A.13	Everolimus – subependymal giant cell astrocytoma
Does the application adequately address the issue of the public health need for the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: 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. 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. 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.
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.	The target population of Everolimus are patients ≥3 year of age with a subependymal giant cell astrocytoma (SEGA) associated to tuberous sclerosis complex (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.
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:

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). 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. 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 ($p<0.001$). 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. 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. In the open-label 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). 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. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? That treatment with everolimus is even feasible in infants <12 month of age too.
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: 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. No drug-related grade 4 or 5 events or death were reported. 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).
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	Phase I/II study (Kreuger) 28 patients. After 6 months treatment, 100% have reduction of tumour (n=28). Phase III study – EXIST-1 (n=117), placebo-controlled RCT. Everolimus treated patients have 100% PFS after 1 year, some progression in the placebo group. Response favours everolimus group. After median follow-up of 28 months, 54/78 patients in the everolimus arm had a response of ≥ 50% reduction in SEGA volume once during study period. No patients underwent tumour surgery due to progression. Most frequent side effects with mouth ulcers and stomatitis (mild-moderate). These results support the use of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis. Additionally, everolimus might represent a disease-modifying treatment for other aspects of tuberous sclerosis (like seizure, renal angiomyolipoma, skins lesions)
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	Considering the good efficacy of everolimus treatment for patients with TSC/SEGA, there is a moderate/high evidence for the medicine. Considering that is a rare disease high number studies are non-realistic, therefore the phase III study performed in the paediatric and young adult setting is enough to justify the indication.
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: First of all to make a good diagnosis of TSC/SEGA a MRI and well trained Radiologist are needed. This point should be taken in account. Regarding appropriate use of Everolimus a Therapeutic Drug Monitoring and dose titration is mandatory. After a defined starting dose, Everolimus has subsequently to be adjusted individually to attain a blood concentration of 5-15ng/ml. Dosing regimen is individually adjusted to attain specific blood levels, with starting doses defined by specific criteria (age, seizures, concomitant therapies). TDM necessary at different time-points.
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:

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:
Briefly summarize your assessment of any issues regarding access, cost and affordability of the medicine in different settings.	There are some concerns about the feasibility of use of everolimus in some settings, noting the requirements for specialist diagnosis and monitoring of the drug. Another main concern in is the high cost of the treatment.
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.	If the inclusion of everolimus on the EMLc for the treatment of SEGA in children will be recommended by the Expert Committee, it should be very clearly communicated that the recommendation is for this indication alone, and not other indications where the evidence for everolimus has not been reviewed. SEGA is a very rare disease with a genetic component. There is evidence of benefit for treatment of children with SEGA. However, the there are some concerns about the feasibility of use of everolimus in some settings, noting the requirements for specialist diagnosis and monitoring of the drug.
References (if required)	Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. The New England journal of medicine. 2010;363(19):1801-11. 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. Annals of neurology. 2015;78(6):929-38. 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 (London, England). 2013;381(9861):125-32. 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. The Lancet Oncology. 2014;15(13):1513-20. 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.