Canadian Journal of Health Technologies
May 2024 Volume 4 Issue 5

CADTH Reimbursement Recommendation

Avatrombopag (Doptelet)

Indication: For the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

Sponsor: Sobi Canada, Inc.

Final recommendation: Do not reimburse

Summary

What Is the Reimbursement Recommendation for Doptelet?

We recommend that Doptelet not be reimbursed by public drug plans for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP).

Why Did We Make This Recommendation?

- Evidence from 1 clinical trial showed that Doptelet improved patients' platelet counts after 6 months of treatment; however, it is not known whether Doptelet can reduce bleeding occurrence, reduce the use of other therapies for ITP used concomitantly with Doptelet, improve symptoms, or improve health-related quality of life when compared to placebo. In addition, evidence from 1 indirect treatment comparison study showed that the comparative efficacy of Doptelet to other established treatments for chronic ITP remains unknown.
- Patients identified a need for treatments that can reduce the risk of bleeding and improve their quality of life. However, there was not enough evidence to show that Doptelet would meet this need.

Additional Information

What Is Chronic Immune Thrombocytopenia?

Chronic ITP is a long-term condition in which the immune system destroys platelets in the blood, which are necessary to help form blood clots and to stop bleeding. Patients with ITP have low platelet counts, fatigue, bruising, and can bleed easily. It is estimated that approximately 10 in 100,000 people living in Canada have chronic ITP.

Unmet Needs in Chronic Immune Thrombocytopenia

Not all patients with chronic ITP respond to available therapies; even if remission is achieved, long-term remission is not guaranteed. There is a need for treatments that are effective, accessible, easy to administer, and have a low risk of adverse effects.

How Much Does Doptelet Cost?

Treatment with Doptelet is expected to cost $41,975 if patients remain on a 20 mg once-daily dose for a full year.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that avatrombopag not be reimbursed for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

Rationale for the Recommendation

CDEC was unable to determine whether treatment with avatrombopag resulted in a comparable benefit on clinical outcomes relative to other treatments for ITP currently used in clinical practice in Canada. One phase III, multicentre, double-blind, randomized controlled trial (RCT) (Study 302; N = 49) demonstrated that treatment with avatrombopag improved platelet count response among adult patients with chronic ITP compared to placebo. However, the magnitude of clinical benefit relative to placebo in terms of lowering bleeding rates, reducing the use of concomitant ITP medications, reducing the need for rescue therapy, and increasing symptom relief was highly uncertain due to the small sample size, lack of control for multiple statistical testing, imbalanced patients' characteristics at baseline, and high dropout rate. CDEC also acknowledged that there are a variety of other treatments currently used for ITP; Study 302 compared avatrombopag to placebo and not to other currently available therapeutic options for ITP. Although the sponsor submitted an indirect treatment comparison (ITC) with thrombopoietin receptor agonists (TPO-RAs) and rituximab, the limitations associated with the ITC precluded definitive conclusions. Overall, the comparative efficacy of avatrombopag to other established treatment options for chronic ITP remains unknown.

Patients identified a need for additional therapeutic options that can reduce their risk of bleeding and improve their quality of life. They also value therapies that would be more convenient, have fewer side effects, and have longer-lasting efficacy relative to existing treatment options. Patients are also seeking options that they can access if their current therapy no longer works. With the evidence reviewed for avatrombopag, CDEC was uncertain if these needs would be met.

Discussion Points

- The sponsor requested a reconsideration of the initial draft recommendation to not reimburse avatrombopag for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment. There were 3 issues outlined by the sponsor in the request for reconsideration that were discussed by CDEC. The first issue was the sponsor indicated that CDEC mischaracterized treatment availability for chronic ITP in Canada, the second issue was the sponsor noted that the treatment goals for chronic ITP in the recommendation are misrepresented, and the third issue was the sponsor indicated that the benefit of avatrombopag is understated in the CDEC recommendation.

- There was uncertainty with the clinical evidence; therefore, the committee deliberated on avatrombopag considering the criteria for significant unmet need that are described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. CDEC acknowledged the rarity of this condition; however, because there are other treatment options currently available, some of which are reimbursed in certain jurisdictions, CDEC concluded that the criteria allowing for additional uncertainty in the evidence were not met.
- During the initial and reconsideration meetings, CDEC recognized that bleeding is considered an important outcome in the treatment of ITP by clinicians and patients. CDEC recognizes that platelet count is a commonly used and clinically accepted surrogate marker for the clinical assessment of risk for bleed and patient response to treatment. There remains uncertainty in the relationship between platelet count threshold and bleeding risk in this patient population. CDEC also noted that the effect of avatrombopag on the outcomes identified as important to patients and clinicians, such as bleeding events, use of concomitant ITP medications, and health-related quality of life (HRQoL), were associated with substantial uncertainty, and CDEC was unable to determine the effect of avatrombopag on these outcomes.
- During the reconsideration meeting, CDEC discussed that TPO-RAs are reimbursed on a case-by-case basis in several jurisdictions, hence other treatment options are currently available. CDEC also noted that the patient group input highlighted the difficulties and inconsistencies with access to TPO-RAs as a significant issue.
- During the reconsideration meeting, CDEC noted that platelet counts, albeit used in practice and a defined goal of therapy, do not predict with certainty the bleeding risk for an individual patient. In addition, patients with ITP treated with avatrombopag resulting in increased platelet counts did not have a reduction in bleeding complications. CDEC also noted that severe bleeding complications in patients with ITP are considered rare; complicating this assessment of risk using the surrogate outcome of platelet count is challenging because bleeding risk is rarely related to any distinct threshold in platelet count.
- During the reconsideration meeting, CDEC discussed that the potential benefits of avatrombopag are acknowledged, and that patient and clinician groups identified the advantage of adding a third TPO-RA approved for use in patients with ITP in Canada. Although avatrombopag does potentially provide greater convenience to clinicians and patients (oral administration, no dietary restrictions, reduced liver adverse events [AEs]), it should be equally acknowledged that there is a lack of head-to-head comparative evidence with the other TPO-RAs; hence, the absence of comparative trials precludes an evaluation and balance of the aforementioned potential benefits of avatrombopag with efficacy and safety outcomes compared with romiplostim and eltrombopag. CDEC also noted that there is limited evidence regarding switching between TPO-RAs after treatment failure or intolerance. In addition, differentiation between agents within the class does not impact the overall assessment of the target clinical outcome (bleeding) common to all agents in the class.
- During the reconsideration meeting, CDEC discussed that conducting a systematic review of the treatments of adult patients with immune thrombocytopenia after the failure of first-line therapies,

including avatrombopag, could provide, if implemented, valuable information for drug programs in managing their exceptional access criteria.

Background

ITP is an autoimmune disorder characterized by low platelet counts and increased bleeding risk. Chronic ITP refers to symptoms that persist for more than 12 months after diagnosis. In Canada, the prevalence of ITP is estimated to be 9.5 per 100,000 people, and the incidence is estimated to be 1.6 per 100,000 persons per year to 3.9 per 100,000 persons per year. Approximately 76% of all patients with ITP in Canada have primary ITP, which is not triggered by a specific condition or event.

Patients with ITP may be asymptomatic, but sometimes bleeding can be more severe or critical, such as intracranial hemorrhage or gastrointestinal bleeding. Severe or critical bleeding is a major concern among patients with ITP. The rate of fatal hemorrhage among patients with ITP has been estimated to be between 0.016 per patient-year and 0.039 per patient-year, and this rate increases with age. Patients with ITP have reduced quality of life, resulting from fatigue, bleeding, and ITP treatments.

The main goals of therapy in ITP are to prevent severe or critical bleeding, reduce or eliminate patients' symptoms, minimize adverse effects from treatments, and ultimately improve patient quality of life. There are no specific treatment guidelines for ITP in Canada. American and International guidelines recommend that for initial treatment of newly diagnosed ITP, corticosteroids or IV immune globulin be used as first-line therapy. There are multiple second- and third-line treatments available for ITP in patients who experience a relapse, such as splenectomy, rituximab, TPO-RAs (e.g., romiplostim or eltrombopag), fostamatinib, and immunosuppressants. The choice of treatment should be individualized based on severity of disease, comorbidities, age, medical and social support networks, patient values and preferences, as well as access (such as cost and availability).

Avatrombopag (20 mg per tablet) is an orally bioavailable, small molecule TPO-RA that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells, resulting in an increased production of platelets. Avatrombopag is indicated for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment. It is recommended that avatrombopag be initiated at a starting dose of 20 mg once daily. Dose adjustments are based on platelet count response. The maximum daily dosage for avatrombopag is 40 mg (2 tablets).

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 RCT (Study 302) in patients with chronic ITP who had received previous ITP treatment and had a baseline platelet count less than 30×10^9/L
- a review of 1 sponsor-submitted ITC

- a review of 2 phase II RCTs (Study 003 and Study 004) and 1 retrospective observational study of adult patients with chronic ITP that provided supportive evidence to the pivotal trial
- patients perspectives gathered by 1 patient group, the Platelet Disorder Support Association (PDSA)
- input from public drug programs that participate in our review process
- input from 1 clinical specialist with expertise diagnosing and treating patients with ITP
- input from 1 clinician group, the Canadian Hematology Society (CHS)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- Information submitted as part of the sponsor's request for reconsideration (described subsequently)
- stakeholder feedback on the draft recommendation.

Stakeholder Perspectives

Patient Input

One response to our call for patient input for the avatrombopag submission was received: a submission from PDSA, which is a nonprofit provides advocacy, education, research, and support for patients with ITP in the US and Canada. Nine comments from patients regarding their experience with avatrombopag were gathered from PDSA's ITP support group Facebook page. The patients reported experiencing an increase and/or stabilization in platelet counts and few side effects while on avatrombopag.

PDSA noted that patients with ITP face a complex set of challenges due to the heterogeneity of ITP's pathophysiology and disease course. Living with ITP can be difficult and unpredictable despite several available therapies with different mechanisms of action. In addition to the risk of life-threatening bleeding, patients with ITP may experience elevated levels of fatigue, anxiety, depression, physical pain, and sleep disturbances. PDSA noted that the goal of treatment is to have an increase in platelet counts which reduces the risk of bleeding while improving patients' quality of life. The input indicated that many currently available treatments have a high burden of toxicity and that that avatrombopag is more convenient to use than attending a clinic or doctor's office for a weekly injection, taking high-dose steroids that cause mood issues and physical side effects, or having a splenectomy. PDSA also suggested that avatrombopag should be available as an alternative treatment option for patients who do not respond or stop responding to another TPO-RA.

Clinician Input

Clinical Expert Input

The clinical expert indicated that not all patients respond to available therapies and, even if remission is initially achieved, long-term remission is not guaranteed. For those currently available treatments, challenges exist in terms of accessibility, reimbursement criteria, costs, ease of administration, and adverse effects or complications related to the treatment.

Given the lack of comparative efficacy data, the influence of patient-specific factors on decisions, and the current reimbursement landscape, it is challenging to identify the optimal place in the therapeutic algorithm for avatrombopag. The clinical expert stated that the safety profile of avatrombopag and the fact that it is administered orally suggest it might be considered a reasonable second-line therapy. Regardless of where it sits in the therapeutic algorithm, however, the addition of avatrombopag as a treatment option would be advantageous for clinicians to have for specific patients.

The expert noted that it is difficult to determine which specific patients will respond best to avatrombopag and which would be most susceptible to the adverse effects. However, the clinical expert agreed that having avatrombopag as an option for patients would be desirable, regardless of where they are in their disease course.

In practice, clinicians rely on platelet response to monitor disease severity and assess treatment effect. In general, an increase in platelet count can be seen as early as 2 weeks into treatment with avatrombopag. If a response is observed, clinicians would likely continue to use the treatment long term with monthly monitoring. A sustained response would generally be considered a platelet count of 30,000/μL to 50,000/μL for the duration of a treatment cycle (e.g., 24 weeks). If a response has not been seen by approximately 12 weeks, clinicians would generally consider that the treatment has not worked and would discontinue it. If there are issues related to safety or tolerability, treatment would generally be discontinued earlier, particularly if it is affecting a patient's quality of life.

Clinician Group Input

One clinician representing the CHS provided input for this review. The information was gathered from the perspectives of Canadian hematologists as well as a review of the literature and current clinical practice guidelines.

In general, this input was not contrary to the 1 provided by the clinical expert we consulted. The input stated that it is vital to improve the quality of life of patients by balancing bleeding prevention and minimizing treatment toxicities. Among the patients with ITP, the greatest unmet need is for those who have persistent or chronic ITP. Such patients require additional treatments after first-line therapy because of continued or recurrent severe thrombocytopenia, which is linked to increased risk of bleeding. Avatrombopag is 1 of the TPO-RAs and nonimmunosuppressant. The input suggested that patients in the earlier stage of their disease course would have better response to avatrombopag. Therefore, if it is used as a second-line therapy, the patient will benefit from a more favourable response and limited exposure to the complications and toxicities of other lines of therapy, such as a splenectomy, which has associated surgical complications and long-lasting immunosuppression, or rituximab, which can cause immunosuppression and vaccine failures, For patients who experience multiple relapses or refractory disease, avatrombopag may fill the gap because other TPO-RAs are not currently available and avatrombopag has more favourable bioavailability and less hepatic toxicities compared to eltrombopag.

The clinician group input indicated that, in practice, a clinically meaningful response would be to achieve and maintain a platelet count greater than 30×10^9/L. This would be correlated with a negligible risk of serious

bleeding, improved quality of life, less fatigue, and avoidance of hospitalization or fewer clinic visits for most patients.

Drug Program Input

Input was obtained from the drug programs that participate in the Reimbursement Review process. The following were identified as key factors that could potentially affect the implementation of a recommendation for avatrombopag:

- considerations for initiation of therapy
- considerations for discontinuation of therapy
- generalizability of trial populations to the broader populations in the jurisdictions.

The clinical experts we consulted provided advice on the potential implementation issues raised by the drug programs.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Study 302 (N = 49) was a multicentre, phase III, double-blind RCT that evaluated the efficacy and safety of avatrombopag versus placebo in patients with chronic ITP who had received previous ITP treatment and had a baseline platelet count less than 30 × 10^9/L. Study 302 consisted of 3 phases: prerandomization, randomization (core phase), and extension. The prerandomization phase had a screening period of up to 4 weeks. The randomization phase (core phase) had 6 periods and lasted for 26 weeks. Patients who met all the eligibility requirements and who were willing and able entered the extension phase. Patients who discontinued the core phase early because of lack of treatment effect remained eligible to continue into the extension phase; all patients who entered the extension phase had a starting dose of 20 mg avatrombopag. During the core phase, 32 patients were randomized to avatrombopag 20 mg (starting dose) and 17 to a matching placebo. The primary efficacy end point was cumulative number of weeks of platelet response (platelet count 50 × 10^9/L or higher) without rescue therapy for bleeding.

In Study 302, the baseline age was similar in both groups (avatrombopag: median = 45 years; placebo: median = 43 years); there were more females in the avatrombopag group (avatrombopag: male = 28%, female = 72%; placebo: male = 53%, female = 47%). The vast majority of patients were white in both groups (avatrombopag: Chinese = 3%, white = 97%; placebo: Black or African American = 6%, Chinese = 6%, white = 88%). More patients in the avatrombopag group had a prior splenectomy compared to patients in the placebo group (34% versus 29%). The baseline platelet count was higher in the avatrombopag group than the placebo group (12.5 × 10^9/L versus 9.5 × 10^9/L). More patients in the avatrombopag group received prior ITP medications or were taking concomitant ITP medications at baseline compared to patients in the placebo group (prior ITP medications: 47% versus 35%; concomitant ITP medications: 47% versus 41%).

Efficacy Results

In Study 302, the incidence of any bleeding event during 6 months of treatment in the core phase was 43.8% in the avatrombopag group and 52.9% in the placebo group. This was an exploratory outcome, and the between-group difference was not statistically significant. No patients in the placebo group had a bleeding event that was higher than WHO Grade 1. There were 2 patients in the avatrombopag group who had WHO Grade 2 bleeding events and 1 patient in the avatrombopag group who had a WHO Grade 3 bleeding event (epistaxis). In the combined core phase and extension phase, 3 patients in the avatrombopag group reported Grade 3 or 4 bleeding events.

The results of Study 302 also showed that treatment with avatrombopag for 6 months led to a favourable platelet response compared to placebo. According to the clinical expert, the following between-group differences in platelet response can be considered clinically important:

- Median cumulative number of weeks with platelet count 50 × 10^9/L or higher: 12.4 weeks (range, 0 to 25 weeks) in the avatrombopag group versus 0 weeks (range, 0 to 2 weeks) in the placebo group (P < 0.0001).
- Proportion of patients with a platelet count 50 × 10^9/L or higher at day 8: 21 patients (65.63%) in the avatrombopag group versus 0 patients in the placebo group (between-group difference = 65.63%; 95% confidence interval [CI], 49.17% to 82.08%; P < 0.0001).
- Durable platelet response rate, defined as the proportion of patients who had at least 6 of 8 weekly platelet responses during the past 8 weeks of treatment over the 6-month treatment period in the absence of rescue therapy was 34.38% (11 of 32 patients in the avatrombopag group and 0 in the placebo group). The between-group difference between avatrombopag and placebo was 34.38% (95% CI, 17.92% to 50.83%). However, durable platelet response was an exploratory outcome and should be interpreted with consideration for the increased possibility of false-positive conclusions.
- The median platelet count of the avatrombopag group appeared to be higher than that of the placebo group over the 6-month core phase starting from day 8; platelet response in the core phase was generally maintained throughout the extension phase up until approximately week 36.

The treatment effect of avatrombopag on improving patients' HRQoL, reducing the use of concomitant ITP medications or need for rescue therapy, or reducing emergency department visits and/or hospitalizations due to thrombocytopenia episodes compared with placebo remain uncertain.

- Patients who needed rescue therapy: 7 of 32 patients (21.9%) in the avatrombopag group versus 2 of 17 patients (11.8%) in the placebo group (P = 0.4668).
- Reduction in use of concomitant ITP medication: 5 of 15 patients (33.3%) in the avatrombopag group versus 0 of 7 patients in the placebo group (P = 0.1348).

Due to the high discontinuation rate in the study and the low event rates for some outcomes (e.g., HRQoL, hospitalizations or emergency department visits), it was not possible to assess whether there were any differences between treatment with avatrombopag and placebo in the study population. It was also challenging to base treatment decisions or draw meaningful conclusions from subgroup analyses.

A post hoc analysis of Study 302 was performed to provide additional information related to treatment with avatrombopag. The results suggested that during the open-label extension phase, response (defined as platelet count ≥ 50 × 10^9/L) was achieved at 96.1% of the extension phase visits and complete response (defined as platelet count ≥ 100 × 10^9/L) was achieved at 60.1% of extension phase visits. Durable response (defined as platelet count ≥ 30 × 10^9/L for 6 of the final 8 weeks of the core study) was reported by 64.0% of patients in the avatrombopag group and 0% in the placebo group. In addition, in the core and extension study periods, more than half of patients who needed corticosteroids at baseline reduced or discontinued corticosteroid therapy.

Harms Results

During the core phase, there were 31 patients (96.9%) in the avatrombopag group and 10 patients (58.8%) in the placebo group who reported any AEs. Patients in the avatrombopag group reported higher-grade AEs compared to those in the placebo group. There were 6 patients (18.8%) in the avatrombopag group who reported a grade 3 or 4 AE compared to none in the placebo group. The most commonly reported AEs were headache, contusion, upper respiratory tract infection, arthralgia, epistaxis, fatigue, gingival bleeding, and petechiae.

There were 9 patients (28.1%) in the avatrombopag group and 1 patient (5.9%) in the placebo group who reported any treatment-emergent serious adverse events (SAEs). There were 3 patients (9.4%) in the avatrombopag group and none in the placebo group who reported AEs leading to discontinuation of study drug (cerebrovascular accident, headache, and polyserositis). No deaths were reported during the study.

For notable harms, in the avatrombopag group, 3 patients (9.4%) reported thromboembolic events, 1 patient (3.1%) reported neoplastic events, and 1 patient (3.1%) reported recurrence of thrombocytopenia. No patients in the placebo group reported treatment-emergent adverse events (TEAEs) of special interest.

The incidences of AEs, SAEs, and AEs leading to discontinuation of study drug during the extension phase were similar to those reported in the avatrombopag group during the core phase.

Critical Appraisal

Internal Validity

Study 302 was a small, phase III, double-blind, placebo-controlled RCT. Some relatively large baseline imbalances between groups were observed, which suggests selection bias but is likely the result of the small sample of patients randomized. The degree to which this may affect data interpretation or bias the results is unclear. The rate of study discontinuation was high in Study 302 and was imbalanced between treatment groups: 22% of patients in the avatrombopag group and 88% of patients in the placebo group withdrew from the study because of inadequate therapeutic effect. The median exposure duration in the placebo group was much shorter than in the avatrombopag group. This affected the assessment of the clinically relevant outcomes of bleeding events and rescue medication. The high dropout rate also had a substantial impact on patient-reported outcomes, such as HRQoL. For example, at the end of the core phase, only 1 patient in the placebo group provided data for the 36-item Short-Form Health Survey (SF-36) and EQ-5D; therefore, it is not

possible to draw meaningful conclusions about the effect of the study drug on patients' HRQoL due to the limited data because of study discontinuation.

In practice, platelet count is considered a surrogate for the risk of bleeding events and survival, although previous research suggests that the relationship between bleeding events and platelet count is not well known. Gains from the number of weeks with platelet response may be correlated to a reduction in the risk of bleeding or improved quality of life in the study population. In Study 302, the cumulative number of weeks with a platelet count of 50 × 10^9/L or higher was the primary outcome measure. According to the clinical expert we consulted, a threshold of 30 × 10^9/L or lower is used by clinicians to determine treatment response and the risk of subsequent bleeding. This is consistent with recommendations from clinical practice guidelines which indicate that treatment should maintain a target platelet level of at least 20 × 10^9/L to 30 × 10^9/L for symptomatic patients. In Study 302, a platelet response threshold of 50 × 10^9/L was used to assess the treatment effect in patients with ITP. Additionally, there were limited or no data on patient-important outcomes, such as bleeding rates, use of concomitant ITP medications, need for rescue therapy, symptoms, and HRQoL.

According to the baseline patient characteristics, the patient population in Study 302 is broadly comparable to patients with ITP in Canada, thus the study findings are likely generalizable to Canada. One challenge with Study 302 is that the comparator was placebo. For patients with chronic ITP whose platelet counts are less than 20 × 10^9/L, treatment would be warranted. However, Study 302 provides no information about how the efficacy and safety of avatrombopag may differ from other available treatments. In addition, patients could receive some allowed concomitant ITP therapies; however, the study was not designed to assess the role of any combination therapy (e.g., avatrombopag in combination with corticosteroids); therefore, the effect of any combination therapy is uncertain.

Indirect Comparisons

Description of Studies

The sponsor submitted a systematic review and ITC report in which avatrombopag was compared to 2 TPO-RAs (eltrombopag and romiplostim), fostamatinib, and rituximab in patients with chronic or persistent ITP.

In this ITC, durable platelet response, need for rescue therapy, use of concomitant ITP medications, bleeding events, WHO Grade 2 to 4 bleeding events, and AEs were assessed. The network meta-analyses (NMAs) were conducted within a Bayesian framework.

Nine RCTs were included and contributed evidence. In the trials included in the ITC, the number of enrolled patients ranged from 11 to 135. According to the patients' baseline characteristics presented in the report, differences were observed for the proportion of patients who had undergone a splenectomy (range, 0% to 50%), the proportion of patients who used concomitant ITP medication at baseline (range, 13% to 48%), and the duration of ITP since the initial diagnosis (median duration of ITP ranged from 0.25 years to 8.7 years) across trials. There was noticeable between-trial heterogeneity in the proportion of patients who prematurely discontinued their allocated treatment (range, 0% to 100%).

Efficacy Results

In the sponsor-submitted ITC, results for durable platelet outcome, need for rescue therapy, use of concomitant ITP medication, and higher-grade bleeding events were very imprecise, with credible intervals including the potential for no difference between treatments or for either treatment to be favoured. Avatrombopag was favoured over eltrombopag, romiplostim, and rituximab for incidence of any bleeding events.

Harms Results

Results of the NMA for AEs were very imprecise with credible intervals including the potential for no difference between treatments or for either treatment to be favoured.

Critical Appraisal

In the sponsor-submitted ITC, trial characteristics and patients' baseline characteristics in the studies included in the systematic review and ITC were reported. Based on the data presented, potential sources of heterogeneity regarding baseline characteristics were identified, such as the proportion of patients who had undergone a splenectomy, proportion of patients who used concomitant ITP medication at baseline, and duration of chronic ITP since initial diagnosis. Other patient characteristics should also be considered when addressing clinical heterogeneity across the included trials, such as cycles and doses of prior corticosteroid therapy, previous lines of therapy, and severity of previous bleeding events. These data were not provided in the ITC, and from the available data, it appears likely that the transitivity assumption was violated. In addition, there was significant between-trial heterogeneity in the proportion of patients who prematurely discontinued the allocated treatment, which would have an impact on the total exposure time of the study drug in the included trials and could affect the results for relative efficacy and safety, for example, by decreasing the chance of bleeding events or AEs in the placebo group. However, the authors of the ITC adjusted for this by summarizing the data using incidence rate ratios, which accounted for the duration of exposure. The definitions of durable platelet response and bleeding episodes were measured using different approaches. The inconsistency in outcome definitions could bias the comparisons across the trials. Due to the small evidence base and potential heterogeneity across all trials, the results of NMA were largely noninformative due to imprecision.

Other Relevant Evidence

Description of Studies

Two additional studies were included in the sponsor's submission that provided supportive evidence regarding the safety and efficacy of avatrombopag. Study 003 was a phase II, double-blind, placebo-controlled randomized trial of avatrombopag taken orally once daily for 28 days in adult patients with chronic ITP. Five patients were randomized to the placebo group and 15 to the avatrombopag 20 mg/day group. Two patients discontinued the trial, both in the avatrombopag group due to an increase in their platelet count to 500 × 10^9/L or greater.

Study 004 was a phase II, long-term extension study, with avatrombopag administered for an additional 6 months in patients with chronic ITP who completed Study 003. A total of 53 patients enrolled into Study

004; 13 of these patients had received the maximum 20 mg/day dosage in Study 003 (10 with a previous platelet response and 3 without a previous platelet response in Study 003). Four of these patients (30.8%) discontinued Study 004, 2 from each group, with each patient discontinuing for a different reason.

A retrospective observational study assessing the effect of patients switching from other TPO-RAs to avatrombopag was provided by the sponsor, to provide evidence for patients with chronic ITP who had been heavily treated. In this study, the median duration of avatrombopag exposure was 9.2 months (range, 2.8 to 17.2).

Efficacy Results

In Study 003, 80% of patients (n = 12) in the avatrombopag group and no patients in the placebo group had a platelet response on day 28. Platelet response was defined as a platelet count of at least 50 × 10^9/L on day 28 if the patients' baseline platelet count was less than 30 × 10^9/L, or if there was an increase from baseline of at least 20 × 10^9/L for patients receiving steroids whose baseline platelet count was at least 30 × 10^9/L but less than 50 × 10^9/L. The median change in platelet count from baseline to day 28 was 84 × 10^9/L (range, −10 × 10^9/L to 1,012 × 10^9/L) in the avatrombopag group and −2 × 10^9/L (range, −12 × 10^9/L to 9 × 10^9/L) in the placebo group. No patients in the placebo group had a platelet count of 50 × 10^9/L or greater on day 28, while in the avatrombopag group, 12 patients (80%) and 8 patients (53.5%) had a platelet count of 50 × 10^9/L or greater and 100 × 10^9/L or greater on day 28, respectively. Using the last observation carried forward method, 13 patients (86.7%) in the avatrombopag group and 1 patient (20%) in the placebo group had their platelet count at least doubled on day 28.

The median change in platelet count from baseline in Study 003 to week 24 in Study 004 was 124 × 10^9/L (range, −11 × 10^9/L to 205 × 10^9/L) among patients with previous platelet response (n = 7) and 199 × 10^9/L (range, not applicable) among patients without a previous platelet response (n = 1). At week 24, 6 patients with previous platelet response (86.7%) and 1 without previous platelet response (100.0%) had a response-level platelet count, respectively. A total of 6 patients with previous platelet response (60.0%) and 1 without previous platelet response (33.3%) had a durable platelet response. Of the 6 patients with previous platelet response and 1 without previous platelet response who were initially also treated with corticosteroids, 2 patients with previous response (33.3%) and 1 without previous response (100.0%) permanently discontinued steroid use during the last 8 weeks of treatment in Study 004.

The results of the retrospective study (N = 44) suggested that after switching from other TPO-RAs to avatrombopag, 41 patients (93%) had a platelet response and 38 patients (86%) had a complete platelet response (defined as platelet count ≥ 100 × 10^9/L and in the absence of bleeding). Among the patients with platelet response, the response was maintained for 84% of their time on treatment. Among the patients who received concomitant ITP medications, 57% discontinued 1 or more concomitant medications after initiating avatrombopag. For patients who were taking concomitant corticosteroids, 63% discontinued the corticosteroids and 32% reduced their dose. Rescue therapy was required in 21% of patients after switching to avatrombopag compared to 34% of patients who required rescue on eltrombopag or romiplostim in the year before switching.

Harms Results

Safety results were presented for the combined study periods in Study 003 and Study 004. All 20 patients in the mean daily dose group of 13.5 mg or higher experienced at least 1 TEAE. The most common TEAEs were fatigue, headaches, and epistaxis, each of which occurred in 8 patients (40.0%). A total of 3 patients (15.0%) withdrew due to an AE. Three patients reported at least 1 SAE, including 2 patients who experienced serious recurrent thrombocytopenia. No deaths occurred throughout the studies.

Critical Appraisal

Study 003 had patients centrally randomized to treatment groups using simple block randomization (block size of 13) without stratification factors. Patients and study personnel involved in patient care or outcome assessment were blinded to treatment; the sponsor noted no partial unblinding at the time of the database lock. Therefore, the findings are unlikely to be affected by bias due to deviation from the intended interventions or measurement of the outcome. The study was not powered to detect statistically significant changes in outcomes, and analyses were not adjusted for multiplicity; therefore, definitive conclusions cannot be drawn. Study 004 enrolled patients who successfully completed Study 003; this may have resulted in a population of patients who were more tolerant of avatrombopag, which could lead to biased estimates of efficacy and safety. The use of concomitant steroid medications among patients throughout the study may have increased the risk of observing additional side effects not attributable to avatrombopag alone. In terms of external validity, doses of avatrombopag administered to some patients throughout the studies were less than the recommended starting dose of 20 mg/day approved by Health Canada, which limits the generalizability of the results. There was no examination of HRQoL outcomes in either study, which were deemed to be important to both patients and clinical experts.

Although findings of the retrospective observational study suggested that switching to avatrombopag was associated with increased platelet response and reduced concomitant ITP medications in patients who had been treated with prior TPO-RAs, the outcomes are limited by concerns with the internal validity, specifically in terms of the retrospective observational study design, lack of comparator, and small sample size. Concerns with external validity included generalizability of the study findings to the patient population in Canada.

Economic Evidence

Cost and Cost-Effectiveness

Table 1: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with chronic ITP that has had an insufficient response to a previous treatment
Treatment	Avatrombopag
Dose regimen	20 mg once daily initially, with dose adjustments made based on platelet counts that could lead to a minimum recommended dosage of 20 mg once weekly and a maximum recommended dosage of 40 mg daily
Submitted price	Avatrombopag, 20 mg tablet: $115.00
Treatment cost	$41,975 if patients remained on a 20 mg once-daily dose for a full year
Comparators	Eltrombopag Romiplostim Rituximab Watch and rescue, consisting of no active treatment Scenario analysis: small molecule drugs consisting of azathioprine, cyclosporine, cyclophosphamide, mycophenolate, danazol, dapsone
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (56 years)
Key data source	Study 302, a phase III, randomized, double-blind trial (avatrombopag vs. watch and rescue); sponsor's submitted NMA (response rates for avatrombopag vs. eltrombopag, romiplostim); NICE submission (response rate for avatrombopag vs. rituximab)
Key limitations	• No conclusions regarding comparative efficacy in terms of response rate between avatrombopag and other TPO-RA ITP treatments can be made due to imprecision and limitations in the sponsor's NMA. Additionally, as the response rate for rituximab was excluded from the sponsor's NMA and because the response rate for rituximab was naively derived, there is no direct or indirect evidence informing the comparative efficacy rates of durable response of avatrombopag compared to rituximab. • Dosing was based on the initial product monograph dosing, which did not account for dose adjustments. • The model was based on blood platelet counts, which were assumed to be a proxy for bleeding risk; however, the threshold at which platelet count corresponds to bleeding risk is uncertain and nonlinear. • Health state utility values lacked face validity. For example, patients who had a bleeding event were assigned a lower utility value if they were patients without a platelet response compared to patients with platelet response, which was deemed to be inappropriate. • The basis for the sponsor's assumption regarding time to response was uncertain and may have been overestimated. In addition, duration of response estimates could not be validated, were not

Component	Description
	based on Study 302 data, and did not account for variations in duration of response over time. • Treatment sequencing in the model may not be reflective of clinical practice in Canada. • The assumption that bleeding rates will double after 4 lines of treatment is unsubstantiated. • Some costs of bleeding management may have been overestimated.
Reanalysis results	• We undertook reanalyses to address limitations relating to no comparative efficacy data for avatrombopag vs. rituximab in terms of response rate, uncertain comparative efficacy for avatrombopag and other TPO-RAs, adjusting the response rate for TPO-RAs to reflect the response rate for avatrombopag observed in Study 302, and incorporating dose adjustments for TPO-RAs. • In the base case for the **proposed** Health Canada–indicated population, all TPO-RAs were equally as effective. Avatrombopag had higher total costs compared with eltrombopag, but lower total costs compared to romiplostim. • Because the most relevant comparators for avatrombopag are other TPO-RAs and the sponsor's NMA did not demonstrate that avatrombopag is superior to other ITP treatments in terms of response rate, there is no clinical evidence supporting a price premium for avatrombopag over other TPO-RAs. • Watch and rescue (assumed to be equal to the placebo group of Study 302) is the only comparator for which there is direct comparative evidence vs. avatrombopag. For this comparison, the ICER is $98,150 per QALY gained (incremental costs = $88,662; incremental QALYs = 0.90). For avatrombopag to be cost-effective compared to watch and rescue at a willingness-to-pay threshold of $50,000 per QALY, a 32% reduction in the price is required.

ICER = incremental cost-effectiveness ratio; ITP = immune thrombocytopenia; NMA = network meta-analysis; QALY = quality-adjusted life-year; TPO-RA = thrombopoietin receptor agonist; vs. = versus.

Budget Impact

We identified the following key limitations with the sponsor's analysis:

- There is uncertainty in the sponsor's approach to estimating the reference scenario's market share. In addition, the sponsor excluded some jurisdictions with claims for TPO-RAs from the reference scenario.
- Uptake of avatrombopag is expected to be higher than that estimated by the sponsor.
- The sponsor's estimated eligible population does not reflect the proposed Health Canada indication because it assumed avatrombopag would only be used for those with primary ITP.
- Doses for TPO-RAs used in the budget impact analysis are not aligned with the dosing used in the pharmacoeconomic analysis.

The reanalyses included adding annual claims for eltrombopag and romiplostim to derive reference scenario market shares in jurisdictions with public claims for comparators from 2016 to 2021, increasing avatrombopag uptake and having all of its market capture come rituximab, and adjusting dosing for TPO-RAs to reflect trial dosing. Although the sponsor suggested avatrombopag would be associated with a budget impact of $19,026,855 over the 3 years, based on the reanalysis, the budget impact to the public drug programs of introducing avatrombopag is expected to be $11,292,967 in year 1, $17,171,433 in year 2, and $23,204,554 in year 3, for a 3-year total of $51,668,953. If avatrombopag was used for all patients with ITP (i.e., not just those with primary ITP), the budget impact could increase to $67,985,465 over 3 years.

However, this is likely an overestimate because, according to the clinical expert consulted for this review, avatrombopag would only be used for secondary ITP when no other treatment options exist, which was deemed rare.

Request for Reconsideration

The sponsor filed a request for reconsideration of the draft recommendation for avatrombopag for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment. In their request, the sponsor identified the following issues:

- The sponsor indicated that CDEC mischaracterized treatment availability for chronic ITP in Canada.
- The sponsor believed that the treatment goals for chronic ITP in the recommendation are misrepresented.
- The sponsor indicated that the benefit of avatrombopag is understated in the CDEC recommendation.

In the meeting to discuss the sponsor's request for reconsideration, CDEC considered the following information:

- feedback on the draft recommendation from the sponsor
- information from the initial submission related to the issues identified by the sponsor
- feedback from 1 clinical specialist with expertise in the diagnosing and treating patients with ITP
- feedback on the draft recommendation from 1 patient group, the PDSA
- feedback on the draft recommendation from a clinician from McMaster University representing 1 clinician group
- feedback on the draft recommendation from the public drug programs that participate in our review process.

All stakeholder feedback received in response to the draft recommendation is available on our website.

CDEC Information

Initial Meeting Date: October 25, 2023

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Regrets: 3 expert committee members did not attend

Conflicts of interest: None

Reconsideration Meeting Date: April 24, 2024

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed.

Regrets: 3 expert committee members did not attend

Conflicts of interest: None

ISSN: 2563-6596

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