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: they did make a good case however , I do not think it is of great impact as mortality is less than 10 % and the indication is for less than 3.7% of cases of impending ventricular obstruction.
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 an m TOR inhibitor with activity in patients presenting with subependymal giant cell astrocytoma by reducing tumour size thereby lowering the risk of life threatening hydrocephalus(SEGA). In SEGA patients, It blocks the activity of mutations in TSC1 and 2 genes which activate the m TOR pathway, stimulating tumor cell growth. It is also indicated for HR + breast cancer, neuroendocrine tumors ,metastatic renal cell cancer and seizure disorder in SAGE patients. Everolimus is not listed in the model list for any of these conditions. This drug is the only medication for surgically unresectable SEGA
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 A et al BMC Neurol 16,126(2016) real world data, a phase 3b trial with n=120, age>3 yrs an important trial supporting efficacy especially has larger patient numbers.
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). From the data provided , this condition arises in few persons and of note the trials are limited in patient numbers (less than 120) with few phase 3 and metanalysis studies, few discussing QoL Many of these trials did not have control arms e.g. radiotherapy or surgical arms. This application is however specific to patients who are not surgical candidates. PFS survival of 100% is reported with medication vers 86% without it , several studies report an average of 50% of cases achieving a 50% tumor regression and 70% with at least 30% regression. The reported gain was 36% , a small trial of 10 cases suggested no change but a recent paper with larger number of patients (Ryoo JS et al . Neuro-Oncology Practice , vol 8 , issue 1, Feb 2021 Pg 98-105) confirmed positive and

	significant gain. The benefit is higher for unresectable disease and avoidance of surgery. Important is the tolerability of the drug. Is there evidence of efficacy in diverse settings (e.g. low-resource settings) and/or populations (e.g. children, the elderly, pregnant patients)? Yes, there is evidence of efficacy in infants and effect on fetus is reported but low resource setting applications not discussed
Does the application provide adequate evidence of the safety and adverse effects associated with the medicine?	☒ Yes ☐ No ☐ Not applicable Comments: Safety precautions in patients with liver dysfunction, CYP3A4/PgP inductor are provided with protocols for dose titration . The data provided indicates high rates of intermediate grade toxicity , less than grade 4 occurring in up to 100% of patients. As much as 91% required dose reduction , 10% treatment withdrawal.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Monitoring in patients with CYP3A4/PgP inductors to avoid toxicity Stomatitis , mouth ulceration and upper respiratory infection the most common in up to > 75% of patients , in a few patients less than 50%
Briefly summarize your assessment of the overall benefit to risk ratio of the medicine (e.g. favourable, uncertain, etc.)	The benefit outweighs the tolerable toxicity , considered favourable in patients who are not surgical candidates.
Briefly summarize your assessment of the overall quality of the evidence for the medicine(s) (e.g. high, moderate, low etc.)	The quality of the evidence provided is low as few of the trials were phase 3 or metanalysis with small patient numbers and no control arm. Very few studies included QoL assessment . Results from majority show reproducible significant benefit which cannot be ignored.
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: Serial measurements of dose levels for titration to optimum levels especially in patient taking CYP3A4/PgP inductor medications , the need for neuro-radiology specialist for diagnosis and assessment .

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: This drug has been approved for this indication not specific to unresectable cases and also for control of seizures from SEGA in US. As an orphan dug in Europe.
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.	The cost effectiveness analysis was shallow with no discussion on access and equity. SEGA is a chronic disease so the long term cost implications should be considered. An average cost of 3000 euro per month could be considered cost effective for many HIC but not accessible to many in LMIC . Future generics could drive down the cost especially as there are other indications for this drug.
Any additional comments	I am not clear if this application is in reference to patients who are not surgical candidates with impending hydrocephalus or for all patients with SEGA to reduce the need to surgery or repeated surgeries?
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.	SEGA management historically has few options other than surgery , as radiotherapy and chemotherapy are not effective. Many patients do not have access to quality surgery and subsequently subjected to several episodes of recurrent disease and poor consequences. For over 11 years , this medication has shown significant local control rates with tolerable toxicity in lieu of surgery in the small trials but with consistent significant results conducted in this rare disease. This drug also shows evidence of efficacy in seizure control for SEGA. I recommend listing of this drug for SEGA My concerns are 1. No comparative studies with surgery 2. No substantive QoL studies in view of high rates of dose adjustments 3. Low evidence available which could be attributed to the rareness of the disease 4. High cost and need for frequent high level care during treatment which may not be accessible to many LMIC.
References (if required)	Ryoo JS et al . Neuro-Oncology Practice , vol 8 , issue 1, Feb 2021 Pg 98-105 Nguyen HS et al. World Neurosurg . 2018 Oct;118e263-268 Fogarasi A et al BMC Neurol 16,126(2016)