Canada's Drug and Health Technology Agency

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

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.

Recommendation: Do Not Reimburse

Version: 1.0
Publication Date: November 2023
Report Length: 13 Pages

Single Technology

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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

Recommendation

The CADTH 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 meaningful benefit on clinical outcomes relative to other treatments for ITP currently used in clinical practice in Canada. One phase 3, 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 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 drop-out rate. Further, CDEC 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. While the sponsor submitted 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 with chronic ITP identified a need for new treatments to improve their health-related quality of life (HRQoL) and reduce their symptoms and rates of bleeding events compared with currently available therapies, which was not demonstrated in the evidence reviewed for avatrombopag.

Discussion Points

- 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, given that 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.
- 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 HRQoL, were associated with substantial uncertainty, and CDEC was unable to determine the effect of avatrombopag on these outcomes.

Background

Immune thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet counts and increased bleeding risk. Chronic ITP refers to symptoms persisting more than 12 months after diagnosis. In Canada, the prevalence of ITP is estimated to be 9.5 cases per 100,000 population, and the incidence is estimated to be 1.6 to 3.9 per 100,000 persons per year. Approximately 76% of all Canadian cases of ITP are primary, 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. Indeed, 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 and 0.039 cases 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 intravenous immune globulin be used as first-line therapy. There are multiple second- and third-line treatments available for ITP for patients who experience a relapse, such as splenectomy, rituximab, thrombopoietin receptor agonists (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/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 dose 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 below 30 x 10^9/L
- a review of 1 sponsor-submitted indirect treatment comparison
- a review of 2 phase 2 RCTs (Study 003 and Study 004) and 1 retrospective observational study of adult patients with chronic ITP which provided supportive evidence to the pivotal trial

- patients perspectives gathered by 1 patient group, the Platelet Disorder Support Association (PDSA)
- input from public drug plans that participate in the CADTH 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

Stakeholder Perspectives

Patient Input

One response to CADTH's call for patient input for the avatrombopag submission was received: a submission from the Platelet Disorder Support Association (PDSA). PDSA is a non-profit provides advocacy, education, research, and support for ITP patients 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 where it reduces the risk of bleeding while improving patients' quality of life. The input indicated that many current available treatments have a high burden of toxicity and stated 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

Input from clinical expert consulted by CADTH

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, influence of patient-specific factors on decisions, and 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 are 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 to 50 000/μL for the duration of a treatment cycle (e.g., 24 weeks). If a response has not been seen by around 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 impacting a patient's quality of life.

Clinician group input

One clinician representing the Canadian Hematology Society (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 one provided by the clinical expert consulted by CADTH. 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 one of the TPO-RAs and non- immunosuppressant. The input suggested that patients in their earlier stage of disease course would have better response to avatrombopag. Therefore, when it is used as a second-therapy, patient will benefit from more favorable response and limited exposure to the complications and toxicities of other lines of therapy, such as a splenectomy and the associated surgical complications and long-lasting immunosuppression, or rituximab, which can cause immunosuppression and vaccine failures, For patients who are experience multiple relapse or with refractory disease, avatrombopag may fill the gap since other TPO-RAs are not currently available, and avatrombopag has more favourable bioavailability and less hepatic toxicities compared to eltrombopag.

The input indicated that in practice, a clinically meaningful response would be to achieve and maintain a platelet count above 30×10^9/L. This would be correlated to 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 CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH 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 consulted by CADTH 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 3, double-blind, randomized controlled trial (RCT) which 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 below 30 x 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 matching placebo. The primary efficacy endpoint was cumulative number of weeks of platelet response (platelet count 50 x 10^9/L or higher) without rescue therapy for bleeding.

In Study 302, the baseline age was similar in both arms (median 45 years in avatrombopag arm versus 43 years in placebo arm) while there were more females in the avatrombopag arm (72% in avatrombopag arm versus 47% in placebo). The vast majority of patients were white in both arms (97% in the avatrombopag arm and 88% in the placebo arm). More patients in the avatrombopag arm had prior splenectomy compared to the placebo arm (34% vs. 29%). The baseline platelet count was higher in the avatrombopag arm than the placebo arm (12.5×10^9/L vs. 9.5×10^9/L). More patients in the avatrombopag arm received prior ITP

medications or were taking concomitant ITP medications at baseline, compared to the placebo arm (prior ITP medications: 47% vs. 35%; concomitant ITP medications: 47% vs. 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, a total of 3 patients in the avatrombopag group reported Grade 3 or 4 bleeding events.

The results of Study 302 also showed that treatment with 6-month avatrombopag leads to favorable platelet response compared to placebo, which according to the clinical expert, the between-group differences in platelet response can be considered clinically important:

- Median (range) cumulative number of weeks with platelet count 50 x 10^9/L or higher: 12.4 weeks (0 to 25) in the avatrombopag group vs. 0 weeks (0 to 2) in the placebo group; $p < 0.0001$.
- Proportion of patients with platelet count 50 x 10^9/L or higher at day 8 (n, %): 21 patients (65.63%) in the avatrombopag group vs. 0 patient in the placebo group, the difference between avatrombopag and placebo treatment groups was 65.63% (95% CI, 49.17% to 82.08%), P<0.0001.
- Durable platelet response defined as proportion of patients who had at least 6 out of 8 weekly platelet responses during the last 8 weeks of treatment over the 6-month treatment period in the absence of rescue therapy was reported in 11 patients (34.38%) in the avatrombopag group and in 0 patients 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 up until around Week 36.

The treatment effect of avatrombopag on improving patients' health-related quality of life, reducing the use of concomitant ITP medications or need for rescue therapy, or reducing emergency room visits and/or hospitalization due to thrombocytopenia episodes compared with placebo remain uncertain.

- Proportion of patients who needed rescue therapy was 21.9% in the avatrombopag group compared with 11.8% in the placebo group, p=0.4668.
- Reduction in use of concomitant ITP medication: 5 out of 15 patients (33.3%) in the avatrombopag group vs. 0 out of 7 patients in the placebo group, p=0.1348.

Note that due to the high discontinuation rate in the study and low event rates for some of these outcomes (e.g., HRQoL, hospitalization or emergency room visit), it was not possible to assess whether there were any differences between 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 the avatrombopag treatment. The results suggested during the open-label extension phase, response (defined as platelet count ≥ 50 x 10^9/L) was achieved at 96.1% of the extension phase visits and complete response (defined as platelet count ≥ 100 x 10^9/L) was achieved at 60.1% of extension phase visits. Durable response rate (defined as platelet count ≥ 30 x 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, over half of the patients who needed corticosteroids at baseline reduced or discontinued corticosteroid therapy.

Harms Results

During the Core phase, there were 31 (96.9%) patients in the avatrombopag group and 10 (58.8%) patients in the placebo group that reported any adverse events (AEs). Patients in the avatrombopag group reported higher grade AEs compared to those in the placebo group. There were 6 (18.8%) patients 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 that reported any treatment-emergent serious adverse events (SAEs). There were 3 patients (9.4%) in the avatrombopag group and none in the placebo group that 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 patient 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 3, double-blind, placebo-controlled RCT. Some relatively large baseline imbalances between groups were observed, which could suggest selection bias, but is most likely the result of the small sample of patients randomized. The degree to which this may have an impact on data interpretation and bias the results is unclear. The rate of study discontinuation was high in Study 302 and was imbalanced between treatment arms: 22% of patients in the avatrombopag group and 88% of patients in the placebo group withdrew the study because of inadequate therapeutic effect. The median exposure duration with placebo was much shorter than with avatrombopag. This affected the assessment of the clinically relevant outcomes of bleeding events and rescue medication; no clear conclusions on the effects of avatrombopag on these outcomes could be drawn. The high drop-out rate also has substantial impact on patient-reported outcomes, such as HRQoL. 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. It is not possible to draw meaningful conclusion for the effect of study drug on patients' HRQoL due to the limited amount of data as a result of study discontinuation. In Study 302, cumulative number of weeks with platelet count 50 x 10^9/L or higher was the primary outcome measure. In practice, platelet count is considered a surrogate for the risk of bleeding events and survival, although previous research suggested that the relationship between bleeding events and platelet count is not well known based on the results of an RCT evaluating the effect of prophylactic platelet transfusion dose on the risk bleeding in patients with hypoproliferative thrombocytopenia. Gains from the number of weeks with platelet response may be correlated to a reduction in the risk of bleeding or improved patient's quality of life in the study population. According to the clinical expert consulted by CADTH, a threshold of 30 x 10^9/L or lower is used by the clinicians to determine treatment response and the risk of subsequent bleeding. This is consistent with the recommendations from clinical practice guidelines which indicates that treatment should maintain a target platelet level of at least 20 to 30 x 10^9 /L at least for symptomatic patients (because risk for major bleeding increases below this level). While in Study 302, a threshold of 50 x 10^9/L for platelet response in patients with ITP was used to assess the treatment effect, there were limited or lack of 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 population of Study 302 is broadly comparable to the patients with ITP in Canada and thus the study findings are likely generalizable in Canada. One challenge with Study 302 is that the comparator is placebo. For patients with chronic ITP whose platelet counts are lower than 20 x 10^9/L, treatment would be warranted. However, Study 302 has provided no information on 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 (for example avatrombopag in combination with corticosteroids) and the effect of any combination therapy is uncertain.

Indirect Comparisons

Description of studies

The sponsor submitted a systematic review and indirect treatment comparison (ITC) report where avatrombopag was compared to two TPO-RAs (eltrombopag and romiplostim), fostamatinib and rituximab among 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 2-4 bleeding events and adverse events were assessed. The network meta-analyses (NMAs) were conducted within a Bayesian framework.

In total, nine RCTs were included and contributed evidence. In the trials included in 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 proportion of splenectomised patients (0 to 50%), proportion of patients used concomitant ITP medication at baseline (13 to 48%) and duration of ITP (median 0.25 to 8.7 years) across trials. There was a noticeable between-trial heterogeneity in the proportion of patients prematurely discontinuing allocated treatment (ranged from 0-100%).

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 (CrIs) including the potential for no difference between treatments or for either treatment to be favoured. Avatrombopag was favored over eltrombopag, romiplostim, and rituximab in the incidence of any bleeding events.

Harms Results

Results of the NMA for AEs were very imprecise with CrIs 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 patient's baseline characteristics of the studies included in the systematic review and ITC were reported. Based on the data presented, potential sources of heterogeneity with respect to the baseline characteristics were identified, such as proportion of splenectomised patients (0 to 50%), proportion of patients used concomitant ITP medication at baseline (13% to 48%) or duration of chronic ITP (median of 0.25 to 8.7 years). Other patient characteristics should also be considered when addressing clinical heterogeneity across the included trials, such as cycles and doses of prior corticosteroids therapy, previous lines of therapy and severity of previous bleeding events. Such data were not provided in the ITC, and from the available data, it appears likely that the transitivity assumption was violated. Furthermore, there was a significant between-trial heterogeneity in the proportion of patients prematurely discontinuing allocated treatment (ranged from 0 to 100%), 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 adverse events in the placebo group. However, the authors of the ITC adjusted for this by summarizing the data using IRRs 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 non-informative due to imprecision.

Other Relevant Evidence

Description of studies

Two additional studies were included in the sponsor's submission to CADTH which provided supportive evidence regarding the safety and efficacy of avatrombopag. Study 003, a phase-2 double-blind, placebo-controlled randomized trial of avatrombopag taken orally once daily for 28 days in adult patients with chronic ITP. A total of 5 patients were randomized into the placebo group and 15

into the avatrombopag 20 mg/day group. Two patients discontinued, both in the avatrombopag group, due to an increase in their platelet count to ≥ 500x10^9/L.

Study 004 was a phase-2 long-term extension study, with avatrombopag administered for an additional 6 months in chronic ITP patients who completed Study 003. A total of 53 patients enrolled into Study 004, of which 13 received the maximum 20mg/d dose in Study 003 (10 responders and 3 non-responders). Four (30.8%) of these patients discontinued Study 004, 2 from each of the responder and non-responder groups, 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, a total of 80% of patients (n = 12) in the avatrombopag group and no patients in the placebo group achieved a treatment response on day 28. A patient was considered a responder if the patient achieved a platelet count of at least 50x10^9/L on day 28 for patients whose baseline platelet count was less than 30 x10^9/L, or an increase from baseline of at least 20x10^9/L for patients receiving steroids whose baseline platelet count was at least 30x10^9/L but less than 50x10^9/L. The median (range) change in platelet count from baseline to day 28 was 84x10^9/L (-10x10^9/L to 1012x10^9/L) in the avatrombopag group and -2x10^9/L (-12x10^9/L to 9x10^9/L) in the placebo group. No patients in the placebo group and a total of 12 patients (80%) and 8 patients (53.5%) in the avatrombopag group had a platelet count ≥ 50x10^9/L or ≥ 100x10^9/L on day 28, respectively. Using the last observation carried forward (LOCF) 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 (range) change in platelet count from baseline in Study 003 to week 24 in Study 004 was 124x10^9/L (-11x10^9/L to 205x10^9/L) among responders (n = 7) and 199x10^9/L (not applicable) among nonresponders (n = 1). At week 24, a total of 6 (86.7%) responders and 1 (100.0%) non-responder achieved a response level platelet count, respectively. A total of 6 (60.0%) responders and 1 (33.3%) non-responder achieved a durable platelet response. Of 6 responders and 1 non-responder initially being treated with corticosteroids, a total of 2 (33.3%) responders and 1 (100.0%) non-responder permanently discontinued steroid use during the last 8 weeks of treatment in Study 004.

Results of the retrospective study (n = 44) suggested that the platelet response was achieved by 93% of patients and the complete platelet response was achieved by 86% after switching. Among the responders, the response was maintained for 84% of their time on treatment. Among the patients who received concomitant ITP medications, 57% discontinued one 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% after switching to avatrombopag, as compared with 34% who required rescue on eltrombopag or romiplostim in the year prior to switching.

Harms Results

Safety results were presented for the combined study periods in Study 003 and Study 004. All 20 patients in 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 adverse event. Three patients reported at least 1 SAE which included 2 patients experiencing 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, and 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 which could have resulted in a population of patients that were more tolerant of avatrombopag which can 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 throughout the studies to some patients were less than the recommended starting dose of 20mg/d 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 by Al-Samkari et al. suggested that switching to avatrombopag was associated with increasing 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, more specifically in terms of the retrospective observational study design, lack of comparator, small sample size, as well as the external validity in terms of generalizability of the study findings to the Canadian patient population.

Economic Evidence

Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adult patients with chronic ITP who have 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 dose of 20 mg once weekly and a maximum recommended dose 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, LYs
Time horizon	Lifetime (56 years)
Key data source	Study 302, a phase 3, 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 non-linear. • Health state utility values lacked face validity. For example, patients who had a bleeding event were assigned a lower utility value if they were non-responders, compared to responders, which was deemed to be inappropriate. • The basis for the sponsor's assumption regarding time to response was uncertain and may have been overestimated.. Additionally, duration of response estimates could not be validated by

Component	Description
	CADTH, were not 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 Canadian clinical practice. • The assumption that bleeding rates will double after four lines of treatment is unsubstantiated. • Some costs of bleeding management may have been overestimated.
CADTH reanalysis results	• CADTH undertook reanalyses to address limitations relating to: no comparative efficacy data for avatrombopag versus 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 CADTH 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. • Given that the most relevant comparators for avatrombopag are other TPO-RAs, and since 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 arm 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 (inc. costs = $88,662; inc. 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; LY = life-year; NMA=network meta-analysis; QALY= quality-adjusted life-year; TPO-RA= thrombopoietin receptor agonist.

Budget Impact

CADTH 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. Additionally, 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, as it assumed avatrombopag would only be used for those with primary ITP.

Doses for TPO-RAs used in the BIA are not aligned with dosing used in the pharmacoeconomic analysis.

CADTH reanalyses included: adding annual claims for eltrombopag and romiplostim to derive reference scenario market shares in jurisdictions with public claims for comparators from 2016-2021; 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 three-year, based on the CADTH reanalysis, the budget impact to the public drug plans 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 three-year total of $51,668,953. If avatrombopag was used for all patients with ITP (i.e., not just those with primary), the budget impact could increase to $67,985,465 over three years. However, this is likely an overestimate, as 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.

CDEC Information

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.

Meeting date: October 25, 2023

Regrets:

3 expert committee members did not attend.

Conflicts of interest:

None