Canada's Drug and
Health Technology Agency

CADTH Reimbursement Recommendation

Eltrombopag

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

Draft 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.

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

FMEC recommends eltrombopag in combination with IST (with horse antithymocyte globulin and cyclosporine) be reimbursed in previously untreated patients with severe or very SAA, if clinical conditions are met.

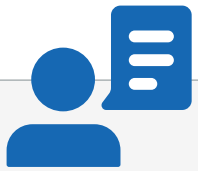
Therapeutic Landscape

What Is Severe Aplastic Anemia?

Severe aplastic anemia (SAA) is a rare blood disorder characterized by bone marrow hypoplasia and pancytopenia. Approximately 2 cases per million people 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, as it met the eligibility criteria outlined in the Procedures for CADTH Nonsponsored Reimbursement Reviews.



Person With Lived Experience

A person with lived experience presented his journey living with severe aplastic anemia after a diagnosis in 2020. He began eltrombopag successfully for several months, with near normal levels although was discontinued in 2021 when blood levels fell, following a surgery to remove a bladder stone. He then received ATG and transfusion treatments, and was prescribed danazol and tacrolimus, but ultimately this regime was not successful. He was then reintroduced to eltrombopag and had significant changes, with improvements in hemoglobin levels and platelets. He expressed that low hemoglobin levels have led to cognitive challenges like brain fog and depression, affecting activities such as reading, exercising, and hobbies. The benefit of Eltrombopag for this individual, lies not only in its limited side effects but more significantly in its positive impact on his quality of life, as well as reducing the need for transfusions. It has 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 some of the symptoms of SAA that negatively impact the patient's quality of life. Patients indicated constant stress from monthly blood tests, fear of relapse, limited treatment options. Cost was the most 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?

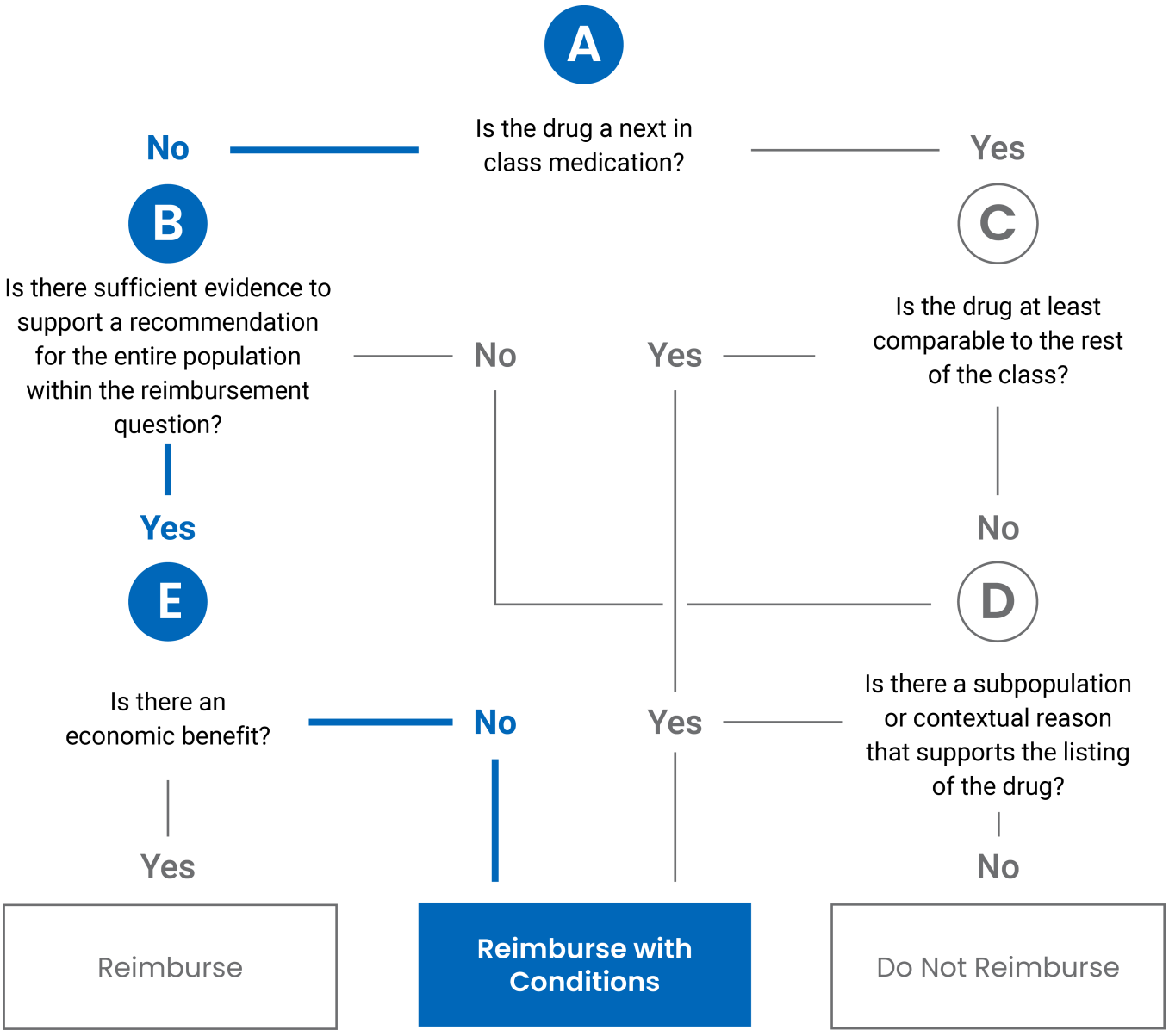
Public drug plans inquired about criteria for initiating therapy, considerations for treatment duration, and discontinuation of therapy. Questions were asked regarding assessment of a clinically meaningful response and the time interval at which response to therapy should be assessed.

Refer to 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 regime after failure of IST alone). • FMEC noted that there is a significant unmet need in the treatment of SAA considering the negative impact on patient's quality of life, challenges associated with allogenic hematopoietic stem-cell transplant (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 on 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 of age and older leaving an evidence gap for children and young adolescents. • FMEC noted that 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 one subgroup of patient 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 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.

Full Recommendation

The CADTH FMEC recommends that eltrombopag be in combination with immunosuppressive therapy in previously untreated patients with severe aplastic anemia if the conditions presented in Table 2 are met.

Table 2

Reimbursement Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
Eltrombopag in combination with IST (with horse ATG and cyclosporine) 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 severe aplastic anemia (vSAA) ◦ At least two of the following: ▪ Absolute neutrophil counts < 0.5x10^9/L (severe) or < 0.2x10^9/L (very severe) ▪ Platelet counts < 20x10^9/L ▪ Reticulocyte counts < 60x10^9/L (using automated counter) or < 20x10^9/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 matches the criteria used in the RACE trial.	The intended use of this recommendation is for previously untreated adult patients with SAA.
Discontinuation		
Eltrombopag should be discontinued in all patients who achieve a complete response.	In the RACE trial, for patients who achieved complete response at 3 months, eltrombopag was discontinued. For patients achieving partial response at 3 months and for patients with no hematological response at 3 months, eltrombopag was continued up to 6 months at the same dose.	There may be clinical circumstances for which patients should continue treatment for up to 6 months. Further suggested implementation guidance on duration of eltrombopag based on clinical response can be found in the *Responses to Questions from Drug Programs*.

Reimbursement condition	Reason	Implementation guidance
	The clinical experts noted that 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 who would be under the care of a treatment team experienced in their care.	–

ATG = anti-thymocyte globulin; CR = complete response; IST = immunosuppressive therapy; PR = partial response; SAA = severe aplastic anemia.

Feedback on Draft Recommendation

< to be updated following the stakeholder feedback period >.

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, patient organizations representing the community of those living with severe aplastic anemia.

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Health Technology Agency

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.

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November 2023