Reimbursement Recommendation

Everolimus

Reimbursement request: For the treatment of patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC)

Requester: Public drug programs

Final recommendation: Reimburse with conditions

Summary

The Formulary Management Expert Committee (FMEC) recommends that everolimus be reimbursed for the treatment of subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC), provided certain clinical conditions are met.

FMEC reviewed the long-term follow-up data from the EXIST-1 trial, including the planned open-label extension phase of the trial.

FMEC concluded that longer-term findings from the EXIST-1 trial suggest sustained SEGA response (e.g., reduction in tumour size, delay in tumour progression) over time, with no additional or late-emerging toxicities. Slowing tumour growth was an outcome identified as important to patients and their caregivers.

Everolimus is expected to generate incremental costs for the publicly funded drug programs.

Therapeutic Landscape

What Is SEGA Associated With TSC?

TSC is a rare genetic disorder, with SEGA as a common neurological manifestation of the disease. SEGAs can be asymptomatic and slow-growing, but some may grow large enough to cause ventricular obstruction or hydrocephalus and may require surgery. Therefore, an important treatment goal is to stop or slow tumour growth to avoid surgery, as it is associated with high risks and complications.

Why Did We Conduct This Review?

The Canadian Drug Expert Committee (CDEC) reviewed and issued a Do Not List recommendation for everolimus in 2015. Given new data on the long-term efficacy and safety of everolimus for TSC available since the original review, publicly funded drug plans have requested a new nonsponsored Reimbursement Review.

Person With Lived Experience

A couple from Quebec shared their experience with their 11-year-old daughter's treatment for SEGA associated with tuberous sclerosis. Diagnosed at birth with TSC, she also developed infantile spasms at 6 months, which were controlled with epilepsy medication. In 2019, a brain tumor was discovered that could obstruct fluid circulation. They spoke to a neurosurgeon about 2 surgical options, 1 affecting fine motor skills and the other affecting speech. After careful consideration, they instead chose treatment with everolimus. Their daughter has been taking it daily since then, with no significant side effects and minimal impact on their daily routine. The drug has been effective, reducing her heart tumors, eliminating arrhythmias, and keeping brain tumors under control, avoiding the need for surgery. They expressed relief and gratitude for the ease of treatment and its outcomes for their daughter.

Input From Community Partners

What Did We Hear From Patients?

One patient group shared about the constant stress of not knowing when or how much a SEGA would grow and whether their child might need urgent surgery. Although SEGAs are typically slow-growing, they can reach emergency status between MRIs and doctor visits. Surgical procedures and repeated MRIs are challenging to perform in young patients, particularly those with developmental delays and those who live far from hospital centres.

What Did We Hear From Clinicians?

We did not receive any input from clinician groups for this review.

What Did We Hear From the Pharmaceutical Industry?

We did not receive any input from the pharmaceutical industry for this review.

What Did We Hear From Public Drug Programs?

The drug plans noted the absence of a suitable comparator; the EXIST-1 trial was placebo controlled, as there are no pharmacological therapies other than mTOR inhibitors for SEGA (sirolimus does not have a Health Canada indication for TSC-related SEGA). The drug plans also inquired about outcomes and appropriate assessments to determine drug efficacy in clinical practice, and considerations for treatment duration and discontinuation of therapy.

►Refer to the Input section of the full report.

Deliberation

With an 8 to 0 vote, FMEC concluded that everolimus demonstrated sufficient evidence of clinical benefit in patients with SEGA associated with TSC that have demonstrated growth, and for whom immediate surgical intervention is not required. Everolimus will be associated with increased drug program spending.

FMEC deliberated using the following 5 domains of value:

- **Unmet clinical need:** Unmet clinical need refers to morbidity and/or mortality arising from a condition or symptom that is not addressed effectively by available treatments.
- **Clinical value:** Clinical value is the value that patients derive from a health technology in terms of its effect on their health and health-related quality of life. The determination of the clinical value of a health technology requires the measurement of its clinical benefits and harms and an assessment of the impact of these effects on patients. Clinical benefits and harms are assessed against relevant comparators.
- **Economic considerations:** Economic considerations refer to economic evidence to inform the financial, human, or other resource implications associated with the technology under review, and whether it is reasonable to allocate resources to the technology under review given its expected clinical benefits. Considerations may include the potential resource or cost impacts of the technology under review versus relevant comparator(s), and/or the potential economic value of the technology under review versus relevant comparator(s). For this review, only the relative cost impacts were considered.
- **Impacts to health systems:** This domain considers 2 distinct but interrelated components: organizational feasibility of adoption is the ease with which the health technology can be implemented in the health system while realizing its clinical value, while economic feasibility of adoption (affordability) considers how the adoption of a health technology will financially impact the

payer or budget holder. For this review, only the first component (i.e., organizational feasibility) was considered.

- **Distinct social and ethical considerations:** This domain considers the distinct social and ethical implications of health technologies (including in their design, evaluation, and implementation) not already assessed in the other domains and how they affect patients, caregivers, populations, and the organization of health systems.

Decision Summary

Table 1: Summary of Deliberation

Overarching question(s)	Discussion point(s)
Unmet clinical need	
Is there significant clinical need arising from the condition despite available treatments?	• FMEC noted that there is a significant clinical need for noninvasive therapies to manage SEGA. • FMEC noted that although SEGA is uncommon, affecting only a small proportion of the 3,500 people in Canada with TSC, it requires urgent specialized care when complications arise. • There are disparities in public funding for the drug across provinces and territories.
Clinical value	
Does the drug under review demonstrate acceptable clinical value versus relevant comparators in the Canadian setting?	• Based on evidence from EXIST-1 trial, everolimus reduced SEGA volume. SEGA response was maintained during the 5-year follow-up of the trial. One patient required neurosurgery. • FMEC discussed the uncertainty in the clinical evidence, given that there are no Health Canada–approved pharmacologic comparators. However, there should be greater allowance for uncertainty given the great unmet need and rarity of the disease. • FMEC noted that there are no Health Canada–approved pharmacologic alternatives for treating SEGA, although sirolimus may be used off-label, and the evidence signals a trend in reducing the need for neurosurgery with everolimus. In the double-blind core phase of the EXIST-1 trial, 27 of 78 patients (35%) in the everolimus arm and none of the 39 patients in the placebo arm had a SEGA response (difference = 35%; 95% CI, 15 to 52; 1-sided exact Cochran-Mantel-Haenszel test, P < 0.0001) However, there is limited evidence on improvements in quality of life or seizure frequency reduction. ◦ In the EXIST-1 trial, a SEGA response was defined as a reduction in 50% of target SEGA volume, in the absence of worsening nontarget SEGAs, new lesions of at least 1 cm in diameter, and new or worsening hydrocephalus. • Adverse effects from the medication are common but remain consistent over long-term use with no additional or late-emerging toxicities. The adverse effects are consistent with the mechanism of action of everolimus and are monitored and managed in clinical practice.
Economic considerations	
Are there economic considerations that are relevant to address when implementing reimbursement of the drug under review?	• Everolimus is expected to generate incremental costs for the publicly funded drug programs. Given the wide variation in wholesale pricing for everolimus across Canada, the impact on some payers would be higher than others. • FMEC noted that generic forms of everolimus are available. However, it was also noted that price differences between jurisdictions were highly variable. • FMEC discussed that the potential for lifelong therapy with everolimus would result in high

Overarching question(s)	Discussion point(s)
	drug acquisition costs per patient. Additionally, managing adverse events such as stomatitis is likely to increase resource utilization costs, although some cost savings may be achieved through the anticipated reduction in neurosurgical interventions associated with reduced SEGA size over time. • The costs associated with surgery (i.e., craniotomy with tumour resection) were not assessed. FMEC noted that surgery is not considered a direct comparator, as the indication explicitly excludes patients for whom immediate surgical intervention is required.
Impacts to health systems	
Are there expected organizational impacts of implementing the drug under review?	• No additional training for pediatric neurologists or neurosurgeons would be required, as many are already familiar with everolimus use.
Distinct social and ethical considerations	
Is there significant nonclinical need arising from the condition, despite available treatments, that would potentially be addressed by the technology under review? Are there any important measures that should be implemented to ensure that the use of the technology addresses relevant social and ethical implications?	• Currently, there are inequities in drug plan payers, as some provinces and territories provide coverage on a case-by-case basis with differing criteria, whereas most others either do not or the reimbursement status is unknown (refer to coverage table). Everolimus can be readily obtained from community pharmacies. • FMEC highlighted that caregivers describe living with SEGA as highly stressful because they fear rapid tumour growth between appointments that could necessitate urgent neurosurgery that is often conducted far from home. Parents initially make treatment decisions for young patients, balancing the risks of everolimus, while adult patients later dictate treatment decisions based on their adult experiences. Long-term use of everolimus requires monitoring for complications like dyslipidemia and hyperglycemia, and caregivers must handle the drug cautiously due to its cytotoxic risk. • FMEC noted that MRI monitoring is a requirement, along with watchful monitoring and surgery or everolimus treatment. However, both patients and clinicians consider everolimus more favourably as everolimus may also treat other disease manifestations that occur. Although the evidence supporting the use for these indications (such as epilepsy, renal AMLs, skin lesions, and cardiac tumours) was not a focus of this deliberation, these added perceived values, referred to as “win-win situations” are meaningful to patients and caregivers.

AML = angiomyolipoma; FMEC = Formulary Management Expert Committee; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex.

Full Recommendation

With a vote of 8 of 0, FMEC recommends that everolimus for the treatment of patients with SEGA associated with TSC be reimbursed, if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
Everolimus should be reimbursed in patients with a definitive diagnosis of TSC as per consensus criteria and presenting	Initiation criteria largely reflect the enrolment criteria in the EXIST-1 trial.	Patients should be medically stable and unlikely to require surgery for SEGA, with no critical hydrocephalus or imminent cerebral

Reimbursement condition	Reason	Implementation guidance
with SEGA lesion(s), with at least 1 of the following: 1. demonstrated growth on imaging 2. new lesion > 1 cm or in high-risk location regardless of size 3. new or worsening hydrocephalus 4. large lesions not amenable to minimally invasive surgery.		herniation. Regular imaging would be required as per standard practice. The reimbursement condition for initiation is largely based on enrolment criteria in the EXIST-1 trial, including the definitive diagnosis of TSC as per consensus criteria.[1,2] These criteria are largely consistent with the TSC diagnostic criteria updated in 2021.[3] Modifications have been made based on expert committee discussion to better align with current practice and to facilitate implementation.
Discontinuation and renewal		
Treatment with everolimus should be discontinued upon the occurrence of any of the following: 1. lack of clinical or radiological response 2. unacceptable toxicity.	Discontinuation criteria are largely based on clinical experts' opinions in managing this disease.	Routine imaging (e.g., MRI) is important to assess treatment response.
Prescribing		
1. Prescribing should be limited to clinicians with expertise in the diagnosis and management of SEGA associated with TSC.	—	—
Cost		
1. Everolimus should be priced in accordance with the pan-Canadian Generic Tiered Pricing Framework.	—	—

SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex.

[1]Roach ES, et al. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol. 1998;13(12):624-628.

[2]Hyman MH, et al. National Institutes of Health consensus conference: tuberous sclerosis complex. Arch Neurol. 2000;57(5):662-665.

[3]Northrup H, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatric Neurology. 2021; 123: 50-66.

Feedback on Draft Recommendation

Feedback was received from 1 of the Public Drug Programs on the draft recommendation report. Additional clarification was requested on the definitive diagnosis of TSC. This has been addressed by revising the statement in the implementation guidance.

FMEC Information

Members of the committee

Dr. Emily Reynen (Chair), Dr. Zaina Albalawi, Dr. Hardit Khuman, Ms. Valerie McDonald, Dr. Bill Semchuk, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and 2 guest specialists from Alberta and Quebec.

Meeting date: September 19, 2024

Conflicts of interest: None

Special thanks: Canada's Drug Agency (CDA-AMC) extends our special thanks to the individuals who presented directly to FMEC on behalf of patients with lived experience and to patient organizations representing the community of those living with TSC-SEGA, notably Tuberous Sclerosis Canada, which includes Cathy Evanochko, Ly Lam, and Jean-Nicolas Paul.

Note: CDA-AMC makes every attempt to engage with people with lived experience as closely to the indication and treatments under review as possible; however, at times, CDA-AMC is unable to do so and instead engages with individuals with similar treatment journeys or experience with comparators under review to ensure lived experience perspectives are included and considered in Reimbursement Reviews. CDA-AMC is fortunate to be able to engage with individuals who are willing to share their treatment journey with FMEC.

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.