

		EMLc	ATC codes: L01EG02
Indication	Other specified gliomas of brain	ICD11 code: 2A00.0Y	
INN	Everolimus		
Medicine type	Chemical agent		
List type	Complementary		
Formulations	Oral > Solid: 2.5 mg ; 5 mg ; 7.5 mg ; 10 mg ; 2 mg tablet (dispersible) ; 3 mg tablet (dispersible) ; 5 mg tablet (dispersible)		
EML status history	First added in 2021 (TRS 1035)		
Sex	All		
Age	Also recommended for children		
Therapeutic alternatives	The recommendation is for this specific medicine		
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit <a href="http://www.MedsPal.org">www.MedsPal.org</a>  Read more <a href="#">about patents.</a> 		
Tags	<span>Cancer</span>		
Wikipedia	<a href="#">Everolimus</a> 		
DrugBank	<a href="#">Everolimus</a> 		

### Expert Committee recommendation

The Expert Committee noted that subependymal giant cell astrocytoma (SEGA) is a rare disease affecting almost exclusively children with tuberous sclerosis complex and is associated with considerable neurological morbidity and mortality. The Committee also noted that diagnosis of SEGA requires specialist paediatric neuroradiology expertise and the availability of facilities for magnetic resonance imaging, as well as multispecialty teams including oncologists and specialists in the treatment of epilepsy, which may be limited or unavailable in some settings. SEGA management historically had few options other than surgery, as radiotherapy and chemotherapy were not effective. The Committee noted that everolimus is associated with reductions in SEGA volume and clinical and subclinical seizure frequency. Evidence of efficacy and safety is limited as the condition is rare. No studies have been done comparing everolimus with surgery, nor and there any substantive studies that report on quality of life with everolimus treatment. Regular monitoring of everolimus treatment for adverse events and toxicity is required, leading to frequent dose adjustments. In addition, the need for and high cost of frequent high-level care during treatment may make this treatment inaccessible to many low- and middle-income countries. The Committee noted that everolimus is mainly used in patients with tuberous sclerosis complex, who are not candidates for surgery because of the location of tumours or because the disease has progressed after SEGA resection. However, everolimus has replaced surgery as first choice in several settings. The Expert Committee acknowledged that the Cancer Working Group supported the inclusion of everolimus on the EMLc to treat SEGA in children, although the treatment requires specialist diagnosis. Based on the available evidence, the Committee considered everolimus to have a favourable benefit-to-harm ratio, especially in patients who are not eligible for surgery or when surgery cannot remove the whole tumour. The Expert Committee therefore recommended the inclusion of everolimus on the complementary list of the EMLc for the treatment of SEGA in children with tuberous sclerosis complex. Recognizing that SEGA is a

life-long condition, the Committee also recommended inclusion of everolimus on the EML for patients older than 12 years. The Expert Committee did not endorse the use of everolimus for indications other than SEGA for which the evidence has not been reviewed. The Committee noted that the inclusion of everolimus on the Model Lists supports the WHO Global Initiative for Childhood Cancer that seeks to improve childhood cancer patient survival to up to 60% by 2030 with access to essential medicines as a main part of the initiative. The Committee advised the Strategic Advisory Group of Experts on In Vitro Diagnostics that everolimus should be considered as a moderate priority candidate for which therapeutic drug monitoring assays should be evaluated for inclusion on the WHO Model List of Essential In Vitro Diagnostics.

## Background

Everolimus has not previously been considered for inclusion on the EMLc. Tuberous sclerosis complex is an autosomal dominant genetic disorder characterized by the development of hamartomas (slow-growing, benign tumours) in different organs. SEGA is a non-infiltrative, slow-growing tumour of the central nervous system occurring predominantly in patients with tuberous sclerosis complex. It is classified as a low-grade glioma corresponding to grade I brain lesions according to the WHO classification of tumours of the central nervous system (1). The typical location of SEGA near the ventricles (subependymal) and the foramen of Monro (the conduit between the lateral ventricles and the third ventricle) and their tendency to grow can lead to obstructive hydrocephalus with substantial morbidity and mortality, including increased intracranial pressure, neurological deficits or deterioration in seizure control. Tuberous sclerosis complex is caused by a mutation in the TSC1 and/or TSC2 gene. These genes are normally involved in regulating cell growth and division by controlling the activity of the mammalian target of rapamycin (mTOR) protein. Mutations in the TSC1 and/or TSC2 gene lead to an activation of the mTOR complex 1 (mTORC1), resulting in uncontrolled cell growth. Everolimus directly inhibits the mTOR pathway (2,3) and thus the uncontrolled division of cells harbouring the tuberous sclerosis complex mutation, leading to a reduction in the size of the tumour. The alternative treatment options to everolimus are surgery and the symptomatic treatment of secondary complications, such as ventriculoperitoneal shunts (4,5).

## Public health relevance

Tuberous sclerosis complex is an autosomal dominant, genetic neurocutaneous disorder characterized by multisystem hamartomas, associated with neuropsychiatric features. With a prevalence of about one in 6000 newborns, tuberous sclerosis complex is a rare disease; nevertheless, nearly 1 million people are affected worldwide (6,7). The Tuberous Sclerosis (TOSCA) registry provides epidemiological data on SEGA in patients with tuberous sclerosis complex. In the TOSCA registry, SEGAs are reported in 25% of patients with tuberous sclerosis complex. The median age at diagnosis of SEGA is 8 years (range < 1–51 years), with 27% diagnosed before the age of 2 years and 82% before 18 years (8). Tuberous sclerosis complex, as the underlying condition of SEGA, is a life-long condition.

## Benefits

A 2007 phase I/II study assessed the effect of everolimus in 28 participants older than 3 years (median 11 years, range 3–34 years) with SEGA progression between two MRI scans (9). At month 6 after the start of treatment, a  $\geq 30\%$  volume decrease of SEGAs was observed in 21 participants (nine had a reduction of  $\geq 50\%$ ). The robustness and consistency of this finding were supported by the fact that the change in SEGA volume was significant when assessed by the local investigator and an independent central outcome reviewer. Everolimus also reduced clinical and subclinical seizure frequency (median change,  $-1$  seizure,  $P = 0.02$ ). In nine of 16 children, seizure frequency decreased, six had no change and seizure frequency increased in one child. An extension of this study showed that at month 60 after the start of treatment, 12/23 participants (52%) experienced a volume reduction of  $\geq 50\%$  and 14/23 (61%) of  $\geq 30\%$  (10). Both studies have the inherent limitations of including only the small number of participants and the lack of a control arm. However, the biological rationale that supports use of everolimus is strong and, for this brain tumour, volume reduction and seizure frequency can be considered clinically relevant outcomes. The EXIST-1 trial was a multicentre, double-blinded, randomized (2:1), placebo-controlled, phase III study that evaluated the efficacy and safety of everolimus in 117 participants aged > 3 years at diagnosis of a SEGA (11). After a median of 9.6 months of everolimus treatment, 35% and 77% of participants experienced a > 50% and > 30% reduction in SEGA volume, respectively. At month 6, the progression-free rate was 100% for everolimus and 86% for placebo ( $P < 0.001$ ). An open-label extension study of EXIST-1 included 111 participants who received at least one dose of everolimus (median age at diagnosis 9.5 years; range 1.1–27.4 years) (12). Overall, 54 participants (49%, 95% confidence interval (CI) 39.0% to 58.3%) had a response of  $\geq 50\%$  or greater reduction in SEGA volume at least once

during the study period. The final results from the EXIST-1 trial showed that 57.7% of participants reached a SEGA volume reduction of  $\geq 50\%$  at least once during the study period (13). No participants needed surgery. Additional clinical benefits observed in this study included a reduction in the volume of renal angiomyolipoma of  $\geq 50\%$  in 73.2% of participants and 58.1% of participants had an improvement in skin lesions. A case series in five infants younger than 12 months showed that treatment with everolimus was feasible in children during the first year of life. All five infants had a reduction in the SEGA volume of  $\geq 50\%$  within 6 months, with the most rapid reduction in the first 3 months (14). In summary, reasonable evidence exists that everolimus treatment reduces SEGA volume. The effect on lesions at other sites (kidney, skin) and on seizure frequency is less clear, although a reduction in all these outcomes have been reported (9–11,13).

## Harms

The most frequent adverse events of everolimus reported in the EXIST-1 trial were mouth ulceration (30%) and stomatitis (43%) of mild to moderate grade (12). Participants included in the open-label phase I/II study also showed upper respiratory tract infection, sinusitis, otitis media, pyrexia and acneiform dermatitis (2,9). No drug-related grade 4 or 5 events or death were reported (9,11). In the final results of the EXIST-1 trial (13), 91% of participants needed at least one dose interruption or reduction, with adverse events being the most frequent reason for dose interruption (72%). Discontinuation of everolimus due to adverse events occurred in about 10% of participants in this study. One death was reported but was not suspected to be treatment-related. In the NCT00411619 extension study (10), all participants 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). Adverse events identified in the case series describing use of everolimus in infants included infection, stomatitis and increase triglycerides (14).

## Cost / cost effectiveness

No comparative cost–effectiveness data are available. The application reported an annual cost of treatment for a 10-year-old child at a dosage of 5 mg everolimus a day, based on medicine prices from the Netherlands, to be € 30 436 and € 34 526 for standard tablets and dispersible tablets, respectively. However, medicine prices will vary from country to country.

## WHO guidelines

WHO Guidelines for the treatment of SEGA are not available nor are WHO guidelines for the treatment of low-grade glioma.

## Availability

Everolimus has regulatory approval from multiple national regulatory agencies for treatment of SEGA associated with tuberous sclerosis complex in patients aged 3 years and older who require therapeutic intervention but who are not candidates for curative surgery. It is available in both branded and generic forms. Everolimus also has regulatory approval for other indications including renal cell cancer, pancreatic neuroendocrine tumours, hormone-receptor-positive advanced breast cancer, and (in lower doses) for prophylaxis of organ rejection in patients receiving organ transplants.

## Other considerations

For the diagnosis of SEGA, MRI must be available and neuroradiologists trained in paediatric neuroradiology are required for the interpretation of the images and clinical implications. If SEGA is detected on imaging, genetic counselling of the patient and family is necessary. After a defined starting dose, everolimus has to be adjusted individually to reach a blood concentration of 5–15 ng/mL. Younger age at treatment (< 6 years) and concomitant treatment with drugs that induce CYP3A4 require higher starting doses. Therapeutic drug monitoring and dose titration for everolimus are required. Treatment of SEGA is guided by follow-up MRI to assess tumour volume and response to treatment. The EML Cancer Medicines Working Group advised that it supports the inclusion of everolimus on the EMLc for the treatment of SEGA in children. If recommended by the Expert Committee, it should be very clearly communicated that the recommendation is for this indication alone, and not for other indications where the evidence for everolimus has not been reviewed. The Working Group noted that SEGA is a very rare disease with a strong genetic component. There is evidence of benefit for everolimus in the treatment of children with SEGA. However, the Working Group had some concerns about the feasibility of safe and appropriate use of everolimus in some settings, noting the requirements for specialist diagnosis and monitoring. Comments were received from the WHO Department of Noncommunicable Diseases. The technical

department advised that everolimus has well established and clinically relevant efficacy for the treatment of SEGA in children. It is important to note, however, that such treatment requires specialist diagnosis (that may include use of magnetic resonance imaging (MRI) and specialized in vitro diagnostic tests such as immunohistochemistry and fluorescence in situ hybridization) and a multispecialty team for monitoring. Furthermore, SEGA is a rare condition mainly affecting children with tuberous sclerosis.

1. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol.* 2016;131(6):803–20.
2. Krueger DA, Care MM, Agricola K, Tudor C, Mays M, Franz DN. Everolimus long-term safety and efficacy in subependymal giant cell astrocytoma. *Neurology.* 2013;80(6):574–80.
3. Pollack IF, Agnihotri S, Broniscer A. Childhood brain tumors: current management, biological insights, and future directions. *J Neurosurg Pediatr.* 2019;23(3):261–73.
4. Fohlen M, Ferrand-Sorbets S, Delalande O, Dorfmueller G. Surgery for subependymal giant cell astrocytomas in children with tuberous sclerosis complex. *Childs Nerv Syst.* 2018;34(8):1511–9.
5. Giordano F, Moscheo C, Lenge M, Biagiotti R, Mari F, Sardi I, et al. Neurosurgical treatment of subependymal giant cell astrocytoma in tuberous sclerosis complex: a series of 44 surgical procedures in 31 patients. *Childs Nerv Syst.* 2020;36(5):951–60.
6. About TSC [website]. Silver Spring, MD:TSC Alliance (<https://www.tscalliance.org/about-tsc/what-is-tsc/>, accessed 9 June 2021).
7. Tuberous sclerosis complex [internet]. Orphanet; 2020 ([https://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=GB&Expert=805](https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=805), accessed 9 June 2021).
8. Jansen AC, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. Clinical characteristics of subependymal giant cell astrocytoma in tuberous sclerosis complex. *Front Neurol.* 2019;10:705.
9. Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. *N Engl J Med.* 2010;363(19):1801–11.
10. Franz DN, Agricola K, Mays M, Tudor C, Care MM, Holland-Bouley K, et al. Everolimus for subependymal giant cell astrocytoma: 5-year final analysis. *Ann Neurol.* 2015;78(6):929–38.
11. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multicentre, randomised, placebo-controlled phase 3 trial. *Lancet.* 2013;381(9861):125–32.
12. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Everolimus for subependymal giant cell astrocytoma in patients with tuberous sclerosis complex: 2-year open-label extension of the randomised EXIST-1 study. *Lancet Oncol.* 2014;15(13):1513–20.
13. Franz DN, Belousova E, Sparagana S, Bebin EM, Frost MD, Kuperman R, et al. Long-term use of everolimus in patients with tuberous sclerosis complex: final results from the EXIST-1 study. *PLoS One.* 2016;11(6):e0158476.
14. Kuki I, Kawawaki H, Okazaki S, Ehara E, Yoshida Y, Kunihiro N, et al. Efficacy and safety of everolimus in patients younger than 12 months with congenital subependymal giant cell astrocytoma. *Brain Dev.* 2018;40(5):415–20.

