



Canada's Drug and  
Health Technology Agency

## CADTH Reimbursement Recommendation

# Everolimus

**Reimbursement request:** For renal angiomyolipoma associated with tuberous sclerosis complex

**Final recommendation:** Reimburse with conditions

# Summary of CADTH Recommendation

The CADTH Formulary Management Expert Committee (FMEC) concluded that the evidence for everolimus supported a reimburse recommendation for patients with renal angiomyolipoma (AML) associated with tuberous sclerosis complex (TSC).

In this reassessment of the Canadian Drug Expert Committee (CDEC) recommendation from 2013, FMEC reviewed long-term follow-up data from the open-label extension phase of the EXIST-2 clinical trial in the adult population and a post hoc analysis of the EXIST-1 clinical trial in a subset of pediatric patients. Everolimus demonstrated long-term efficacy, which included absence of renal AML-related clinical events (e.g., bleeding and need for procedural interventions such as embolization) with minimal side effects.

FMEC recommends everolimus be reimbursed in adult and pediatric patients with renal AML associated with TSC if clinical conditions are met.

# Therapeutic Landscape

## What Is Renal AML Associated With TSC?

TSC is a rare genetic disorder that affects 3,500 individuals in Canada. It is characterized by benign tumour-like lesions in multiple organ systems, including the brain, skin, lungs, and kidneys. Renal AMLs are a manifestation of TSC that occur in 80% of patients. Renal AMLs larger than 3 cm and serial growth are risk factors for complications such as aneurysms, which can rupture and result in hemorrhaging. Renal AMLs are a significant cause of morbidity and mortality in patients with TSC.

## Why Did CADTH Conduct This Review?

Publicly funded drug plans supported a request by patients and caregivers for this nonsponsored reimbursement review, as it met the eligibility criteria outlined in the *Non-Sponsored Reimbursement Review Procedures*.



### Person With Lived Experience

A mother, caregiver, and school principal with a Master of Education and a Doctor of Educational Leadership shared her family's journey as she cares for her 17-year-old daughter, who was born with TSC, in a suburban area of Ontario. Managing her daughter's complex medical, behavioural, social, emotional, and educational needs often feels like juggling, with the constant issues that arise. Two years ago, when her daughter developed a kidney lesion, her family advocated for exploring less invasive options before resorting to surgery, fearing the potential risks to her daughter's health and kidney tissue. She underscored the nonmedical aspects of the condition, such as developmental and behavioural challenges, which can make medical procedures more difficult. After months of advocacy and consultation, they secured a prescription for everolimus, which has resulted in a 50% reduction in lesion volume and has had no side effects or tolerance issues. Accessing this important treatment posed financial burdens, as their insurance wouldn't cover it, which required them navigating complex health care systems to continue treatment.

# Stakeholder Feedback

## What Did We Hear From Patients?

Current therapies, surgery and embolization, are invasive, painful, and burdensome to patients, as well as challenging to perform in younger patients, particularly those with developmental delays and those who live far from hospital centres. Patients and caregivers value treatments that are noninvasive, easily accessible, simple to administer, preserve healthy kidney tissue, and reduce risk of AML hemorrhaging. The patient input also noted that because TSC affects multiple organ systems, systemic treatments such as everolimus provide the benefit of addressing several manifestations of TSC simultaneously. Patients reported facing inequitable access to specialists with TSC expertise, lack of public funding, and lack of insurance coverage.

## What Did We Hear From Clinicians?

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

## What Did We Hear From the Pharmaceutical Industry?

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

## What Did We Hear From Public Drug Programs?

The drug plans highlighted the absence of a suitable comparator, as sirolimus does not have a Health Canada indication for the treatment of AML associated with TSC, and the off-label use of sirolimus is not funded by most drug plans. Limited or lack of timely access to diagnostic imaging like renal CT or MRI in some regions was identified as a potential challenge for treatment monitoring.

 Refer to the [Stakeholder Input](#) section of the CADTH report.

# Deliberation

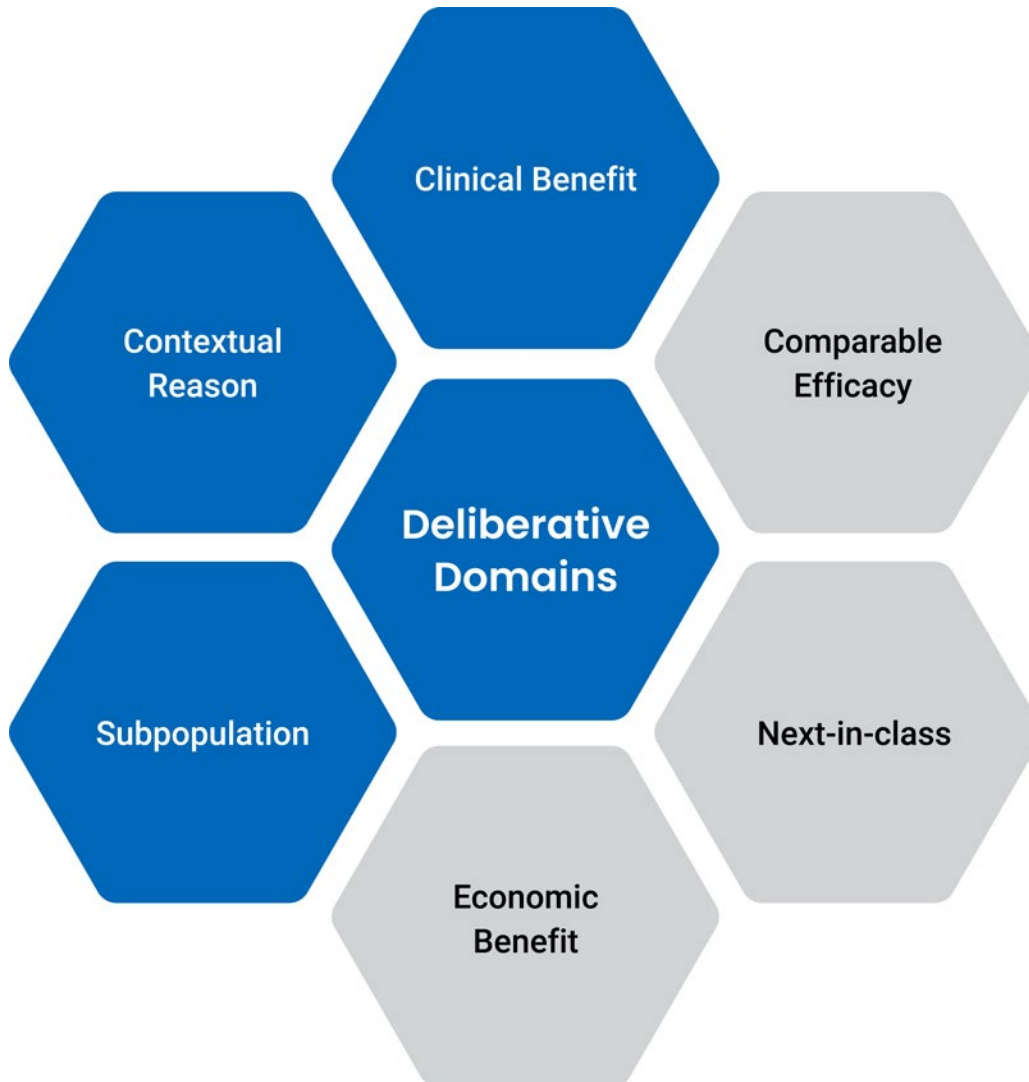
With a vote of 7 to 0 (1 member absent), FMEC concluded that everolimus demonstrated sufficient evidence for clinical benefit in the indicated adult population under review. There is a pediatric subpopulation that would benefit from this drug as well. Although everolimus will be associated with increased drug program spending, the cost-effectiveness of this drug remains unknown.

FMEC deliberated on the following 6 domains as illustrated in the Deliberative Framework ([Figure 1](#)):

- Clinical benefit: whether there is sufficient clinical evidence to support the population under consideration for reimbursement
- Comparable efficacy: whether there is evidence to support at least comparable efficacy between the drug under review and relevant comparator(s)
- Next-in-class drug (drug using an already exploited molecular mechanism): whether there are other therapies with a similar mechanism of action currently available or whether the drug under review has a novel mechanism of action
- Economic benefit: whether the drug under review represents potential cost savings compared to appropriate comparator(s)
- Subpopulation: whether there is a subpopulation that would benefit from the drug under review, if there is too much uncertainty in the broader population studied
- Contextual reasons: whether there are contextual reasons for reimbursing the drug under review that are not captured in the clinical or economic evidence

The 3 domains of clinical benefit, contextual reason, and subpopulation were the focus of FMEC's deliberative and reimbursement recommendation ([Figure 1](#)). The other 3 domains (comparable efficacy, economic benefit, and next-in class), while discussed, were less of a focus of the deliberation.

## Figure 1: Deliberative Framework



Note: The darker shaded deliberative domains were considered most relevant and contributed the most to the reimbursement recommendation by the committee. The lighter shaded domains were less of a focus in the deliberation.

# Decision Summary

## Table 1: Why Did FMEC Make This Recommendation?

Decision question	Discussion
Does the drug demonstrate sufficient evidence for clinical benefit?	<ul style="list-style-type: none"> <li>FMEC considered the evidence of the follow-up data from the EXIST-2 trial to be sufficient to support the adult population under consideration for reimbursement.</li> <li>FMEC noted that the evidence for the use of everolimus in the pediatric population is weaker given the limited data available. There is a subpopulation that would benefit from the drug (as noted later in this table).</li> </ul>
Is the drug a next-in-class medication? Is the benefit of the drug at least comparable to the rest of the class?	<ul style="list-style-type: none"> <li>FMEC noted that mTOR inhibitors have a unique mechanism of action that specifically targets the pathophysiology of TSC.</li> <li>FMEC identified sirolimus, another mTOR inhibitor; however, there is limited clinical evidence for this drug (including no comparative trial with everolimus) in renal AML associated with TSC. Furthermore, sirolimus has no Health Canada indication for this condition.</li> </ul>
Is there an economic benefit?	<ul style="list-style-type: none"> <li>The costs associated with standard of care (i.e., surgery and embolization) were not assessed.</li> <li>In the absence of a cost-effectiveness analysis, and based on list prices only, the addition of everolimus is expected to generate incremental costs for the publicly funded drug programs.</li> <li>FMEC noted that generic forms of everolimus are available. However, it was also noted that the price difference between jurisdictions was highly variable.</li> </ul>
Is there a subpopulation that would benefit from the drug, if there is too much uncertainty in the broader population studied? Is there a contextual reason for reimbursing the drug that isn't captured in the clinical or economic evidence?	<ul style="list-style-type: none"> <li>FMEC noted an unmet need for noninvasive treatments, especially in younger patients and those with developmental delays or intellectual disabilities, which are common in patients with TSC.</li> <li>FMEC noted that there is a significant unmet need in the treatment of renal AML associated with TSC considering the negative impact on patients' quality of life and the limited treatment options.</li> <li>FMEC acknowledged that there is an unmet need in the pediatric population despite the limited evidence in this subpopulation.</li> </ul>

AML = angiomyolipoma; FMEC = Formulary Management Expert Committee; mTOR = mammalian target of rapamycin; TSC = tuberous sclerosis complex.

# Full Recommendation

With a vote of 6 to 0 (with 2 members absent), FMEC recommends that everolimus be reimbursed for the treatment of renal AML associated with TSC in both adults and children aged 3 years or older, if the conditions presented in [Table 2](#) are met.

## Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
<b>Initiation</b>		
Everolimus should be reimbursed in patients who meet all of the following diagnostic criteria for renal AML associated with TSC: <ul style="list-style-type: none"> <li>at least 1 AML 3 cm or larger in its longest diameter in adults or 1 cm or larger in children</li> <li>a definite diagnosis of TSC per consensus criteria.</li> </ul>	The initiation criteria reflect the enrolment criteria in the EXIST-2 trial.	—
<b>Renewal</b>		
Patients must demonstrate clinically stable disease, such as no progression in AML size or no clinically significant episode of renal AML bleeding compared to baseline at 12 months and every 24 months thereafter.	This condition is based on the EXIST-2 trial response and FMEC clinical experts' opinion.	Physician's assessment of the patient's response should form the basis of each renewal.
<b>Prescribing</b>		
Prescribing should be limited to clinicians with expertise in the diagnosis and management of renal AML associated with TSC.	There are a number of significant adverse events, drug-drug interactions, potential teratogenicity, and other considerations with this drug, and individuals should be under the care of a specialist or specialty team.	This is a specialized population of patients who would be under the care of a treatment team experienced in their condition. Given the relative lack of clinicians with expertise in the condition and the use of the drug, virtual assessment or consultation with a more local practitioner could be considered after initial assessment.
<b>Cost</b>		
Everolimus should be priced in accordance with the pan-Canadian Generic Tiered Pricing Framework.	—	—

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# Feedback on Draft Recommendation

CADTH received feedback on the draft recommendation from the public drug programs. This feedback was reviewed and only editorial revisions to clarify the use of everolimus in the pediatric population and the renewal criteria were made to the recommendation.

## FMEC Information

**Members of the committee:** Dr. Emily Reynen (Chair), Dr. Alun Edwards, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, and Ms. Valerie McDonald, as well as Dr. Andrew House and Dr. Philippe Major (guest specialists)

**Meeting date:** February 1, 2024

**Conflicts of interest:** None

**Special thanks:** CADTH extends our special thanks to the individual who presented directly to FMEC on behalf of patients with lived experience and to the patient organizations representing the community of those living with renal AML associated with TSC, notably Tuberous Sclerosis Canada, which includes Cathy Evanochko and Dr. Jennifer Flinn.

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