CADTH

CADTH REIMBURSEMENT REVIEW

# Stakeholder Feedback on Draft Recommendation

**avatrombopag (Doptelet)**

(Sobi Canada, Inc.)

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

**December 7, 2023**

# CADTH Reimbursement Review

# Feedback on Draft Recommendation

| Stakeholder information | |
|---|---|
| CADTH project number | SR0721-000 |
| Brand name (generic) | DOPTELET (avatrombopag) |
| Indication(s) | Adults with ITP who have had an insufficient response in the past to other therapies |
| Organization | Platelet Disorder Support Association |
| Contact information[a] | Name: Jennifer DiRaimo |

| Stakeholder agreement with the draft recommendation | | |
|---|---|---|
| **1. Does the stakeholder agree with the committee's recommendation.** | Yes | ☐ |
| | No | X |

The Platelet Disorder Support Association (PDSA) is a patient organization that supports individuals and families living with platelet disorders, particularly with immune thrombocytopenia (ITP). As a patient organization, we have been involved with several health technology assessments and drug review submissions for stakeholders, representing patients and families with platelet disorders such as immune thrombocytopenia (ITP). As a registered not-for profit organization in both the US and Canada, PDSA we would like to express our frustration at the CDEC's decision to not recommend avatrombopag, a thrombopoietin-receptor agonist (TPO-RA), for reimbursement for adults with ITP who have not been able to respond to other therapies.

There are two important benefits to avatrombopag not available from the other thrombopoietic agents. First, in the randomized phase 2 study of 64 patients with chronic ITP published in Blood (2014) https://pubmed.ncbi.nlm.nih.gov/24802775/ it was clear that patients responded very well to this agent even lower doses. One site, for instance, enrolled 27 patients of the total 64 patients from this multicenter study because of the benefits of avatrombopag.

What were these benefits: There was not only a very high response rate at the top doses in the Phase 2 study, but also there are 2 other relevant studies demonstrating the benefits of avatrombopag. One was a report of 8 multi-refractory patients who had all previously been on romiplostim and eltrombopag and lost their responses: 6 responded to avatrombopag published in the British Journal of Haematology. A 45-patient study published in the British Journal of Haematology explored switching from eltrombopag or romiplostim to avatrombopag. In many cases it was for convenience either the major oral intake limitations associated with eltormbopag or the need to weekly injections (romiplostim). More than ten of these patients had lost their response or never responded to the previous agent and the clear majority responded to avatrombopag. https://pubmed.ncbi.nlm.nih.gov/35179784/.

This is also confirmed in a very recent study: https://ashpublications.org/blood/article-abstract/141/23/2867/494859/Prolonged-response-after-TPO-RA-discontinuation-in?redirectedFrom=fulltext.

The major advantage of avatrombopag is the lack of dietary restrictions: the recommendation to take it WITH FOOD is only to ensure stable absorbtion. Eltrombopag requires 1 hour before and 2 hours afterwards no oral intake and 4 hours before and after no divalent cations (calcium, magnesium, and iron among others). This means in practice that patients with ITP must plan their entire days eating around taking eltrombopag. Those not eating dinner at home at a consistent time every night often

has great difficulty with it. Putting milk in coffee is enough to inactivate it in the morning! Finally, on eltrombopag there is always a risk of hepatic injury and liver tests are required indefinitely whereas there are no issues of this type with avatrombopag.

Adults in Canada living with ITP deserve to have avatrombopag available to them SHOULD they need to use an alternative TPO-RA for treatment. Patients cannot control what drugs they will or won't respond to.

Every Canadian deserves the right to appropriate medical treatments that can keep them safe and save their life. What works for one ITP patient, may not work for another. The importance of this cannot be overstressed. The CADTH review stated "… CDEC acknowledged that there are a variety of other treatments currently used for ITP". Apart from first-line therapies, ITP patients in Canada struggle to access all second-line therapy agents (such as rituximab, TPO-RAs, Syk inhibitors, BTK inhibitors… etc). If the CDEC is suggesting the alternative is to continue first line 'rescue' therapies which guidelines recommend against due to excessive long-term health implications of steroid use, and a looming IVIG shortage, that is not acceptable *or ethical*. It should also be understood that a failure to respond to a first line therapy does not only mean there is a lack of response, it also means there is a lack of a DURABLE response – which means first line therapies are really 'rescue' therapies, and are not meant to be long term chronic management solutions.

Our Ask:

***The ITP patient community hopes that this draft decision could be revised to a 'reimburse with condition(s)' recommendation.*** Our suggested conditions could be mandatory enrolment of all treated patients into a registry to captured greater efficacy and safety data. This would be in line with Health Canada's indication for use. The ITP community does not want to see any more lives lost to ITP in this day and age when there are so many therapies available, and many more in development too.

**We would also like CADTH to consider a one- or two-year pilot where reimbursement for DOPTELET (avatrombopag) would be granted, with a commitment from us and from our physician partners to collect registry data to inform the rates of bleeding, hospital visits (including visits to hospital for critical bleeds and long-term health outcomes) and adverse events. This information will inform efficacy and safety using real world data and provide information on resource utilization.**

Summary of PDSA's Response to CADTH: We respectfully request that CADTH consider changing the recommendation for DOPTELET (avatrombopag) to 'reimbursement with condition(s)'. These conditions might include mandatory enrolment in a patient registry to capture real world data on efficacy and safety.

| **Expert committee consideration of the stakeholder input** | | |
|---|---|---|
| **2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?** | Yes | X |
| | No | X |

If not, what aspects are missing from the draft recommendation?

While it's clear the committee did consider our stakeholder feedback, it's not clear our feedback was completely understood. It was never our goal for CADTH to compare TPO-RAs or other treatments to see what's the best one. It's irrelevant if someone does not respond to one but does another or needs to switch due to a developed resistance over time. The disease is heterogenous not only in

clinical presentation, but also in treatment response. There are many ITP patients who do not respond to eltrombopag or romiplostim, or lose a response to these medicines over time, and they can switch and have a successful response to avatrombopag.

**We feel that CADTH should recommend reimbursement for avatrombopag so that treatment can be individualized and if a patient does not respond to other second line therapies, they are not 'out of luck' for something they have no control over.**

CADTH's last adult HTA review of second line therapies agreed that TPO-RAs (specifically eltrombopag and romiplostim) have benefits and that the provinces/territories could consider funding these despite the economic uncertainty which is inevitable when dealing with rare diseases. We therefore ask CADTH to consider adding avatrombopag to this list because for some ITP patients, this may be the only thing that will work for them.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8977771/#cit0019. And there is enough literature available to show how this drug is helpful, and just as effective if not more compared to eltrombopag and romiplostim.

CADTH's statement: *"Patients with chronic ITP identified a need for new treatments to improve their health related QoL (HRQoL) and reduce their symptoms and rates of bleeding events compared with currently available therapies… not demonstrated with DOPTELET (avatrombopag)"* **does not reflect the real-world global individual patient experience.** Furthermore, CADTH does not define what is included in 'current available therapies? As mentioned above, Canadian ITP patients can only access via the provinces and territories IVIG and corticosteroids through public drug plans. EAP in some provinces may help IF patients have failed second-line treatments, already had a splenectomy (which isn't recommended by medical guidelines and your latest HTA also could not find evidence to support this need) and in some cases not used another agent such as dapsone, not recommended as a stand-alone ITP therapy. In fact, some of the other therapies clinicians have used when nothing else is available (such vincristine) can cause lasting impacts on fertility and are not even recommended by experts as a stand-alone ITP treatments https://www.sciencedirect.com/science/article/abs/pii/095980499290016U.

Access to mainstream TPO-RAs such as eltrombopag and romiplostim are extremely difficult to obtain even for generic brands of eltrombopag. PDSA recently received a letter from a patient member in one of the provinces stating she was denied coverage because CADTH does not recommend eltrombopag or romiplostim for ITP treatment. Even through the last adult ITP HTA left the decision up to the provinces and territories, they are leaving the decision to your organization.

There is plenty of evidence to indicate that HRQoL, bleeding rates, and symptom management are greater with second line therapies such as avatrombopag compared to IVIG and steroids! And IVIG is almost in short supply in Canada not to mention expensive and does not even work for very long.

Some of the many benefits in terms of QoL that should have been highlighted via CADTH include there are no food-type restrictions, no liver monitoring, and no weekly injections which all ensure compliance and reduce health care costs. For some patients, the lack of food restrictions means better daily QoL. What is also not highlighted to the extent that it should is that many studies have reported that there is a significant proportion of patients (approximately 30%) who can use a TPO-RA and then discontinue without losing a response, meaning their platelet count and bleeding symptoms are improved even when the drug has stopped. With such a limited number of adults needing to use avatrombopag, and 30% being able to discontinue, has CADTH's economic analysis captured and accounted for this[1-3]?

1. Gonzalez-Lopez TJ, Pascual C, Alvarez-Roman MT, et al. Successful discontinuation of eltrombopag after complete

remission in patients with primary immune thrombocytopenia. *Am J Hematol*. 2015;**90**:E40–E43. [PubMed] [Google Scholar]

2. Cervinek L, Mayer J, Doubek M. Sustained remission of chronic immune thrombocytopenia after discontinuation of treatment with thrombopoietin-receptor agonists in adults. *Int J Hematol*. 2015;**102**:7–11. [PubMed] [Google Scholar]

3. Mahevas M, Fain O, Ebbo M, et al. The temporary use of thrombopoietin-receptor agonists may induce a prolonged remission in adult chronic immune thrombocytopenia. Results of a French observational study. *Br J Haematol*. 2014;**165**:865–869. [PubMed] [Google Scholar]

This is another very helpful publication that just came out and could be factored into the decision: https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.18908

What's also missing is that there is no evidence that CADTH's real world evidence tools were used – rather, the review was focused on which therapy is better and a lack of head-to-head comparison trials that do not exist.

| Clarity of the draft recommendation | | |
|---|---|---|
| **3. Are the reasons for the recommendation clearly stated?** | Yes | X |
| | No | X |
| If not, please provide details regarding the information that requires clarification.<br><br>They are stated clearly but that isn't the issue. | | |
| **4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?** | Yes | ☐ |
| | No | X |
| N/A - the recommendation is not to reimburse. Access to this medication will continue to be an issue for Canadian adult patients living with ITP, and this may be difficult to obtain even with private insurance. | | |
| **5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?** | Yes | ☐ |
| | No | ☐ |
| N/A for the same reason as above. | | |

[a] CADTH may contact this person if comments require clarification.

## Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

### A. Patient Group Information

| | |
|---|---|
| **Name** | *Jennifer DiRaimo* |
| **Position** | *Research Program Manager* |
| **Date** | *Please add the date form was completed December 1, 2023.* |
| X | I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation. |

## B. Assistance with Providing Feedback

| | | |
|---|---|---|
| **1. Did you receive help from outside your patient group to complete your feedback?** | No | X |
| | Yes | ☐ |

If yes, please detail the help and who provided it.

| | | |
|---|---|---|
| **2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?** | No | X |
| | Yes | ☐ |

If yes, please detail the help and who provided it.

## C. Previously Disclosed Conflict of Interest

| | | |
|---|---|---|
| **1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.** | No | X |
| | Yes | ☐ |

## D. New or Updated Conflict of Interest Declaration

**3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.**

| **Company** | **Check Appropriate Dollar Range** | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Amgen* | ☐ | ☐ | ☐ | X |
| *Novartis* | ☐ | ☐ | ☐ | X |
| *Rigel* | ☐ | ☐ | ☐ | X |

# CADTH Reimbursement Review
# Feedback on Draft Recommendation

| Stakeholder information | |
|---|---|
| CADTH project number | |
| Brand name (generic) | Avatrombopag |
| Indication(s) | ITP |
| Organization | Clinician |
| Contact information[a] | Name: Donald M. Arnold |

**Stakeholder agreement with the draft recommendation**

| | | |
|---|---|---|
| **1. Does the stakeholder agree with the committee's recommendation.** | Yes | ☐ |
| | No | ☒ |

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

I don't agree that there are other superior, or equivalent medical treatment options available besides the thrombopoietin receptor agonists (TPO-RAs). Rituximab is not licensed for ITP and its response rate is lower. All other oral ITP medications are immune suppressant medications with unfavorable toxicity profiles. So far, TPO-RAs are either inaccessible or only accessible to patients of high socioeconomic status. From a clinical perspective, avatrombopag is the most appealing of the TPO-RAs because 1) it can be administered orally, unlike romiplostim; and 2) it has predictable bioavailability, unlike eltrombopag.

**Expert committee consideration of the stakeholder input**

| | | |
|---|---|---|
| **2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?** | Yes | ☐ |
| | No | ☒ |

If not, what aspects are missing from the draft recommendation?

I understand that the data on bleeding and HRQOL is limited by small numbers. However, there is robust data demonstrating a link between platelet count levels and those clinical endpoints. Additional reports of real world data using Avatrombopag continue to emerge from other countries including the US, where it has become the TPO-RA of choice.

TPO-RA's are the most effective treatment for patients with ITP at raising platelet count, and indirectly reducing bleeding events and improving quality of life. The effect of avatrombopag on platelet count response is similar to other TPO-RAs, but avatrombopag is the most favorable of the TPO RAs because of its route of administration (oral) and excellent bioavailability.

**Clarity of the draft recommendation**

| | | |
|---|---|---|
| **3. Are the reasons for the recommendation clearly stated?** | Yes | ☒ |
| | No | ☐ |

If not, please provide details regarding the information that requires clarification.

| | | |
|---|---|---|
| **4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?** | Yes | ☒ |
| | No | ☐ |

If not, please provide details regarding the information that requires clarification.

| | | |
|---|---|---|
| | Yes | ☐ |

| | | |
|---|---|---|
| **5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?** | No | ☒ |

If not, please provide details regarding the information that requires clarification.

Please consider a time-limited reimbursement (e.g. 1 year). This would allow patients to access the medication when they need it the most, and will give an opportunity for a subgroup of patients to enter a remission. For those patients who end up dependent on the medication after 1 year, other more definitive treatments should be considered (e.g. rituximab, splenectomy).

[a] CADTH may contact this person if comments require clarification.

## Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

| **A. Assistance with Providing the Feedback** | | |
|---|---|---|
| **2. Did you receive help from outside your clinician group to complete this submission?** | No | ☒ |
| | Yes | ☐ |
| If yes, please detail the help and who provided it. | | |
| **3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?** | No | ☒ |
| | Yes | ☐ |
| If yes, please detail the help and who provided it. | | |
| **B. Previously Disclosed Conflict of Interest** | | |
| **4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.** | No | ☐ |
| | Yes | ☒ |
| If yes, please list the clinicians who contributed input and whose declarations have not changed:<br>• Clinician 1- Donald M. Arnold | | |

### C. New or Updated Conflict of Interest Declarations

| **New or Updated Declaration for Clinician 1** | |
|---|---|
| **Name** | *Please state full name* |
| **Position** | *Please state currently held position* |
| **Date** | *Please add the date form was completed (DD-MM-YYYY)* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |
| **Conflict of Interest Declaration** | |

| List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. | | | | |
|---|---|---|---|---|
| **Company** | **Check Appropriate Dollar Range** | | | |
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| **New or Updated Declaration for Clinician 2** | |
|---|---|
| **Name** | *Please state full name* |
| **Position** | *Please state currently held position* |
| **Date** | *Please add the date form was completed (DD-MM-YYYY)* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

| **Conflict of Interest Declaration** | | | | |
|---|---|---|---|---|
| List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. | | | | |
| **Company** | **Check Appropriate Dollar Range** | | | |
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| **New or Updated Declaration for Clinician 3** | |
|---|---|
| **Name** | *Please state full name* |
| **Position** | *Please state currently held position* |
| **Date** | *Please add the date form was completed (DD-MM-YYYY)* |
| ☒ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

| **Conflict of Interest Declaration** | | | | |
|---|---|---|---|---|
| List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. | | | | |
| **Company** | **Check Appropriate Dollar Range** | | | |
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| New or Updated Declaration for Clinician 4 | |
|---|---|
| **Name** | *Please state full name* |
| **Position** | *Please state currently held position* |
| **Date** | *Please add the date form was completed (DD-MM-YYYY)* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

| New or Updated Declaration for Clinician 5 | |
|---|---|
| **Name** | *Please state full name* |
| **Position** | *Please state currently held position* |
| **Date** | *Please add the date form was completed (DD-MM-YYYY)* |
| ☐ | **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation. |

**Conflict of Interest Declaration**

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

| Company | Check Appropriate Dollar Range | | | |
|---|---|---|---|---|
| | **$0 to 5,000** | **$5,001 to 10,000** | **$10,001 to 50,000** | **In Excess of $50,000** |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add company name* | ☐ | ☐ | ☐ | ☐ |
| *Add or remove rows as required* | ☐ | ☐ | ☐ | ☐ |

# CADTH Reimbursement Review

# Feedback on Draft Recommendation

| Stakeholder information | |
|---|---|
| CADTH project number | SR0721 |
| Name of the drug and Indication(s) | Avatrombopag (Doptelet)<br>For the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. |
| Organization Providing Feedback | FWG |

| **1. Recommendation revisions**<br>Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation. | | |
|---|---|---|
| **Request for Reconsideration** | **Major revisions:** A change in recommendation **category** or patient **population** is requested | ☐ |
| | **Minor revisions:** A change in reimbursement **conditions** is requested | ☐ |
| **No Request for Reconsideration** | **Editorial revisions:** Clarifications in recommendation **text** are requested | X☐ |
| | **No requested revisions** | ☐ |

| **2. Change in recommendation category or conditions**<br>Complete this section if major or minor revisions are requested |
|---|
| Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation. |

| **3. Clarity of the recommendation**<br>Complete this section if editorial revisions are requested for the following elements |
|---|
| **a) Recommendation rationale** |
| Please provide details regarding the information that requires clarification. |
| **b) Reimbursement conditions and related reasons** |
| Please provide details regarding the information that requires clarification. |
| **c) Implementation guidance** |
| Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here. |