Canada's Drug and
Health Technology Agency

CADTH Reimbursement Recommendation

Rivaroxaban Granules for Oral Suspension

Reimbursement request: For the treatment of VTE and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents < 18 years old, after at least 5 days of initial parenteral anticoagulation treatment

Final recommendation: Reimburse with conditions

Summary of CADTH Recommendation

The CADTH Formulary Management Expert Committee (FMEC) concluded that options that are more convenient (e.g., oral liquid formulation) with less monitoring are required in the treatment of pediatric populations with venous thromboembolism (VTE).

The EINSTEIN Jr trial demonstrated efficacy and safety of rivaroxaban for pediatric patients with VTE as compared to low molecular weight heparin (LMWH). FMEC highlighted that there were greater uncertainties with the evidence for preterm neonates, pediatrics aged 2 or younger, those with cancer and/or unprovoked VTE.

The expected cost of rivaroxaban is less than the most frequently used anticoagulation, which is currently LMWH.

FMEC concluded that while there should be greater allowance for uncertainties in the evidence in pediatric populations, rivaroxaban should be initiated by or in consultation with a pediatric specialist.

Therapeutic Landscape

What Is VTE?

VTE includes venous thrombosis and/or pulmonary embolism. The estimated incidence of VTE in childhood is substantially lower than adults (~0.07 per 10,000 individuals). Most VTE cases are related to identifiable conditions such as indwelling central venous catheter or malignant diseases. Without timely management, VTE can have high mortality rates and complications (e.g., postthrombotic syndrome).

Why Did CADTH Conduct This Non-Sponsored Reimbursement Review?

Publicly funded drug plans requested this nonsponsored reimbursement review, as it met the eligibility criteria outlined in the *Non-Sponsored Reimbursement Review Procedures*.

Patient With Lived Experience

CADTH actively engages and collaborates with relevant patient groups to identify individuals, such as patients, caregivers, or family members, who have firsthand experience with the condition and drug under review. These individuals are invited to present their perspectives and share their experiences with the Formulary Management Expert Committee. The aim is to ensure that CADTH reviews and the subsequent recommendations from the committee are more closely aligned with the needs of patients and their families through the incorporation of lived experiences into our work.

CADTH made attempts to connect with a suitable patient to present, however, was unable to identify an appropriate person for this review.

Calls for stakeholder feedback and respective deadlines are posted on the Open Calls for Feedback page on the CADTH website. If you have questions, please contact Requests@cadth.ca.

Stakeholder Feedback

What Did We Hear From Patients?

CADTH did not receive input from patient groups during the open call for stakeholder feedback.

What Did We Hear From Clinicians?

CADTH did not receive input from clinician groups during the open call for stakeholder feedback. The clinical experts noted that rivaroxaban has the potential to cause a shift in the treatment paradigm if reimbursed. Rivaroxaban would be used in place of LMWH or another anticoagulants, where appropriate.

What Did We Hear From the Pharmaceutical Industry?

CADTH received feedback from 1 manufacturer who supported the scope of the reimbursement review and highlighted that dabigatran should not be considered as a comparator as it does not have an approved pediatric indication from Health Canada for VTE and is not recommended by clinical guidelines in the pediatric setting.

What Did We Hear From Public Drug Programs?

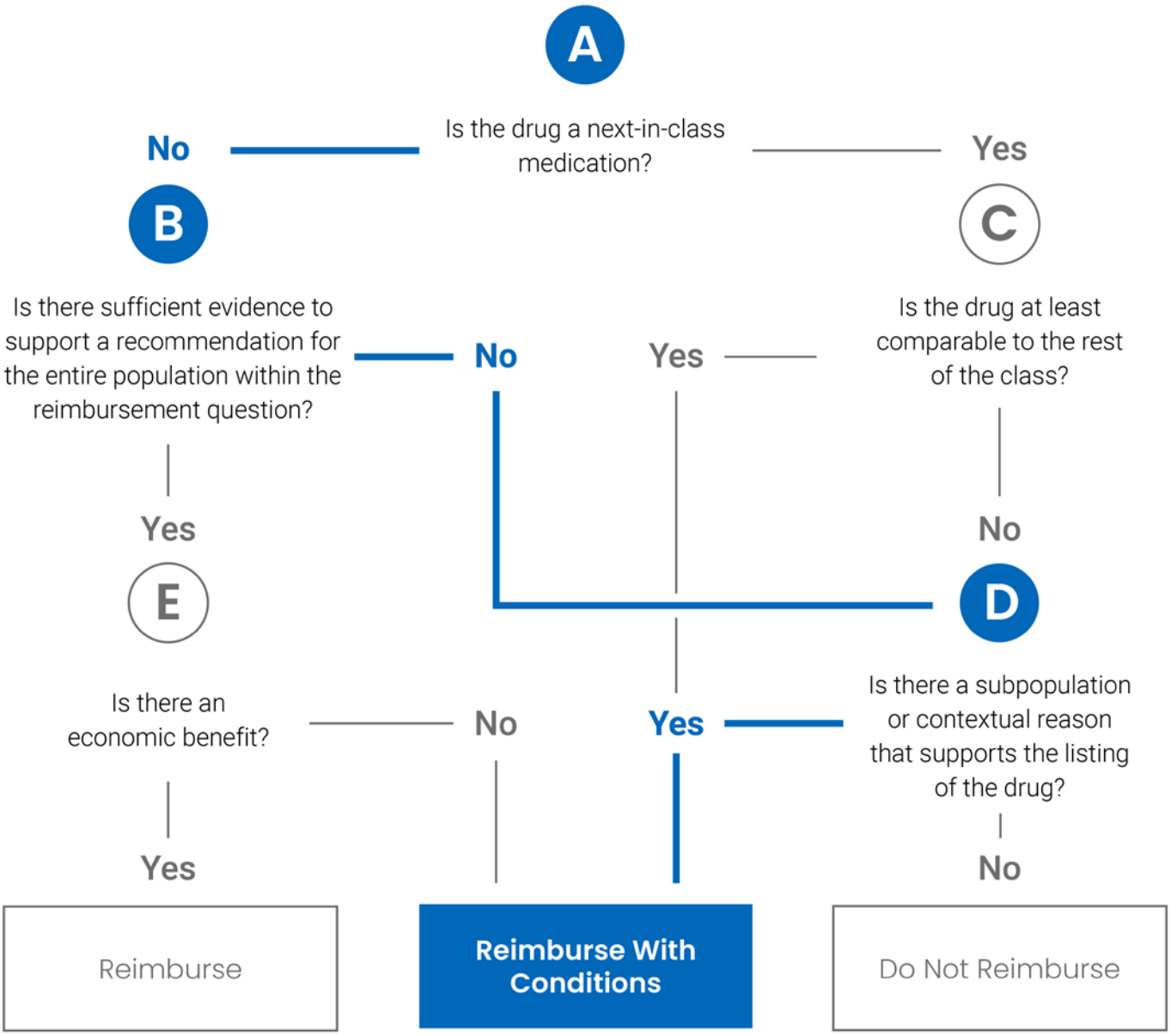
The public drug programs have requested this review as rivaroxaban availability as an oral route of administration without routine bloodwork requirement is a desirable treatment alternative for the pediatric population. They also provided input on questions related to treatment implementation.

Refer to the Stakeholder Input section of the CADTH report.

Deliberative Framework

Figure 1

Decision Path



Decision Summary

Table 1

Why Did FMEC Make This Recommendation?

Decision Node	Vote	Reason
A **Is the drug a next-in-class medication?**	**Yes (1)**	• FMEC acknowledged that there is currently no evidence to inform whether a liquid formulation of rivaroxaban can improve compliance in the treatment of VTE. FMEC also acknowledged that the availability of a liquid formulation does not necessarily meet the criterion for a next-in-class medication.
	No (6)	• FMEC noted that rivaroxaban is not a next-in-class medication. While other direct oral anticoagulants (e.g., apixaban) may be available and used in the pediatric setting, they are not available as a liquid formulation. • FMEC considered that there is a significant unmet need in the treatment of VTE in the pediatric population, especially with options that are more convenient (e.g., oral liquid formulation) and require less monitoring (e.g., no routine bloodwork requirement).
B **Is there sufficient evidence to support a recommendation for the entire population within the reimbursement question?** **Population under consideration for reimbursement:** **Patients aged < 18 years (i.e., term neonates, infants and toddlers, children and adolescents) who require treatment for VTE or prevention of VTE recurrence following ≥ 5 days of initial parenteral anticoagulation treatment**	**Yes (2)**	• FMEC considered that while the benefits of improved compliance are unclear with the oral liquid formulation, the improvement in QoL associated with fewer injections and less monitoring should not be overlooked. These benefits apply to the entire population under consideration.
	No (5)	• FMEC acknowledged that the evidence from the EINSTEIN Jr study informs the efficacy of rivaroxaban for pediatric patients with VTE as compared to LMWH. Within the EINSTEIN Jr study, the population subgroups, including pediatrics patients aged 2 or younger, and those with cancer and/or unprovoked VTE, were small and associated with greater uncertainties in the evidence. Furthermore, preterm neonates were excluded from the study. • FMEC considered the potential differences in efficacy between the oral tablet and oral liquid formulations. The bioequivalence evidence for these formulations was not part of the CADTH review that informed the FMEC deliberation. FMEC acknowledged that such information would reside with the regulatory body (e.g., Health Canada) and is considered as part of the approval requirements.

Decision Node	Vote	Reason
D **Is there a subpopulation or contextual reason that supports the listing of the drug?**	**Yes (7)**	• FMEC noted that overall, there should be greater allowance for uncertainties in special populations such as pediatrics. While ease of use and HRQoL have not been systematically evaluated in the EINSTEIN Jr trial, the easier route of administration and less monitoring requirements are important clinical considerations to support the reimbursement of rivaroxaban granules for oral suspension. • To address uncertainties in the evidence for the aforementioned subpopulation, such as preterm neonates, pediatric patients aged 2 or younger, and those with cancer and/or unprovoked VTE, FMEC discussed the need to engage a pediatric subspecialist with experience in managing anticoagulation. • FMEC noted the lower cost of rivaroxaban when compared to LMWH.
	No (0)	—

FMEC = Formulary Management Expert Committee; HRQoL = health-related quality of life; LMWH = low molecular weight heparin; QoL = quality of life; VTE = venous thromboembolism.

Full Recommendation

CADTH's FMEC recommends that rivaroxaban granules for oral suspension be reimbursed for the treatment of VTE and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents younger than 18 years old, after at least 5 days of initial parenteral anticoagulation treatment, if the conditions presented in Table 2 are met.

Table 2

Reimbursement Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Rivaroxaban granules for oral suspensions should be reimbursed for the treatment of VTE and prevention of VTE recurrence in term neonates, infants and toddlers, children and adolescents aged younger than 18 years after at least 5 days of initial parenteral anticoagulation treatment for: 1.1. pediatric patients who require anticoagulant therapy for at least 90 days, or 1.2. pediatric patients with catheter-related VTE aged younger than 2 years and requiring anticoagulant therapy for at least 30 days, or 1.3. pediatric patients younger than 6 months who require anticoagulant therapy and meet all of the following criteria: 1.3.1. gestational age at birth of at least 37 weeks, and 1.3.2. oral feeding and/or nasogastric feeding for at least 10 days, and 1.3.3. body weight of at least 2,600 g.	HC has approved the use of rivaroxaban granules for oral suspension for a broad range of pediatric populations, including neonates, infants and toddlers, and children and adolescents < 18 years. The initiation criteria of the EINSTEIN Jr trial were more limited in the studied population (e.g., excluded preterm neonates) due to the nature of conducting studies in this special population.	For specific subpopulations such as cancer-related VTE, unprovoked VTE, and children under 2 years, where there is less clinical evidence of safety, a pediatric subspecialist should be involved (refer to condition 2 — prescribing).

Reimbursement condition	Reason	Implementation guidance
Prescribing		
2. Rivaroxaban granules for oral suspension must be initiated by, or in consultation with, a pediatric hematologist or other pediatric subspecialist(s) with experience managing anticoagulation.	Given the complexities of managing thromboembolic disease in pediatric patients and uncertainties in the evidence for specific subpopulations, FMEC members agreed that prescribing of rivaroxaban should always be done in conjunction with a pediatric hematologist or other pediatric subspecialist(s) with experience managing anticoagulation.	—

FMEC = Formulary Management Expert Committee; HRQoL = health-related quality of life; HC = Health Canada; VTE = venous thromboembolism.

Feedback on Draft Recommendation

CADTH received feedback on the draft recommendation from Bayer Inc. This feedback was reviewed with additional revisions made to the recommendation. CADTH also received feedback from provincial drug plans for editorial changes.

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Alun Edwards, Ms. Valerie McDonald, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, Dr. Suzan Williams (guest specialist)

Meeting date: August 24, 2023

Conflicts of interest: None

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CADTH was established by Canada's federal, provincial, and territorial governments to be a trusted source of independent information and advice for the country's publicly funded health care systems. Health administrators and policy experts rely on CADTH to help inform their decisions about the life cycle management of drugs, devices, and services used to prevent, diagnose, and treat medical conditions.

CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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November 2023