Canada's Drug and
Health Technology Agency

CADTH Reimbursement Recommendation

Eltrombopag

Reimbursement request: In combination with immunosuppressive therapy to treat previously untreated patients with severe aplastic anemia

Final recommendation: Reimburse with conditions

Summary of CADTH Recommendation

The CADTH Formulary Management Expert Committee (FMEC) concluded that the evidence from the RACE trial on the efficacy and safety of eltrombopag in addition to immunosuppressive therapy (IST) in previously untreated patients with severe aplastic anemia (SAA) supported a reimburse recommendation in the requested population.

A cost-utility analysis was not part of the CADTH review, but FMEC acknowledged that eltrombopag plus IST is associated with incremental costs and incremental benefit compared with IST alone. FMEC noted the reduced time of transfusion dependence might generate cost savings; however, these costs were not estimated.

FMEC recommends eltrombopag in combination with IST be reimbursed in previously untreated patients with severe or very SAA if clinical conditions are met.

Therapeutic Landscape

What Is Severe Aplastic Anemia?

SAA is a rare blood disorder characterized by bone marrow hypoplasia and pancytopenia that affects approximately 2 people per million in Europe and North America. Common symptoms include weakness, fatigue, frequent infections, unexplained or easy bruising, and shortness of breath. If left untreated, it can rapidly result in end-organ complications and may eventually be fatal.

Why Did CADTH Conduct This Review?

Publicly funded drug plans requested this nonsponsored Reimbursement Review because it met the eligibility criteria outlined in the Procedures for CADTH Nonsponsored Reimbursement Reviews.

Person With Lived Experience

A person with lived experience presented their journey living with severe aplastic anemia after a diagnosis in 2020. They were treated successfully with eltrombopag for several months, with near-normal levels. However, eltrombopag was discontinued in 2021 when their blood levels fell after surgery to remove a bladder stone. They then received antithymocyte globulin and transfusion treatments, and were prescribed danazol and tacrolimus, but ultimately this regimen was not successful. They were then reintroduced to eltrombopag and had significant improvements in hemoglobin and platelet levels. They expressed that low hemoglobin levels led to cognitive challenges, such as brain fog and depression, which affected activities such as reading, exercising, and hobbies. The benefits of eltrombopag for this individual were its limited side effects and, more significantly, its positive impact on their quality of life. Eltrombopag also reduced the need for transfusions and helped alleviate brain fog, eliminating limitations in volunteering and socialization.

Stakeholder Feedback

What Did We Hear From Patients?

Fatigue, brain fog, unexplained bleeding, shortness of breath, and dizziness were among the most bothersome symptoms of SAA. Patients indicated they had constant stress from monthly blood tests, fear of relapse, and limited treatment options. Patients most valued treatments that limit long-term disease consequences. Cost was a common barrier to access to treatment.

What Did We Hear From Clinicians?

No input was received by clinician groups.

What Did We Hear From the Pharmaceutical Industry?

No input was received from the pharmaceutical industry.

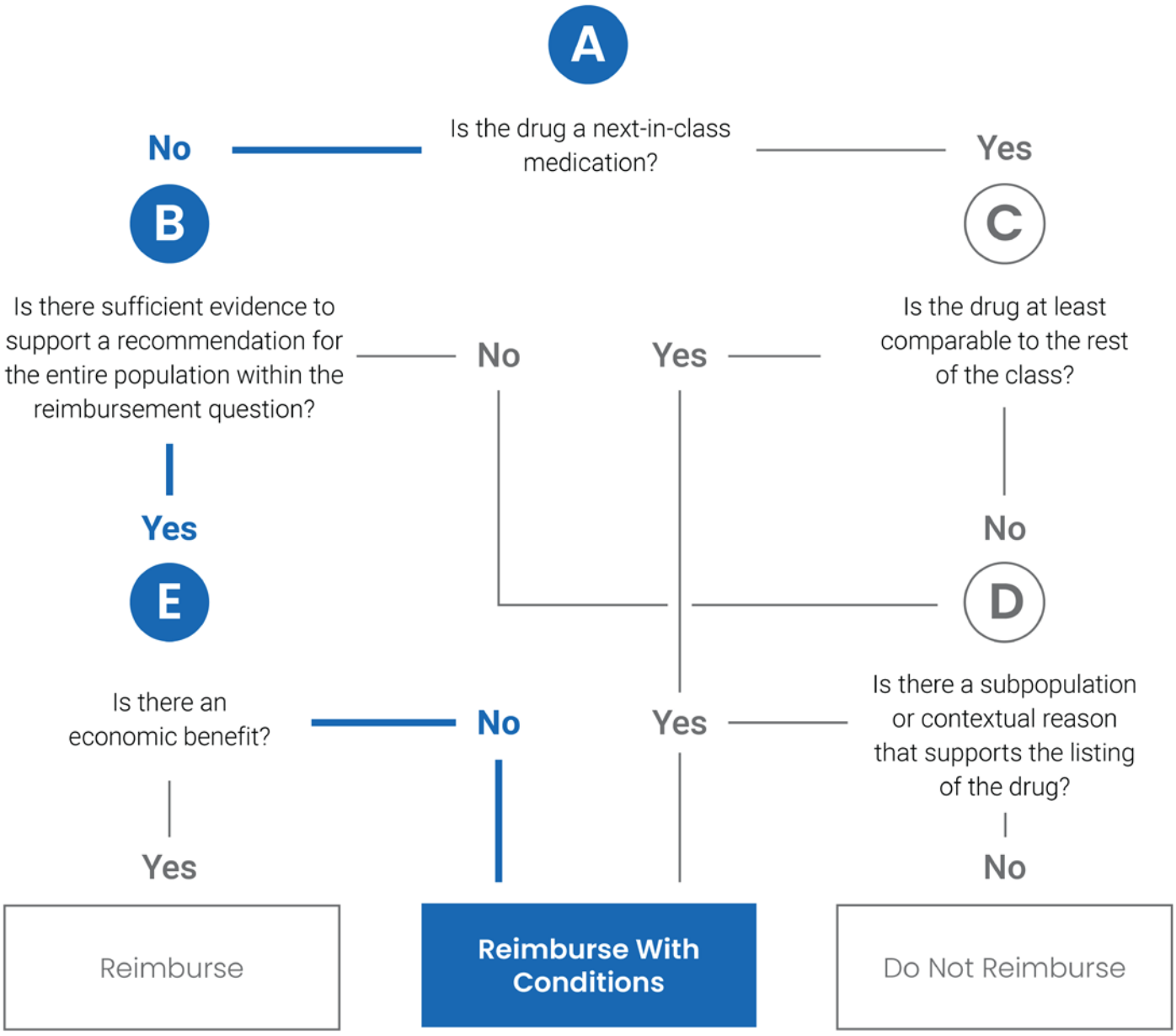
What Did We Hear From Public Drug Programs?

Public drug plans inquired about criteria for initiating therapy and considerations for treatment duration and discontinuation of therapy. Questions were asked regarding assessment of a clinically meaningful response and the time interval at which response to therapy should be assessed.

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 (0)	—
	No (7)	• FMEC noted that eltrombopag is a therapy with a unique mechanism of action that is an addition to conventional IST for SAA (rather than added to the regimen after failure of IST alone). • FMEC noted there is a significant unmet need in the treatment of SAA considering the negative impact on patient's quality of life, challenges associated with allo-HSCT, complications and challenges associated with multiple transfusions, and limited treatment options. • FMEC considered that the RACE trial demonstrated that the addition of eltrombopag to IST showed benefit in important outcomes (i.e., complete hematological response and transfusion independence) compared to available therapy (IST alone) for patients with few treatment options.
(B) Is there sufficient evidence to support a recommendation for the entire population within the reimbursement question?	Yes (7)	• FMEC considered the evidence from the RACE trial to be sufficient to support the population under consideration for reimbursement (i.e., adult population with previously untreated SAA). • Patients included in the RACE trial were 15 years and older, leaving an evidence gap for children and young adolescents. • FMEC noted the inclusion and exclusion criteria in the RACE trial generally match the clinical characteristics that direct treatment in Canadian clinical practice. • There was no evidence signal that 1 subgroup of patients may be more likely to benefit or be harmed by the addition of eltrombopag to IST. • FMEC acknowledged that long-term sustainability of reported effects, safety, and other important outcomes to patients (disease-free survival and overall survival) remain an evidence gap.
	No (0)	—
(E) Is there an economic benefit?	Yes (2)	• The cost associated with reduced transfusions were noted to potentially have health system cost savings; however, whether this completely offsets the cost of the drug funded through public drug programs is unknown. • The potential for eltrombopag to allow patients to avoid allo-HSCT, and the associated costs, is unknown. • FMEC noted that a generic form of eltrombopag is available.
	No (5)	• A cost-utility analysis was not available and was not considered as part of the scope of the reimbursement request. • In the absence of a cost-effectiveness analysis, and based on cost differences only, the addition of eltrombopag is expected to generate an incremental cost for the publicly funded drug programs. Although the reduced time of transfusion dependence might generate cost savings to the health care system, these costs were not estimated.

allo-HSCT = allogenic hematopoietic stem cell transplant; FMEC = CADTH Formulary Management Expert Committee; IST = immunosuppressive therapy; SAA = severe aplastic anemia.

Full Recommendation

CADTH FMEC recommends that eltrombopag in combination with IST in previously untreated patients with SAA be reimbursed if the conditions presented in Table 2 are met.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
Eltrombopag in combination with IST should be reimbursed in patients who meet the diagnostic criteria for severe or very severe aplastic anemia. 1. Per the RACE trial population – confirmed diagnosis of SAA or very SAA • At least 2 of the following: ◦ absolute neutrophil counts < 0.5 × 10^9/L (severe) or < 0.2 × 10^9/L (very severe) ◦ platelet counts < 20 × 10^9/L ◦ reticulocyte counts < 60 × 10^9/L (using automated counter) or < 20 × 10^9/L. • Associated with a hypocellular bone marrow (< 30% cellularity), without evidence of fibrosis or malignant cells. 2. No prior IST with cyclosporin, ATG (horse or rabbit), or any other lymphocyte-depleting agent. 3. Not planned for upfront allogeneic stem cell transplant.	Initiation criteria reflect the enrolment criteria in the RACE trial. The diagnostic criteria for SAA used in clinical practice in Canada match the criteria used in the RACE trial.	This recommendation is intended for previously untreated adult patients with SAA.
Eltrombopag should be discontinued in all patients who achieve a complete response. For patients who do not achieve at least a partial hematological response to eltrombopag plus IST at a total of 6 months, eltrombopag should be discontinued.	In the RACE trial, for patients who achieved complete response at 3 months, eltrombopag was discontinued. For patients who achieved partial response at 3 months and patients with no hematological response at 3 months, eltrombopag was continued up to 6 months at the same dose.	There may be clinical circumstances in which patients should continue treatment up to 6 months. Further suggested implementation guidance on duration of eltrombopag treatment based on clinical response can be found in the Responses to Questions From Drug Programs.

Reimbursement condition	Reason	Implementation guidance
Discontinuation		
	The clinical experts noted they consider 6 months to be the minimum duration of therapy at which to evaluate response. In this treatment setting, absence of a response before 6 months would not be interpreted as a definitive lack of response to treatment.	
Prescribing		
Limited to clinicians with expertise in the treatment of SAA.	This is a specialized population that would be under the care of a treatment team experienced in their care.	—

ATG = antithymocyte globulin; IST = immunosuppressive therapy; SAA = severe aplastic anemia.

Feedback on Draft Recommendation

CADTH received feedback on the draft recommendation from public drug programs. This feedback was reviewed, and editorial revisions were made to the recommendation.

FMEC Information

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

Meeting date: October 17, 2023

Conflicts of interest: None

Special thanks: CADTH 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 severe aplastic anemia, notably the Aplastic Anemia & Myelodysplasia Association of Canada, Cindy Anthony, and Philip Veness.

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

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