Canada's Drug Agency
L'Agence des médicaments du Canada

Everolimus

Formulary Management Expert Committee Responses to Questions From the Drug Programs

Table 1: Response Summary

Drug program implementation questions	Clinical expert response	FMEC response
What are the primary goals of the current treatment paradigm for SEGA associated with TSC? How can everolimus be effectively integrated into the current treatment paradigm for SEGA associated with TSC?	The primary goal of treatment for SEGA associated with TSC is to prevent acute intracranial hypertension that would necessitate urgent neurosurgery, which carries significant risk. Everolimus has been used since 2005 as the main therapeutic option for SEGA that does not require immediate surgery due to its efficacy and acceptable side effect profile. It is the main therapeutic option in the current treatment paradigm. It complements surgery by reducing the size of SEGAs and is unique in its ability to alter the disease process rather than just treating symptoms.	FMEC defers to the experts. This is the primary nonsurgical therapy.
Diagnosis of TSC relies on MRI assessment and the internationally recognized Gomez criteria, which evaluate other physical manifestations of the disease. Treatment outcomes are monitored through follow-up MRIs to confirm tumour size reduction. Other outcomes that were explored were seizure frequency per 24 hours and skin lesion response rate. Are these other outcomes common practice? Would the treatment of SEGA require clinicians to make these assessments to determine drug efficacy?	The primary outcome is typically reduction in tumour size, as confirmed by follow-up MRIs.	FMEC defers to the experts. In addition, FMEC notes that patients may benefit from treatment if it continues to maintain stable disease, as manifested by no further tumour growth.

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What are the specific gaps and unmet needs in the current treatment options for SEGA associated with TSC that should be addressed to improve patient outcomes? Which patients are considered most suitable for treatment with everolimus?	Current unmet needs include the limitations of surgical interventions, which can be invasive and have risks including mortality. Minimally invasive treatments like laser or endoscopic procedures are only feasible for smaller lesions and may still result in morbidity. For larger or multiple lesions, complete resection is often not possible, leading to a need for treatments that prevent regrowth and address multiple lesions simultaneously. Additionally, no treatments are available to reverse the disease course or interact with the underlying pathophysiology. Patients best suited for everolimus include those with multiple lesions, large SEGA not accessible to minimally invasive methods, difficult-to-resect lesions, or small lesions with potential for future growth. Patients least suitable are those with acute symptoms of hydrocephalus, clear signs of growth on MRI, or rapid tumour growth in young children, where the risks of everolimus outweigh the benefits.	FMEC defers to the clinical experts. Patients most likely to benefit from treatment are outlined in the primary review.
Is there an ideal fixed duration of treatment, or is treatment considered to be lifelong?	Treatment duration with everolimus is not fixed and may vary based on individual patient response and disease progression. Long-term or potentially lifelong treatment may be necessary, but the possibility of intermittent discontinuation or "drug holidays" could be considered to manage adverse effects and minimize toxicity.	The lack of long-term evidence for patients to continue well into adulthood limits the ability to answer this question.
Regarding treatment discontinuation and re-treatment: 1. Are there suggested criteria for discontinuation of therapy? Would EXIST-1 primary end points be considered as the	Factors to consider when deciding to discontinue everolimus include disease progression to a symptomatic state requiring immediate surgical intervention, lack of effect after a prolonged period	FMEC defers to the experts for the response to question 1. FMEC defers to the experts for responses to questions 2 and 3. Also refer to the discontinuation

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thresholds for discontinuing treatment? 2. In patients who have no disease progression and are taken off everolimus, should they be able to have re-treatment with everolimus? 3. Given that the EXIST-1 and Study 2485 trials are suggesting long-term treatment with mTORi, would there be a point at which drug therapy can be intermittently discontinued (i.e., drug holiday)? If so, what would be the reasoning for this? (Would it be to minimize adverse effects or toxicity? Can there be a resistance to tumours in prolonged mTORi treatment?) What would be the duration? 4. Discontinuing everolimus has the risk of tumour progression, which has the risk of seizures. Would antiepileptic agents also be discontinued as they can also pose fetal toxicity? Or would antiepileptic drugs be continued with the supplementation of folic acid?	(typically 6 months), or intolerable side effects such as severe infections, allergic reactions, severe diarrhea, or severe mouth ulcers.	criteria in the reimbursement conditions (Table 2). Question 4 is outside the scope of this review.

FMEC = Formulary Management Expert Committee; mTORi = mammalian target of rapamycin inhibitor; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex.