A.13	Everolimus - Subependymal giant cell astrocytoma (SEGA) associated with Tuberous sclerosis complex (TSC)
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: The prevalence of TSC is approximately 1/600, with around 1 million people affected worldwide. Around 25% of this patients develop SEGA. SEGA is an uncommon condition particular to patients with TSC. It can lead to obstructive hydrocephalus (increased intracranial pressure, neurological deficits, increased seizure frequency) massive haemorrhage[1], permanent sequealae and death. Surgery is considered to be first line therapy for this condition but due to the location of these tumours, many of them can not be removed or only partial removal is possible. Also since TSC is associated to multiple health problems, some of these patients are not good surgical candidates. In these cases everolimus is the only available option.
Briefly summarize the role of the proposed medicine(s) relative to other therapeutic agents currently included in the Model List, or available in the market.	Everolimus is not included in the Model list so far. The only alternative for the treatment of this condition is surgery.
Have all important studies and all relevant evidence been included in the application?	☐ Yes ☒ No ☐ Not applicable If no, please provide brief comments on any relevant studies or evidence that have not been included: Fogarasi 2016 (EFFECTS)[2] is a phase 3b open-label multicentre study that evaluated patients >= 3 years with a diagnosis of TSC and at least 1 lesion compatible with SEGA. Patients received 1 dose of everolimus daily. It evaluated 120 patients (100 completed the study). This study focused mainly on safety. It showed that 74.2% of patients developed at least 1 adverse event (AE), 2.5% of patients developed severe AEs and 6.7% of patient discontinued the treatment due to AE. In terms of efficacy it showed that 67.5 % of patients had a partial response, 29.2 % had a stable disease, 0.8 % had progressive disease. The response was unknown in 2.5% of patients.

Does the application provide adequate evidence of efficacy/effectiveness of the medicine for the proposed indication?	☒ Yes ☐ No ☐ Not applicable Briefly summarize the reported benefits (e.g. hard clinical versus surrogate outcomes) and comment, where possible on the actual magnitude and clinical relevance of benefit associated with use of the medicine(s). Evidence from small prospective studies (1 RCT, Franz 2013 and prospective cohort studies) have consistently shown significant reduction in tumour size (surrogate outcome). Patient receiving everolimus did not require surgical treatment. Some of them showed decreased seizure frequency. Once study showed improvement in quality of life. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Studies included children and adult patients. One of the studies was developed in the US while the other included patients in 10 countries (Australia, Belgium, Canada, Germany, UK, Italy, Netherlands, Poland, Russian Federation, and USA)
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Most patients developed an AE secondary to treatment. Most of them were mild, manageable and did not lead to treatment discontinuation. Most common AE were upper respiratory infections, stomatitis. Frequently, AEs required dose adjustments.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Blood cell count abnormalities (anemia, decreased platelets, decreased WBC) and hypercholesterolemia were also reported. These AEs may require monitoring.
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Everolimus is an effective option for the treatment of SEGA. Based on limited evidence, focusing mainly on a surrogate outcome, we can conclude that it presents a favourable profile.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	I consider that the overall quality of the evidence is low. Most of the evidence comes from small non-randomized studies. Unfortunately, since this is an uncommon disease the ability and resources needed to develop high quality evidence are limited. A study comparing everolimus vs. surgical intervention is not available.

Are there any special requirements for the safe, effective and appropriate use of the medicine(s)**?** (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☒ Yes ☐ No ☐ Not applicable Comments: To diagnosis SEGA centres have to be able to perform an MRI and have a trained neuroradiologist. MRI is also used to monitor treatment response. Drug levels have to be monitored.
Are you aware of any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: Everolimus received regulatory approval in United States, Canada, and Europe for patients with SEGA associated with TSC who require therapy but are not candidates for surgical resection.
Is the proposed medicine recommended for use in a current WHO Guideline approved by the Guidelines Review Committee? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: There are no WHO guidelines for the management of TSC or any of it clinical features.
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	Access: This drugs is available in the US, Canada and Europe. It is not included the British or International pharmacopoeia. Access to this drug in many countries of Latin America is limited. Cost: Limited information available. Costs can vary significant between countries. Also doses are variable since it is based on weight. In the US the cost for 120 tablets of 0.5mg is >$2000 without insurance. This cost is prohibitive for a significant proportion of the population.
Any additional comments	
Based on your assessment of the application, and any additional evidence / relevant information identified during the review process, briefly summarize your proposed recommendation to the Expert Committee, including the supporting rationale for your conclusions, and any doubts/concerns in relation to the listing proposal.	I consider this medication should be included in the EML. This recommendation is based on low certainty evidence but until new evidence arises this seems to be the best available option in patients with SEGA who are not eligible for surgery (or surgery can not resect the whole tumor).

References (if required)	1. Kim SK, Wang KC, Cho BK, Jung HW, Lee YJ, Chung YS, Lee JY, Park SH, Kim YM, Choe G, Chi JG. Biological behavior and tumorigenesis of subependymal giant cell astrocytomas. J Neurooncol. 2001 May;52(3):217-25. doi: 10.1023/a:1010664311717. PMID: 11519851. 2. Fogarasi A, De Waele L, Bartalini G, Jozwiak S, Laforgia N, Verhelst H, Petrak B, Pedespan JM, Witt O, Castellana R, Crippa S, Gislimberti G, Gyorsok Z. EFFECTS: an expanded access program of everolimus for patients with subependymal giant cell astrocytoma associated with tuberous sclerosis complex. BMC Neurol. 2016 Aug 8;16:126. doi: 10.1186/s12883-016-0658-4. PMID: 27502586; PMCID: PMC4976509.