including subependymal giant cell astrocytoma (SEGA) in tuberous sclerosis complex disease. In 2007 and forward, Krueger et al ran a phase I/II study to assess the effect of everolimus in 28 patients older than 3 years (median 11 years, range 3-34 years) with progression of SEGA between two MRI (10). At months 6 after start of treatment, they saw a ≥30% volume decrease of SEGAs in 21 patients and 9 had a reduction of ≥50%. Robustness and consistency of this finding was supported by the fact, that the change in SEGA volume was significant when assessed by the local investigator ($p<0.001$) and the independent central reviewer ($p<0.001$). Everolimus also reduced clinical and subclinical seizure frequency (median change, -1 seizure, $p=0.02$). In 9 of 16 children seizure frequency decreased, 6 had no change and in 1 it increased. The extension study by Franz et al showed that 79% (22/28) of initially enrolled patients finished the study. At month 60 of treatment 12 patients (52%) experienced a volume reduction of ≥50% and 14 (61%) of ≥30%. No patient discontinued treatment due to adverse events (11). Both studies have the inherent limitation of lacking the control arm.

Franz et al performed a multicenter, double blinded, placebo controlled, phase 3 study (EXIST-1 trial) including 78 patients age >3 years at diagnosis of a SEGA in the everolimus arm and 39 in the control arm (12). The median age at diagnosis in the everolimus arm was 9.5 years (range 1.0 – 23.9 years). After a median of 9.6 months of everolimus treatment 35% and 77% of patients experienced a >50% and 30% reduction in SEGA volume. At month 6, the progression-free rate was 100% for everolimus and 86% of placebo ($p=0.0002$) for the whole cohort (**Figure 1**).

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In the open-lable extension study included 111 patients who received at least one dose of everolimus (median age at diagnosis 9.5 years; range 1.1-27.4 years) (13). The median duration of everolimus exposure was 29 months (IQR 19-34 months) with a median follow-up of 28 months (IQR 19-33). Overall, 54 patients (49%, 95%CI 39.0-58.3) had a response of ≥ 50% or greater reduction in SEGA volume once during the study period. No patient had to undergo tumor surgery during the study period due to progression. Most frequent side effects were mouth ulceration (30%) and stomatitis (43%) of mild to moderate grade. This study supports the longer-term use of everolimus in patients with SEGA.

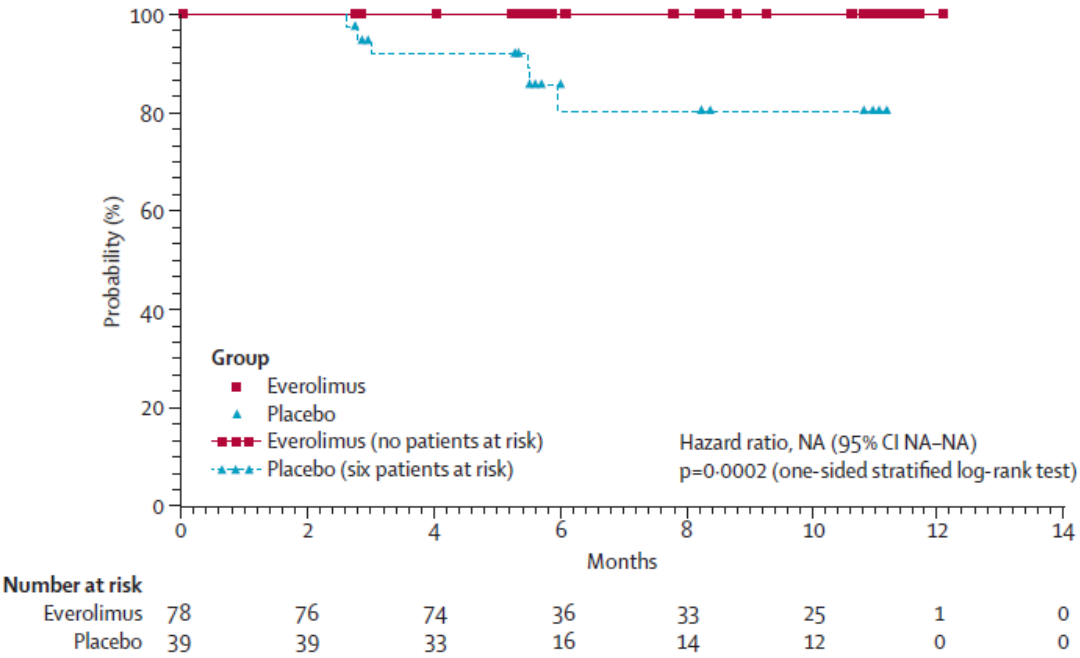

Figure 1: Kaplan-Meier curve of the estimated time to progression of SEGA, including children and adults, randomised to receive everolimus or placebo (12)

The final results from the EXIST-1 trial support the results from the first extension study and showed that 57.7% of patients reached at least once during the study period a SEGA volume reduction of ≥50% (14). No patient needed surgery. Additional clinical benefits observed in this study included a reduction in the volume of renal angiomyolipoma of ≥50% in 73.2% of patients (30/41) and a response of skin lesions in 58.1% of patients (n=105).

Kuki et al could show in a case series, that treatment with everolimus is even feasible in infants <12 month of age. All five infants achieved a reduction in the SEGA volume of ≥50% within 6 months with

the most rapid reduction in the first 3 months. The infants underwent treatment for average 27 month (range 4-55 months) and adverse events included infection, stomatitis and increase triglycerides.

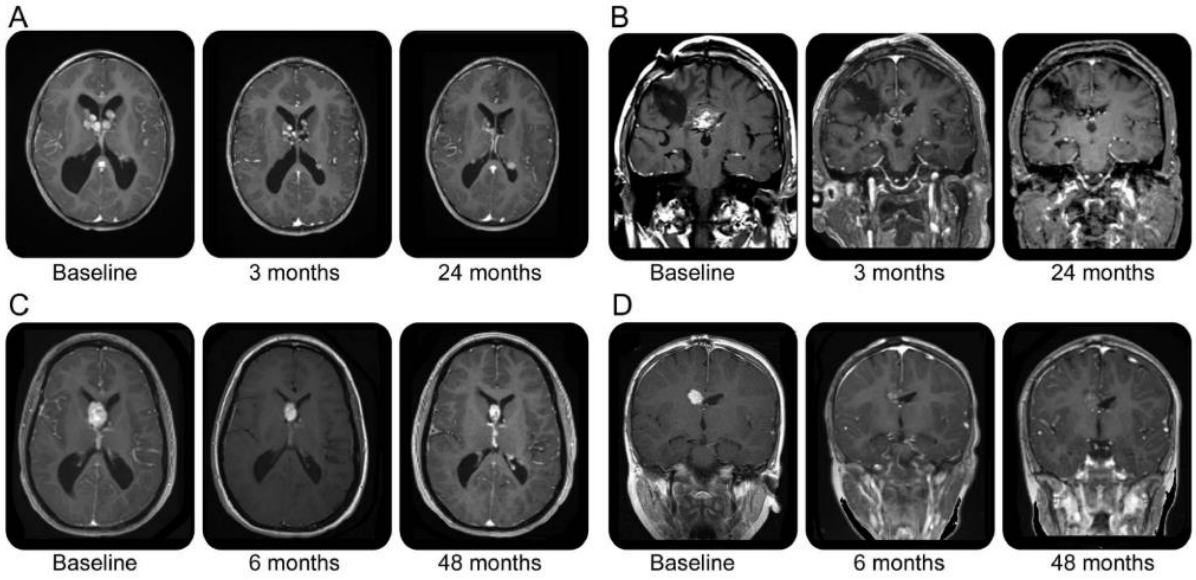

Figure 2: Illustration of effect of Everolimus on SEGA volume over time in four patients (2)

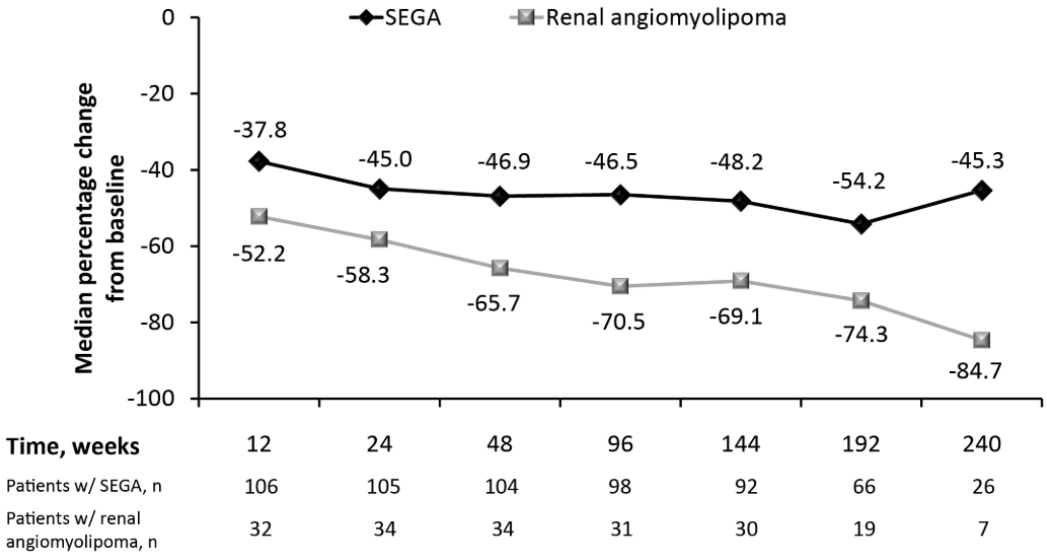

Figure 3: Median reduction of SEGA volume over time (includes also renal angiomyolipoma) (14)

For **safety**, we only report results from two studies with a long follow-up period (11, 14). In the EXIST-1 trial most patients needed at least one dose interruption or reduction (91%), where adverse events were the most frequent reason for dose interruption (72.1%). Discontinuation of Everolimus due to an

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adverse event occurred in 11 patients (9.9%). In the EXIST-1 trail one patient died (accidental asphyxiation) and was not suspected to be treatment related by the investigator. In the NCT00411619 study, all patients (n=28) needed at least one dose modification, including dose interruption, dose reduction and/or dose increase due to adverse events or because it was required by the protocol (blood concentration too low or high).

Regarding **toxicity**, the most frequently reported adverse events suspected as being drug-related in the open-label phase I/II by Krueger et al included stomatitis, upper respiratory tract infection, sinusitis, otitis media, pyrexia and acneiform dermatitis (Table xx) (2, 10). No drug-related grade 4 or 5 events or death were reported (10, 12).

In the final EXIST-1 analysis 99% experienced at least one adverse event during the whole study period, where more events occurred in the first years (97.3% in first 12 months, 85.7% in months 25-36; 49.1% if >48 months). Most patients (89.2%) experienced ≥1 event suspected to be related to Everolimus. The most common adverse events possibly be treatment-related were stomatitis (43.2%), mouth ulceration (32.4%), pneumonia (13.5%), blood cholesterol level increase (11.7%), hypercholesterolemia (11.7%), nasopharyngitis (10.8%), and pyrexia (10.8%). Grade 3 adverse events occurred in 36.0% of patients with stomatitis (10.8%), pneumonia (8.1%), and neutropenia (5.4%) being the most frequent. Grade 4 adverse events occurred in 5 patients: neutropenia (n=2), pneumonia, febrile infection, gastroenteritis, and pneumothorax (n=1 each).

In summary, all evidence for Everolimus in the treatment of SEGA is based on analysis of change in SEGA volume. Reductions in seizure frequency, volume of renal angiomyolipoma, and skin lesions seem to be an additional clinical benefit in patients treated with Everolimus (10-12, 14). No study compared surgical intervention only versus Everolimus treatment.

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Table 3: Adverse events reported in 28 patients enrolled in phase I/II study (10)

Event*	Adverse Event		Adverse Drug Reaction	
	Any	Grade 3 or 4	Any	Grade 3†
	number (percent)			
Any	28 (100)	11 (39)	28 (100)	5 (18)
Stomatitis	22 (79)	1 (4)	22 (79)	1 (4)
Upper respiratory tract infection	22 (79)	0	22 (79)	0
Sinusitis	11 (39)	1 (4)	11 (39)	1 (4)
Otitis media	10 (36)	0	10 (36)	0
Pyrexia	10 (36)	0	8 (29)	0
Convulsion	7 (25)	3 (11)	0	0
Acneiform dermatitis	7 (25)	0	7 (25)	0
Diarrhea	7 (25)	0	6 (21)	0
Vomiting	6 (21)	1 (4)	2 (7)	0
Cellulitis	6 (21)	0	6 (21)	0
Body tinea	5 (18)	0	4 (14)	0
Cough	5 (18)	0	3 (11)	0
Headache	5 (18)	0	1 (4)	0
Rash	5 (18)	0	1 (4)	0
Personality change	5 (18)	0	0	0
Dizziness	4 (14)	1 (4)	0	0
Gastroenteritis	4 (14)	0	4 (14)	0
Otitis externa	4 (14)	0	4 (14)	0
Skin infection	4 (14)	0	3 (11)	0
Allergic rhinitis	4 (14)	0	0	0
Contact dermatitis	4 (14)	0	0	0
Acne	3 (11)	0	3 (11)	0
Gastric infection	3 (11)	0	3 (11)	0
Dry skin	3 (11)	0	1 (4)	0
Constipation	3 (11)	0	0	0
Skin disorder	3 (11)	0	0	0
Laboratory abnormalities reported as adverse events				
Decreased white-cell count	3 (11)	1 (4)	3 (11)	1 (4)
Hypertriglyceridemia	3 (11)	0	3 (11)	0

* Each adverse event is listed as the preferred term of the *Medical Dictionary for Regulatory Activities* (MedDRA).
† No grade 4 adverse drug reactions were reported. Grade 3 adverse drug reactions not listed here include single cases of pneumonia, viral bronchitis, and tooth infection.

Table 4: Summary of studies providing evidence for Everolimus in the treatment of SEGA

Author, year	Journal	Patients	Study	Description of Compounds	Outcome / Benefit	Harms / Toxicity
Krueger, 2010	N Engl J Med	n=28 Patients ≥3 years of age with serial growth of SEGA (n=16 with seizures with 24-hour video EEG available)	Prospective, open-label, phase I/II (NCT00411619) 2007-2008	Experimental: Everolimus p.o. starting 3mg/m^2/day (titrated to target blood levels of 5–15ng/ml) Control: No	- Reduction in volume of SEGA between baseline and 6 months ≥30% in n=21 and ≥50% in n=9; reduction from baseline p<0.0001 - Seizure frequency decreased: median change -1 seizure, p=0.02; decrease in 9/16, not change in 6/16, increase 1/16 - Quality of life: QILCE score at baseline 57.8±14, after 6 months 62.1±14.2 - No surgical intervention needed - No development of new lesions	- Adverse drug reactions in 100% - No grade 4 or 5 adverse drug reaction - Stomatitis (83%), upper respiratory infections (79%), sinusitis (43%), otitis media (36%) (see Table xx)
Krueger, 2013	Neurology	n=28 patients Patients ≥3 years of age with serial growth of SEGA	Open-label extension of NCT00411619	Experimental: Everolimus p.o. starting 3mg/m^2/day (titrated to target blood levels of 5–15ng/ml) Median dose: 5.3mg/m^2/day Control: No	- Evaluation at months 18, 24, 30, and 36: ≥50% reduction between 41.2% and 55.6%; ≥30% reduction between additional 22.2% and 29.2% of patients - Tumor growth in one patient at months 18 and 24 and in 2 patients at months 30	- 100% reported ≥1 AE, mostly grade 1/2 in severity - no discontinuation due to AE - AEs: upper respiratory infections (85.7%), stomatitis (85.7%), sinusitis (46.4%), and otitis media (35.7%) - No drug-related grade 4 or 5 AE
Franz, 2015	Ann Neurol	n=28 Patients ≥3 years of age with definite diagnosis of TSC and increasing SEGA lesion (≥2 magnetic resonance imaging scans)	Prospective, open-lable, extension of study by Krueger at al 2010 2007-2014	Experimental: Everolimus p.o. starting 3mg/m^2/day (titrated to target blood levels of 5–15ng/ml) Control: No	- Reduction in volume of SEGA from baseline to month 60: ≥30% in n=14/23 and ≥50% in n=12/23 - 82.1% with SEGA reduction ≥50% at some time - 92.9% with SEGA reduction ≥30% at some time - No surgical intervention needed - Reduction in daily seizure frequency from 7/26 (27%) to 2/18 (11%)	Treatment related AEs mostly upper respiratory tract infection (93%) and stomatitis (89%)

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Franz, 2013	Lancet	n=78 everolimus n=30 placebo Definite diagnosis of TSC and min. 1 lesion with a diameter of ≥1cm, and either serial growth of a SEGA, a new lesion of ≥1cm, or new or worsening hydrocephalus	Double-blind, placebo-controlled phase 3 trial (NCT00789828) EXIST-1 trial 2009-2010	Experimental: Everolimus p.o. 4.5mg/m^2/day (titrated to target blood levels of 5–15ng/ml) Control: Placebo	SEGA volume reduction ≥50% - Everolimus: 35% - Control: 0% → difference 35% (95%CI 15-52, p<0.0001) Tumor response: - Everolimus: 35% - Control 0% → difference 36% (95%CI 17-53, p<0.0001) Change in seizure frequency at week 24: 0 in both groups	AEs mostly grade I and II, mouth ulcerations, stomatitis, convulsions, pyrexia
Franz, 2014	Lancet Oncol	n=111 with at least one dose of everolimus Median everolimus exposure 29,3 months (range 1,9−40,5) Median follow-up 28,3 months (range 1,9−38,8)	Prospective, open-label extension of EXIST-1 trial (NCT00789828) 2009-2013	Experimental: Everolimus p.o. 4.5mg/m^2/day (titrated to target blood levels of 5–15ng/ml) Control: No	- SEGA volume reduction ≥50% in 49% (95% CI 39·0–58·3) during the study period - Duration of response: 2,1 – 31,1 months - Reduction of SEGA volume ≥50% in 39/105 (37%) at 24 weeks, 48/104 (46%) at 48 weeks, 36/76 (47%) at 96 weeks, and 11/29 (38%) at 144 weeks - No surgical intervention needed	AEs mostly grade I or II, mostly stomatitis (43%) and mouth ulceration (30%)
Franz, 2016	PLoS One	n=111 with at least one dose of everolimus Median everolimus exposure 47.1 months	Prospective, open-label extension of EXIST-1 trial (NCT00789828) 2009-2014	Experimental: Everolimus p.o. 4.5mg/m^2/day (titrated to target blood levels of 5–15ng/ml) Control: No	- SEGA volume reduction ≥50% in 57.7% at any time (central review) - Median time to SEGA response: 5.32 months (95%CI 3.02-5.59) - n=13 with SEGA progression (5/13 had previous response) - 3-year progression free survival rate was 88.8% (95%CI 80.6-93.6) - no patient required surgery - n=41 with renal angiomyolipoma, 73.2% achieved response -n=105 with skin lesions at baseline, 58.1% achieved response	- Most frequent AEs: stomatitis (43.2%), mouth ulcerations (32.4%)

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Trelinska, 2016	Pediatr Blood Cancer	n=10 TSC-related SEGA, previously treated with everolimus in standard dose for min.12 months resulting in stabilisation or reduction of SEGA volume	Single-arm prospective trial 2013-2015	Experimental: Everolimus p.o., daily, starting dose 2.5mg if BSA ≤1.2m^2; 5mg if BSA 1.3-2.1 m^2; 7.5mg if BSA ≥2.2 m^2 (titrated to target blood levels of 5–15ng/ml) Control: No	Tumor volume (cm^3) - pretreatment: 2.12 (0.72–6.24) - day 0: 0.93 (0.28–2.27) - day 90: 1.00 (0.34–3.18) - day 180: 0.99 (0.44–3.30) - day 360: 0.96 (0.49–1.97) → no statistically significant differences (p=01785)	AEs in all patients, grade I&II, hypercholesterinemia (7/10), anemia (3/10), thrombocytopenia (3/10)

SEGA, subependymal giant-cell astrocytomas; EEG, electroencephalography; QOLCE, Quality-of-Life in Childhood Epilepsy, TSC, tuberous sclerosis complex; AE, adverse event; BSA, body surface area

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10. Summary of available data on comparative cost-effectiveness of the medicine

The only comparator to the treatment of SEGA with Everolimus would be surgery, but no study compared these two treatment methods. The results provided by Krueger at al and Franz et al provide evidence of **efficacy** of Everolimus against SEGA lesions. In the open-label phase I/II, the main effect observed was the shrinkage of primary SEGA volume at month 6. Most patients showed a response, although there was variation between patients which depended on absolute SEGA volume at baseline (10). At month 60 in the extension study, 52% (n=12) experienced a SEGA volume reduction of ≥50% and an additional 8.7% (n=2) a reduction of ≥30% (11). In addition, no patient needed surgery during the study period.

Providing the costs for the treatment of SEGA with Everolimus is difficult, as prizes vary from country to country. The following sections summarizes the costs for a 10 year old child treated in the Netherlands.

Votubia Tablets	2.5mg	5mg	10mg
Costs 30 tablets	€ 1443.93	€ 2536.36	€ 3539.39
Votubia Disp. Tablets	2mg	3mg	5 mg
Costs 30 tablets	-	€ 1726.32	€ 2877.21

Considering the average body surface area (BSA) values for children of various ages, men, and women (**Table 5**), a child of 10 years would be treated with 5mg per day. This corresponds to an annual cost for the tablets of € 30'436 or € 34'526 CHF in case of dispersible tables.

Table 5: Average body surface area (BSA)

Neonate		0.25 m^2
Child	2 years	0.5 m^2
	9 years	1.07 m^2
	10 years	1.14 m^2
	12-13 years	1.33 m^2
Women		1.6 m^2
Men		1.9 m^2

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11. Summary of regulatory status and market availability of the medicine

- US Food and Drug Administration (FDA):
    - Approved on 30.03.2009 for renal cell carcinoma (first approval for Everolimus)
    - Approved on 29.10.2010 for SEGA, including children
- European Medicines Agency (EMA):
    - Approved as orphan medicinal product on 04.08.2010 (EU/3/10/764)
    - Marketing authorization of Votubia on 02.09.2011 (EMEA/H/C/002311)
    - Recommendation for maintenance of orphan designation at the time of marketing authorisation on 03.10.2011 (EMA/COMP/518763/2011)
- Health Canada
    - Authorized on 14.12.2009 for metastatic renal cell carcinoma

12. Availability of pharmacopoeial standards

- The British Pharmacopoeia: no
- The International Pharmacopoeia: no
- The United States Pharmacopoeia: yes
- The European Pharmacopoeia: yes

13. Summary and conclusion on Everolimus to treat children and adolescent with SEGA

According to the SIOPE Essential Medicines working group Everolimus is essential in the treatment of SEGA in children and adolescents with TSC. This compound is currently not on the WHO EMLc but approved by major regulatory agencies for patients with TCS ≥3 years of age. In addition, literature supports it benefit and effectiveness, which outweigh the mild and reversible side effects.

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