CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

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.

February 18, 2022

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CADTH in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings.

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CADTH and do not necessarily represent or reflect the views of CADTH. No endorsement by CADTH is intended or should be inferred.

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CADTH does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the content are included in the posted submission.

Patient Group Input

Name of the Drug and Indication	**Avatrombopag (Doptelet)** SR0721-000
Name of the Patient Group	Platelet Disorder Support Association
Author of the Submission	Jennifer DiRaimo, MS, CCGC
Name of the Primary Contact for This Submission	Jennifer DiRaimo, MS, CCGC
Email	[redacted]
Telephone Number	[redacted]

1. About Your Patient Group

If you have not yet registered with CADTH, describe the purpose of your organization. Include a link to your website.

The Platelet Disorder Support Association (PDSA) is dedicated to enhancing the lives of patients with immune thrombocytopenia (ITP) and other platelet disorders through advocacy, education, research, and support. Founded in 1998, PDSA is a U.S. based non-profit with an international reach, and we are registered as a non-profit corporation in Canada.

We have on average 80,000 (not unique) visits to our website per month (www.pdsa.org). In 2020 and 2021, Canada was one of the top three countries providing unique visitors to the PDSA website. We have 16,958 contacts in our data base (14,045 adults and children; 2,953 physicians) from 180 countries. In Canada alone, we have 676 adults and children in our data base, and 104 physicians. We have 62 support groups throughout the US, Canada, and New Zealand. In Canada specifically, we have seven support groups including in the London, Niagara, Toronto, Waterloo, Ottawa and Vancouver regions. We also have a full time Research Program Manager, Jennifer DiRaimo, MS, CCGC, who is Canadian and works remotely from London Ontario. PDSA has a Canadian board member, Dr. Donnie Arnold, from McMaster University in Hamilton.

PDSA holds a Canadian Regional Meeting for patients/caregivers annually when conditions permit for an in-person event outside of a pandemic. During our annual three-day patient conference, we host a separate Canadian ITP meeting with two of our medical advisors, Donald Arnold, M.D. from McMaster University in Hamilton, Ontario and John Semple, PhD who recently left St. Michaels hospital in Toronto, Ontario to accept a prestigious academic position at Lund University in Sweden. We are frequently invited to speak about the patient experience at Canadian events. This year, PDSA has been invited to speak at the National ITP Advisory Board Meeting in May (2021), sponsored by Novartis Canada.

Our website: pdsa.org

2. Information Gathering

*CADTH is interested in hearing from a wide range of patients and caregivers in this patient input submission. Describe how you gathered the perspectives: for example, by interviews, focus groups, or survey; personal experience; or a combination of these. Where possible, include **when** the data were gathered; if data were gathered **in Canada** or elsewhere; demographics of the respondents; and **how many** patients, caregivers, and individuals with experience with the drug in review contributed insights. We will use this background to better understand the context of the perspectives shared.*

- Avatrombopag: Currently indicated in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. FDA approved.

Our ITP Natural History Study Registry collects information from ITP patients related to their experience with the disease, treatments, and health-related quality of life (HRQoL). Our HRQoL surveys incorporate all domains represented within the EQ-5D that CADTH may be using for assessing such impacts. However, at this time we only have two registry participants (out of close to 2000 participants) who have disclosed they have used (or are currently using) avatrombopag (Doptelet). We recognize the lack of robust data on the use of avatrombopag. To address this gap, we would be willing (with our physician partners) to collect registry data to inform the rates of bleeding, hospital visits (including visits to the hospital for critical bleeding and long-term outcomes) and adverse events. This information will help to further inform the efficacy and safety using real world data and provide information on resource utilization.

The following patient comments were collected from PDSA's ITP support group (private) Facebook page. The following (see below) are comments from adults with ITP regarding avatrombopag:

- "found the side effects were minimal compared to promacta and my counts have stabilized so I stopped taking it about 2 months ago"
- "I've been on it now for about two months and it has worked like a charm for me. I have tried every other treatment on the market and only NPlate and now Doptelet NPlate worked for me but my numbers were never stable (roller coaster) Since I have been on Doptelet, my numbers have been between 230 and 430, so far"
- "I have not had ANY side effect with Doptelet. I suppose that someone could have side effects that other might have, but I haven't noticed any ill effects from Doptelet."
- "My son is taking it and it has been a miracle for him."
- "It worked but I became anemic. It took a few months to feel normal again. But everyone is different. Good luck! I wish I could have continued. Back on Tavallise and NPlate"
- "I have been on it since it was approved for treatment of itp. It has worked well for me. I couldn't take it everyday because it gave me a migraine and rose my counts way too high. I take it Monday through Thursday and my counts stay 50-300. I have had occasional drop to below 20 with illness but then I bounce right back up. No side effects with the four days a week regimen. I have tried many others such as promacta(didn't work) tavalisse (didn't work and gave me high blood pressure) IVIG (I get horrible migraines from and end up in the Er every time) NPlate (works well but I have to get weekly shots) splenectomy (didn't work). Good luck!!"
- "I have been on doptelet (which is what avatrombopag is) for a year and a half. It is the best decision I ever made. Couldn't get my levels stabilized and I tried all the other meds. I had too many side effects with some. Some lowered my immune system. Others were just inconvenient having to go in for weekly shots.
- "With doptelet my levels are stable and I've had zero side effects."
- "MY PLATELETS ARE 421 FROM 3 IN TWO WEEKS AFTER 30 YEARS OF REFRACTORY ITPTAKING DOPTELET HOPE IT KEEPS WORKING 421 "

3. Disease Experience

CADTH involves clinical experts in every review to explain disease progression and treatment goals. Here we are interested in understanding the illness from a patient's perspective. Describe how the disease impacts patients' and caregivers' day-to-day life and quality of life. Are there any aspects of the illness that are more important to control than others?

Having a bleeding disorder impacts not only the individual, but their entire family. 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.

The multifaceted burden of living with ITP impacts the overall health-related quality of life (HRQoL) of patients and their families. Aside from the constant risk for serious life-threatening bleeding, patients experience both physical and emotional consequences living with their disease daily. ITP is associated with elevated levels of fatigue, anxiety, depression, physical pain for some, and sleep disturbances despite having good support systems in place. The levels of fatigue, anxiety, pain, and depression reported within the ITP registry participants exceeds what is reported in the general population. For many ITP patients, these symptoms are front and center among their concerns, rather than the clinical measures of platelet counts.

Guilt and disappointment over limited abilities and restricted activities due to a low platelet count likely further contribute to the negative emotional burden on ITP patients. The symptoms that accompany the disease and the constant monitoring of platelet counts interfere with daily activities also lead to anxiety, fear, depression, and embarrassment over unexplained bruises or blood blisters, isolation, inadequacy, and frustration with a patients' inability to control their body and their health. To minimize bleeding risks, patients with ITP need to routinely weight the risks associated with their daily activities, and sometimes forgo travelling or participating in sporting or social events. ITP presents an additional layer of complexity for patients who require a specialized medical procedure or surgery, or become pregnant, or find themselves in the care of a health care provider in an emergency who might not be current in their knowledge about ITP. Fatigue associated with ITP is often debilitating. Together, this demonstrates the multifaceted effect ITP has on overall QoL.

ITP does not have to go into remission for a patient's quality of life to improve – to have an increase in platelet count where it reduces the risk for bleeding while improving (or not worsening) quality of life is always the goal. While it may seem like ITP is a simple 'benign' disease on the surface, nothing could be farther from the truth. There are many complexities associated with ITP regarding disease etiology, risks, treatment responses, and heterogeneity in clinical symptoms.

4. Experiences With Currently Available Treatments

CADTH examines the clinical benefit and cost-effectiveness of new drugs compared with currently available treatments. We can use this information to evaluate how well the drug under review might address gaps if current therapies fall short for patients and caregivers.

Describe how well patients and caregivers are managing their illnesses with currently available treatments (please specify treatments). Consider benefits seen, and side effects experienced and their management. Also consider any difficulties accessing treatment (cost, travel to clinic, time off work) and receiving treatment (swallowing pills, infusion lines).

There are many treatments for ITP. They all have different risks, benefits, and limitations. Not to mention, many have a high burden of toxicity. Hematologists may use several treatments at once to increase their success rate. This is common due to the impact ITP has on the immune system.

- **Prednisone** — Prednisone is a synthetic medicine (i.e., corticosteroid) like cortisone, a natural substance produced in the body's adrenal glands. It is used in the treatment of ITP because it has been shown to increase the platelet count while it is being taken. However, the effects are short term, while the side-effects are often long-term. In the past, ITP patients were forced to rely on steroids daily putting their health at risk. As a result, the revised updated 2019 professional American Society of Hematology (ASH) ITP guidelines suggest using steroids for no longer than 6 weeks, and that if the platelet count is still low, to consider an alternative therapy such as a TPO-RA (such as Revolade® or Nplate®).

Possible side effects: Prednisone is generally only given for a few weeks at a time because it can have serious side effects with long-term use. And even when it is given for a short time, side effects include irritability, stomach upsets, sleep disturbances, increased appetite, weight gain, puffy cheeks, frequent urination, sugar in the urine, loss of bone density, cataracts, or acne.

- **Intravenous gamma globulin (IVIg)** — IVIg is a liquid concentrate of antibodies purified from the plasma (the liquid portion of the blood that doesn't contain red blood cells) of healthy blood donors.

Possible side effects: Some patients treated with IVIg experience nausea and vomiting, headaches, or fever and rarely, aseptic meningitis, abnormal blood clots or kidney failure. This is an expensive short term therapy solution as often after a week or so the platelet count will drop. It is designed to be a 'rescue' therapy like corticosteroids for patients with ITP.

- **Anti-Rho(D) immune globulin** (WinRho SDF ®, Rhophylac ®) — Anti-D is also a liquid concentrate of antibodies derived from healthy human plasma. However, this medicine is targeted against the Rh factor* on red blood cells. It is thought that anti-D binds to red blood cells to such an extent that the spleen is fully occupied eliminating red blood cells and does not have much opportunity to remove the antibody-coated platelets. Like IVIg, the response is usually rapid but temporary. It also is designed to be a 'rescue' therapy like corticosteroids for patients with ITP, and can only be utilized by Rh+ patients, and those who have not had a previous serious serum reaction to IVIG.

Possible side effects: Temporary side effects from anti-D include fever, headache, chills, nausea and vomiting, anemia, and rarely, kidney failure.

- **Monoclonal antibodies — Rituximab** (Rituxan ®) is a monoclonal antibody approved by the FDA in November 1997 for treatment of lymphoma, a type of cancer. It is increasingly being used to treat ITP. It reduces the number of B cells. After rituximab treatment, the body can take up to a year to replace the eliminated B cells and have the immune system and antibody production back in full working order.

Possible side effects: Side effects that developed following 7% of infusions included headaches, chills, fever, and body aches. For patients with hypersensitivity to blood products there is a remote risk of anaphylaxis (shock response). A very small number of patients may experience severe anemia, which requires immediate medical attention. This is very rare. This therapy is used to elevate the platelet count more 'long-term' however for some ITP patients do not respond, or their platelet count drops after a few months. Some ITP patients have reported longer-term success.

- **Platelet growth factors** (such as Revolade®, Nplate®) — Platelet growth factors or thrombopoietin (TPO) receptor agonists are a class of treatments for ITP that stimulate the bone marrow to produce more platelets.

Possible side effects: Side-effects are not common, however those that have been reported include joint and muscle pain, dizziness, insomnia, indigestion, and 'pins and needles' sensations. Potential exists for patients to develop reticulum (fibrous growths) in the bone marrow however this is ultra-rare. The platelet count to drop below the pre-treatment count if the treatment is discontinued. ***Note: For avatrombopag (Doptelet® side effects reported included: In clinical trials with avatrombopag specifically, headache, fatigue, and arthralgia (joint stiffness) were the most common side effects reported.***

- **Splenectomy -** A splenectomy is the surgical removal of the spleen. The spleen acts like a large lymph node, helping to maintain a healthy immune system and cleaning the blood of foreign matter. In ITP, the antibody-coated platelets are often removed from circulation by the spleen. Thus, if the spleen is removed, the platelets will remain in the blood stream. However, a significant proportion (30-40%) of ITP patients will not see a change in their platelet count after having their spleen removed.

Possible side effects: The immediate complication rate from surgery is about 10%, require even more time in the hospital, although estimates vary. The fatality rate from the surgery is about 1% (1 in every 100 people) for an open splenectomy and much less for a laproscopic procedure. Since the spleen is responsible for making antibodies, filtering the blood, and removing bacteria, those without a spleen have an impaired immune system, difficulties recovering from pneumonia, meningitis, Hib flu, sepsis, hospital-based infections, malaria and other parasitic diseases, babesiosis (a tick-borne disease) and gram-negative bacterial diseases from animal bites. People who have had a splenectomy have more microparticles in their blood, giving them an increased risk of dementia and heart attacks from blood clots. They are also more prone to blood vessel complications. This surgical procedure results in taking up limited surgical space, occupying a limited hospital bed, and requires ongoing medications while putting the patient at risk for complications requiring even more time off work/school, and death.

- **Fostamatinib** - A new approach to treating ITP is the use of a spleen tyrosine kinase (SYK) inhibitor. The agent fostamatinib disodium hexahydrate (TAVALISSE®) may slow the destruction of antibody-coated platelets in people with chronic ITP by specifically targeting SYK. Spleen tyrosine kinase (SYK) is part of a network of proteins (found in certain cells of the immune system) that triggers platelet destruction.

Possible side effects: Adverse reactions reported included high blood pressure, elevated liver enzymes, diarrhea, and a decrease in white blood cell counts. Common less serious side effects include nausea, rash, dizziness, tiredness, respiratory infection, chest pain, and stomach (abdomen) pain.

5. Improved Outcomes

CADTH is interested in patients' views on what outcomes we should consider when evaluating new therapies. What improvements would patients and caregivers like to see in a new treatment that is not achieved in currently available treatments? How might daily life and quality of life for patients, caregivers, and families be different if the new treatment provided those desired improvements? What trade-offs do patients, families, and caregivers consider when choosing therapy?

Avatrombopag (Doptelet) is one of three thrombopoetin receptor agonists (TPO-RAs), a class of platelet growth factors used to treat patient with chronic immune thrombocytopenia (cITP). Other TPO-RAs include eltrombopag (Revolade/Promacta) and romiplostim (Nplate). Avatrombopag is usually used for ITP treatment in those who have not responded well (or at all) to other available TPO-RAs, or to a first-line agent (such as steroids or IVIG). Avatrombopag is taken once daily with food, with no dietary restrictions. Since the drug can be taken without dietary restrictions, it is much more convenient to take and safer to take as doses are not affected by common nutrients such as fat or divalent cations present in a single serving of difficult dairy, grain, and vegetable products. With

eltrombopag diet modifications must be made for the drug to be properly absorbed into the system. As a result of these dietary restrictions, many patients with ITP are getting up at 3am before requiring breakfast so they don't have to worry about any dairy products interfering with the metabolism of the drug. Due to eltrombopag's absorption being impacted by common nutrients, it essentially means cITP patients need to fast for 4-6 hours (depending on their dose) prior to taking the medicine. Avatrombopag is also more convenient to use compared to romiplostim which requires chronic ITP patients to take a day off work once a week for clinic visit and a subcutaneous infusion. Overall, cITP patients want to use what will work, however avatrombopag offers many advantages that its competitors do not. And that is worth considering, especially in terms of overall costs.

Currently, TPO-RAs of any kind are not readily available to adults with cITP. They often cannot access these therapies without private insurance or self-pay.

Patients often do not have a choice over what therapies they can use, or how they will respond. There is no way to predict who will respond to a certain treatment, and who will not. It is also not clear who will develop a resistance to a particular drug over time, and who will not. Patients need options available to them to switch if their current therapy is no longer worker, and their bleeding is not under control, or they are at risk to have a critical bleed.

TPO-RAs such as avatrombopag are generally well tolerated, and as a result they do not have as many side-effects compared to other available therapies. In clinical trials with avatrombopag specifically, headache, fatigue, and arthralgia (joint stiffness) were the most common side effects reported. Headache was the most frequent of these three and were shown to be managed with acetaminophen (Tylenol) and dose reduction if necessary (Allen et al, 2018). Avatrombopag has other advantages over other TPO-RAs, specifically eltrombopag, in that there are no short-term risks for liver failure, does not require monitoring for liver abnormalities thus less clinic visits, and does not seem to chelate iron (https://aob.amegroups.com/article/view/6335/html). In fact, avatrombopag has been shown to be safe and effective in the treatment of thrombocytopenia for patients who have chronic liver disease and does not show significant differences (like eltrombopag does) in terms of platelet count responses based on race (Cheloff and Al-Samkari, 2019).

Avatrombopag can be used in the perioperative setting to avoid platelet transfusions, which also carry a lot of risks to the patient, not to mention is costly and in limited supply. Avatrombopag has been shown to increase platelet counts in less than eight days and has been shown (on average) to keep platelet counts above 50, 000 µL for at least 3 months which avoids risks for critical bleeding at that level. Unfortunately, a side effect can be gum bleeding or petechiae, so it could look like bleeding isn't reduced for some, but the reality is the risk for critical bleeding is based on avoiding a critically low platelet count.

Ideally, patients want therapies that do not impact their schedule and daily life since they often already miss a lot of work due to their multiple appointments and fatigue. It is much easier and more convenient to take a daily pill then go into the hospital or clinic for a weekly injection or to have a six-hour infusion like IVIG. Time off work and parking are expenses. Patients also want something that has little to no side effects and aren't willing to feel terrible all the time like they do on steroids, highlighting the need for therapies to improve quality of life, not further reduce. Patients want a therapy that lasts longer than a week. They don't want to live when and where the next bleed will be. Fear and anxiety of nose bleeds that can last for hours, mouth blisters, bruises all over their body, and debilitating fatigue. ITP is a rare disease. Even rarer are those that require therapy daily. It perhaps is more cost-effective to treat ITP and cover the cost of the drugs those that need it require, than to deal with the long-term costs of hospitalizations, life-support if an intra-cranial hemorrhage (ICH) or other life-threatening bleeding occurs, and the cost on society if ITP patients are unable to work and require disability because they cannot attend work regularly. The cost of IVIG weekly is very high. Supply is limited. The cost of treating steroid related long term health concerns is perhaps even greater. It's time to treat ITP patients with humanity and cover drugs that treat with minimal side effects and last. Prevention is key with ITP.

6. Experience With Drug Under Review

CADTH will carefully review the relevant scientific literature and clinical studies. We would like to hear from patients about their individual experiences with the new drug. This can help reviewers better understand how the drug under review meets the needs and preferences of patients, caregivers, and families.

How did patients have access to the drug under review (for example, clinical trials, private insurance)? Compared to any previous therapies patients have used, what were the benefits experienced? What were the disadvantages? How did the benefits and disadvantages impact the lives of patients, caregivers, and families? Consider side effects and if they were tolerated or how they

were managed. Was the drug easier to use than previous therapies? If so, how? Are there subgroups of patients within this disease state for whom this drug is particularly helpful? In what ways?

Avatrombopag is not an up-front therapy for ITP patients, so often this drug is accessed (in places where it's available) by patients who have tried multiple therapies in past and their platelet count continues to be low, and they continue to be at risk for critical bleeding. For many ITP patients who have not had a response to Rituximab or a TPO agent, avatrombopag may be their only hope.

Avatrombopag is taken orally on a daily basis with food (no food restrictions), so it is easier and more convenient to use than other medications compared to other treatments requiring patients to come into the 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 where a major organ is removed not always addressing the low platelet count and then leaving the individual unable to fight of various infections without a spleen. These scenarios are recommended against, in the new updated ASH (2019) guidelines.

7. Companion Diagnostic Test

***If** the drug in review has a companion diagnostic, please comment. Companion diagnostics are laboratory tests that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies or monitor clinical responses to optimally guide treatment adjustments. What are patient and caregiver experiences with the biomarker testing (companion diagnostic) associated with regarding the drug under review?*

Consider:

- *Access to testing: for example, proximity to testing facility, availability of appointment.*
- *Testing: for example, how was the test done? Did testing delay the treatment from beginning? Were there any adverse effects associated with testing?*
- *Cost of testing: Who paid for testing? If the cost was out of pocket, what was the impact of having to pay? Were there travel costs involved?*
- *How patients and caregivers feel about testing: for example, understanding why the test happened, coping with anxiety while waiting for the test result, uncertainty about making a decision given the test result.*

There is no companion diagnostic test for Avatrombopag.

8. Biosimilar

***If** the drug in review is a biosimilar (also known as a subsequent entry biologic), please outline any expectations or concerns held by patients, caregivers, and families about the biosimilar. If the biosimilar was less expensive than the brand name drug, what would the impact be for patients, caregivers, and families?*

There is no biosimilar for Avatrombopag.

9. Anything Else?

Is there anything else specifically related to this drug review that CADTH reviewers or the expert committee should know?

As acknowledged in other submissions to CADTH, there are several treatments for ITP, but for many with ITP these current therapies do not work, or they are not accessible (financial barriers or age barriers) to all. Patients often cycle on and off various therapies in the hopes that the treatment will raise the platelet count. For the small number of ITP patients requiring this therapy, what would be the downside in covering the cost for them when this drug may save their life? ITP patient's refractory to steroids and/or other ITP therapies are at a high-risk for critical bleeding. The side-effects that could happen because of taking this drug can be successfully managed (described above). The trade-off seems simple – treat the side effects because you cannot bring back an ITP patient who has died.

It is important for CADTH to understand that often cITP patients need to switch to a different TPO-RA if one doesn't work or has stopped working overtime. For instance, "Published retrospective studies showed that >75% of patients who switched to the alternate TPO-RA maintained or achieved a response with the new treatment. Notably, most patients who switched due to lack of efficacy with

the first TPO-RA responded to the alternate TPO-RA, which demonstrates an absence of cross-resistance between the two drugs. Therefore, switching to an alternate TPO-RA (if the first TPO-RA fails to demonstrate a response) should be considered before the use of a less-preferable option (Carpendo et al. 2019)". As a result, it's important for ITP patients to have options as they have no control over what they will respond to.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH CDR and pCODR programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. *Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.*

   No

2. *Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.*

   No

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.*

   PDSA has received funding from the following pharma companies:

   Argenx, Amgen, Dova/Sobi, Novartis, UCB, CSL Behring, Principia, Pfizer, Sanofi, Momenta, Rigel.

   Novartis and Amgen currently have ITP drugs in Canada.

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
Argenx				
Dova/Sobi				
UCB				
CSL Behring				
Principia				
Pfizer				
Sanofi				
Momenta				
Rigel				

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.

Name: Jennifer DiRaimo, MS, CCGC

Position: Research Program Manager

Patient Group: Platelet Disorder Support Association

Date: February 16, 2022

Below is a support letter from the Network of Rare Blood Disorders Organization.

February 11, 2022

CADTH

865 Carling Ave, Suite 600

Ottawa, ON K1S 5S8

Re: Support for PDSA's stakeholder input regarding the reimbursement review for avatrombopag

To the Review Committee,

I am writing today in support of the Platelet Disorder Support Association (PDSA)'s response to CADTH's call for stakeholder input regarding the reimbursement review for avatrombopag, a thrombopoetin-receptor agonist. Avatrombopag is used to treat ITP when other therapeutic agents have failed to work well.

The Network of Rare Blood Disorder Organizations (NRBDO) would like to reiterate the need for improved access to second line therapies for the treatment of immune thrombocytopenia (ITP), particularly for those who have not had success responding to more traditional first-line therapies available to treat this condition, such as steroids and IVIG.

Steroids and IVIG are not long-term solutions to a low platelet count, and some individuals with ITP require long-term, ongoing treatment. Steroids have many long-term health effects, and for ITP patients, IVIG is only a short-term rescue therapy. Canadian Blood Services has also indicated that the blood plasma sufficiency issue in Canada is "critical," signalling it is a benefit to remove barriers to access to therapies such as avatrombopag to decrease IVIG demand.

Each patient with ITP responds differently to particular therapies. For some, avatrombopag may be the only medication that will successfully elevate their platelet count and prevent critical bleeding. Equitable access is needed urgently. All patients deserve to receive treatment that works and could save their life.

The NRBDO is committed to ensuring that the patient voice be heard. We strongly support the efforts of the PDSA and the ITP patient community to seek reimbursement for avatrombopag for the treatment of those with ITP when other therapeutic options have failed to work well.

Sincerely,

Jennifer van Gennip

Executive Director, NRBDO

[redacted]

https://www.nrbdo.ca/

Clinician Group Input

Canadian Hematology Society (CHS)

Generic Drug Name (Brand Name): **Avatrombopag**
Indication: **Immune thrombocytopenia (ITP)**
Name of Clinician Group: **Canadian Hematology Society (CHS)**
Author of Submission: [redacted]

About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

The CHS is a professional association founded in 1971, whose membership includes adult and pediatric hematologists and hematopathologists. The mail goal of the organization is to maintain the integrity and vitality of the specialty of hematology, by participating with the Royal College of Physicians and Surgeons of Canada in designing training programs for our successors, encouraging and rewarding scholarly research, and providing a forum for communication and mutual support for all of our colleagues in community and academic settings.

https://canadianhematologysociety.org/

Information Gathering

Please describe how you gathered the information included in the submission.

Information was gathered from the perspectives of Canadian hematologists who treat ITP through direct communication with the Canadian Hematology Society and hematologists with expertise in this area. We performed a review of the literature and a review of current clinical practice guidelines by the American Society of Hematology (2019), the International Consensus Report on Immune Thrombocytopenia (2019) and guidelines from other international societies (British Hematology Society. The information was incorporated into the submission from the perspective of treating physicians in Canada.

Current Treatments

Describe the current treatment paradigm for the disease.

- Focus on the Canadian context.
- Please include drug and non-drug treatments.
- Drugs without Health Canada approval for use in the management of he indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?
- Treatments available through special access programs are relevant.
- Do current treatments modify the underlying disease mechanism? Target symptoms?

Immune thrombocytopenia (ITP) is a hematological autoimmune disease characterized by premature platelet destruction and impaired platelet production leading to a profound reduction in platelet count levels (thrombocytopenia). The incidence of ITP is estimated to be 2 to 5 per 100,000 persons per year, and the prevalence is 10 – 25 per 100,000 persons. The multi-peak incidence of ITP occurs in women, young children and older adults. Individuals with ITP are at risk of severe bleeding and life-threatening hemorrhage due to the severe thrombocytopenia. Other clinical outcomes are infection (from immunosuppressant treatments), fatigue and overall reduced quality of life. ITP is classified as acute (from initial presentation to 3 months), persistent (3 – 12 months) and chronic (>12 months) reflecting the natural history of this disorder. ITP becomes a chronic disease in 80% of adults. Patients also experience anxiety and depression. They often require multiple visits to the clinic, long chair times in the day units from intravenous treatments and transfusions, and hospital stays due to bleeding complications. The toll on the healthcare system is substantial since sudden relapses require emergency visits, hospitalizations and interventions for bleeding complications. Patients with severe and refractory ITP have are at 4-times higher risk of mortality than the general population.

The most widely accepted guidelines for the management of ITP are the clinical guidelines from the American Society of Hematology (Neunert et al, Blood Advances 2019) and the International Consensus Report (Provan et al, Blood Advances 2019). In brief, these clinical practice guidelines recommend the following:

- For patients with ITP who have platelet counts above 30 $x10^9$/L without bleeding symptoms, regular monitoring with careful observation is warranted.

- For patients with severe thrombocytopenia (platelet count <20 – 30 $x10^9$/L) with, or at risk of bleeding, first line therapy should be instituted using corticosteroids such as prednisone or dexamethasone. If a more rapid response is required because of bleeding or severely reduced platelets counts in high risk patients, then intravenous immunoglobulin (IVIg) is also recommended.

- Most adult patients with ITP (>80%) will relapse following first line therapy. For second-line therapy, the ASH guideline recommends TPO-receptor agonists (romiplosim, eltrombopag, avatrombopag), rituximab (monoclonal anti-CD20) or splenectomy. The international consensus report also recommends fostamatinib, the oral SYK inhibitor, and both guidelines suggest that splenectomy should be delayed by at least a year so that surgery and its associated long-lasting immune suppression can be avoided as much as possible. Splenectomy is associated with surgical and anaesthetic complications, risks of major overwhelming sepsis that is greatly reduced (but not eliminated) by current vaccinations, and risks of clotting (thrombosis). Due to concerns of increased risk of infection during the Covid-19 pandemic, international ITP experts from the British Society of Hematology and American Society of Hematology have recommended avoiding rituximab and other immune suppressive mediations and rather prioritizing non-immune suppressant medications such as the TPO-receptor agonists (Pavord S, et al. Br J Haematol. 2020;189:1038–43; Bussel J, et al. American Society of Hematology COVID-19 resources.

https://www.hematology.org/covid-19/covid-19-and-itp)

- Other second-line treatments that have been used in ITP patients with some success include immunosuppressive medications such as azathioprine, cyclophosphamide, cyclosporine and mycophenolate; danazol; and dapsone. These are generally less favourable because of their side effect profile and risk of infection, especially in the context of the Covid-19 pandemic.

In the current Canadian context, this algorithm is rarely followed because: 1) TPO receptor agonist medications are difficult to access; 2) splenectomy is unfavorable as a treatment option for many patients and providers given the surgical risks and long term immunosuppression, and 3) rituximab access is limited and associated with vaccine failures, including Covid-19 vaccine failures. As an example, in Ontario, the Exceptional Access Program, will only cover a TPO receptor agonist medications after a patient has undergone a splenectomy and failed two other second line therapies. A group of authors recently summarized the different criteria for accessing TPO receptor agonist medications across provinces and territories and found wide differences in these criteria (see Appendix 1: *Access to thrombopoietin receptor agonist medications for patients with immune thrombocytopenia in Canada: An example of health inequity*- confidential, included here with permission from the authors). A recent study of second-line treatments for ITP specifically in the Canadian context showed that the most common second-line therapies were immunosuppressant medications (n = 106; 52.0%), splenectomy (n = 106; 52.0%), TPO-RAs (n = 75; 36.8%), danazol (n = 73; 35.8%), and rituximab (n = 67; 32.8%). (see Appendix 2: Nazaryan et al, Can J Int Med, 2020).

Splenectomy, and to a lesser extent, rituximab and TPO receptor agonists may change the natural history of ITP. For splenectomy, approximately 70% off patients will respond initially and of those, 80% will have a long lasting remission (>5 years). For Rituximab (4 infusions once per week), 50 – 60% will show an initial response, and of those 20% will have a lasting remission >5 years. For TPO receptor agonists (daily or weekly maintenance), 80% of patients with respond, and recent reports suggest that up to 30% will have a lasting response once the drug is discontinued after a treatment period of 3 – 6 months. Note that the TPO-receptor agonists romiplostim and eltrombopag, and the oral Syk inhibitor, fostamatinib, are Health Canada approved for the treatment of ITP. Avatrombopag (Doptelet) is currently under Health Canada review.

Treatment Goals

What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

The goals of treatment may be different depending upon whose perspective you are attempting to capture: patient vs treating physician.

The most important goal for a treatment in ITP is to raise the platelet count in patients with ITP. Below a severe level (approximately 30 $x10^9$/L or less) the platelet count correlates tightly with the clinical endpoints of bleeding and quality of life (Arnold DM. Am J Hematol. 2012). Moreover, the platelet count provides an objective measure of the bleeding risk and a method of stratifying risk among patients with additional risk factors for bleeding e.g. patients on anticoagulant medications or patients requiring surgical interventions. Severe bleeding outcomes in patients with ITP are generally quite rare – in one report, only 18% of patients presenting to the emergency department with ITP and a platelet count less than 20 x 109/L had severe bleeding complications (Mithoowani et al, J Thrombosis and Haemostasis 2020). Thus, it is very difficult to show improvements in bleeding complications in clinical trials in this rare disease population.

For both patients and clinicians, improving the quality of life by balancing bleeding prevention and minimizing treatment toxicities is paramount. This became highly relevant in the era of the COVID-19 pandemic. Many of the second-line (rituximab, splenectomy) and third-line therapies (azathioprine, cyclophosphamide, mycophenolate mofetil) are immunosuppressive, and have the potential of increasing the severity of COVID-19 infection and attenuating the response to vaccination. This is especially relevant for rituximab, a monoclonal antibody against CD20, which causes prolonged B cell depletion, secondary hypogammaglobulinemia and marked attenuation of vaccine responses including Covid-19 vaccines.

The ideal treatment for ITP would alter the natural history and 'cure' the underlying disease process. This has proven to be very difficult in ITP and in virtually all other autoimmune conditions. While splenectomy and rituximab have been associated with long term remissions, their use is less favored because of toxicities especially during the Covid-19 pandemic. TPO receptor agonists were designed as maintenance treatments, but they too have been shown to induce remission in up to 30% of patients with ITP after 3 – 6 months of treatment. Second most important priority is to raise the platelet count so that bleeding can be averted and quality of life, fatigue and other patient important outcomes can be improved. The TPO receptor agonists, including avatrombopag, can raise platelet counts and maintain an improved platelet count level in approximately 80% of patients, which is higher than any other ITP therapy.

Patients want to reduce the number of laboratory tests they do, the number of clinic visits they attend, and the time away from their personal and family lives. Patients and health care providers are concerned about side effects, the need for on-going monitoring, and lasting effect on physical and mental health, Most of the current ITP treatments have significant side effects especially corticosteroids, which are often used as rescue therapy. Corticosteroids lead to mood swings, irritability, agitation, insomnia, acid reflux, poor diabetic control, and increased risks of infections just to name a few. IVIg requires a significant amount of chair time, is expensive and in short supply. Besides side effects, many of the second-line ITP treatments are inaccessible to patients because of their cost. Patients without private insurance simply cannot afford these treatments.

The treating physician goals are somewhat complementary to those listed above but have other unique features. The goal certainly is to prolong life by reducing the risk of life-threatening bleeding. To be able to accomplish this, the goal is to increase platelet counts to "safe" ranges that may differ for day-to-day activities, perioperatively, and during pregnancy. Further, physician goals are to try to minimize costs to the patient and to the healthcare system (such as indiscriminate use of IVIg for weekly maintenance of ITP).

Treatment Gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- Not all patients respond to available treatments
- Patients become refractory to current treatment options
- No treatments are available to reverse the course of disease
- No treatments are available to address key outcomes
- Treatments are needed that are better tolerated

- Treatment are needed to improve compliance
- Formulations are needed to improve convenience

The unmet goals of current ITP treatments include:

- Current second-line treatments have unacceptable toxicity profiles. Splenectomy carries a life long risk of infection and immediate surgical and anesthetic risks. Rituximab causes immune suppression and vaccine failures and increases the risk of severe Covid-19 infection (hospitalization, ICU admission or death) (Avouac J et al, Lancet Haematology 2021; BachillerCorral J et al, J Rheum 2021).

- Cyclophosphamide and azathioprine are associated with a life-long risk of hematological malignancy or leukemia (therapyrelated myelodysplastic syndrome or acute myeloid leukemia) years later, due to exposure to cytotoxic agents.

- The need to prioritize non-immune suppressant medications. In UK, another publicly funded health care system, the British Society of Haematology has prioritized the use of TPO receptor agonists (as first-line ITP therapy) since the pandemic to reduce the risk of severe COVID-19 infection and recently published findings from their prospective study, demonstrating excellent response.

- Eltrombopag has poor bioavailability and patients must adhere to strict dietary limitations (no dairy x at least 4 hours around drug dosing) and drug-drug interactions.

- Romiplostim is a once per week subcutaneous injection, which is difficult or impossible for some patients.

- Other second line therapies such as immune suppressant medications (cyclosporine, mycophenylate, azathioprine), chemotherapeutics (cyclophosphamide) and danazol only work in a small proportion of ITP patients e.g. 50% or less for each treatment.

    - Not all patients respond to available treatments. Most adult patients with ITP have a chronic relapsing and remitting course requiring multiple lines of therapy.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

- Would these patients be considered a subpopulation or niche population?
- Describe characteristics of this patient population.
- Would the drug under review address the unmet need in this patient population?

In adults with ITP, the greatest unmet need is for those patients who have persistent or chronic ITP; that is, patients who require additional treatments after first-line therapy because of continued or recurrent severe thrombocytopenia with, or at risk for, bleeding. The drug under review, avatrombopag, would provide an alternative to the current unsatisfactory second-line therapies including splenectomy, immunosuppressive agents, rituximab and its biosimilars. It would be considered one of the TPO-RAs options in the right clinical context given the patient profile, the drug tolerability and safety profile, patient preference, and drug availability. Given its unique features that sets it apart from other TPO-RAs, avatrombopag may be better suited for various patients based on patient characteristics. Like eltrombopag, it can be taken orally but does not have dietary restrictions and has no significant hepatotoxicity.

In clinical trials, avatrombopag appears to be efficacious even in patients who have previously received romiplostim or eltrombopag.

The other population that stands to benefit from the addition of avatrombopag is the population of patients with severe refractory disease. This population includes patients who have failed other second-line therapies. These patients are at highest risk of poor outcomes including severe bleeding events and hospitalizations. These patients often have significant burden of disease with personal stress, anxiety, depression and impact on their families.

Place in Therapy

6.1. How would the drug under review fit into the current treatment paradigm?

- Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?
- Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?
- Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?
- Is the drug under review expected to cause a shift in the current treatment paradigm?

The mechanism of action of avatrombopag (Doptelet) is similar to other thrombopoietin receptor agonist (TPO-RAs), romiplostim and eltrombopag. It can be used as a single agent in those who have failed another ITP treatment and theoretically may be combined with other ITP treatments to provide a synergistic effect. Also, like eltrombopag, it can be taken orally. However, it has advantages over eltrombopag in that it does not have dietary restrictions and has no significant hepatotoxicity.

The drug under review is not the first treatment approved that will address the underlying disease process. The TPO-Ras help to increase the platelet production to overcome the degree of platelet destruction in ITP to maintain a higher platelet count in order to reduce negative outcomes in patients with ITP. This class of drug works by boosting platelet production from the bone marrow and thus overcoming the thrombocytopenia in ITP. It works as a maintenance therapy for symptomatic management. However, in recent studies, the TPO receptor agonist class of medications has been shown to induce remission in up to 30% patients after 3 – 6 months of drug exposure.

The drug under review would likely be used as a single agent after first-line therapy. Specifically, avatrombopag would be used as second-line therapy for patients who failed one or more course of treatment with corticosteroids and IVIG. In addition, avatrombopag would be an important therapeutic option for patients who were multiply resistant or refractory to other therapies, including other TPO receptor agonist medications.

The drug under review would likely cause a shift in the current treatment paradigm in Canada by enabling access to TPO receptor agonists in second line therapy. Currently the other TPO receptor agonists are not easily accessible and thus, non-immune suppressant treatment choices are not currently available. Avatrombopag would provide a very well tolerated and easy to administer oral drug option for second-line (and subsequent) treatments for patients with persistent or chronic ITP. It would be a welcome alternative to splenectomy, rituximab and other immune suppressant medications. It would be considered one of the TPO-RAs options in the right clinical context given the patient profile, the drug tolerability and safety profile, patient preference, and drug availability.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Avatrombopag would be appropriate after patients failed first-line therapy. First-line therapy should remain as corticosteroids such as prednisone or dexamethasone and in some cases where a rapid response is required IVIg should be given.

For patients with multiply resistant disease, it would be appropriate for avatrombopag to be used after patients failed a different second-line treatment (e.g. rituximab or some other immune suppressant medication). Avatrombopag should be considered prior to the off-label use of immunosuppressive agents such as cyclophosphamide, cyclosporine and azathioprine, as these agents not only have poor data in ITP, but also high toxicities including serious infections and hematological malignancies. Splenectomy should not be a requirement before avatrombopag.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

The drug under review should be used in second and subsequent line therapies. It should be considered along with splenectomy, rituximab and its biosimilars and before other immunosuppressive agents, and be comparable to maintenance treatments along with the other currently available TPO-RAs, romiplostim and eltrombopag. Thus, this would not be a departure from the sequence of treatments recommended by international guidelines, but would represent a great advancement for the care of patients in Canada.

If no improvement in ITP is obtained after a trial of avatrombopag, then options such as splenectomy, immunosuppressive agents, rituximab and its biosimilars would be considered. This would not be a significant departure to the typical sequencing of therapies.

6.4. Which patients would be best suited for treatment with the drug under review?

- Which patients are most likely to respond to treatment with the drug under review?
- Which patients are most in need of an intervention?
- Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

It is likely that ITP patients earlier in their disease course will respond better to the drug under review. Thus, utilizing avatrombopag in 2nd line likely has the advantages of better and more robust response and limiting exposure to the complications and toxicities of other lines of therapy such as splenectomy, immunosuppressive agents, rituximab and its biosimilars.

In addition to patients who require second-line therapy, patients who are multiply relapsed/refractory are most in need of an intervention. Avatrombopag could fill that important gap in care since other TPO RAs are not currently available, and avatrombopag has more favourable bioavailability and less hepatic complications than eltrombopag.

6.5. How would patients best suited for treatment with the drug under review be identified?

- Examples: Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)
- Is the condition challenging to diagnose in routine clinical practice?
- Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)
- Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?
- Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

ITP patients are managed predominantly by hematologists, or internal medicine specialists. Patients with relapsed disease are invariably referred to hematologists and therefore, patient best suited for treatment with avatrombopag would be identifiable from hematology clinics. Patients with relapsed disease sometime end up in the emergency room or admitted to hospital where they are also referred to hematologists.

ITP relapses are characterized by a drop in platelet count (typically below 30 $\times 10^9$/L) with or without bleeding. The ITP condition may be challenging to diagnose in routine clinical practice initially because ITP is a diagnosis of exclusion. However, a transient platelet count response to corticosteroids or IVIG is a good indicator of the ITP diagnosis. Thus, since patients would have been exposed to first line therapy before receiving avatrombopag, ambiguity for the diagnosis would be minimized.

For relapsed ITP, the diagnosis is less ambiguous and when relapse occurs is more easily defined as a drop in platelets less than 30 $\times 10^9$/L or with bleeding symptoms. Platelet counts are done on a standard CBC that is readily available in all laboratories, not very invasive for patients, and accessible to patients.

There is a role for treatment for asymptomatic patients with platelets < 30 $\times 10^9$/L who are at risk of bleeding. This is especially true for patients with additional bleeding risk factors including anticoagulant medications or who require invasive procedures or surgery. This is aligned with recommendations from the American Society of Hematology 2019 guidelines.

6.6. Which patients would be least suitable for treatment with the drug under review?

As discussed above, the drug under review, avatrombopag, would be least suitable in first line therapy as other therapies are preferred in that setting including corticosteroids and IVIG if a faster response is required.

In the phase 3 trial of avatrombopag (Jurczak W et al, Br J Haematol 2018), patients with recent thromboembolic events, cirrhosis, and myelodysplastic syndrome were excluded. These patients would be less suitable for treatment with the drug under review.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Currently, there is no predictor of platelet count response with avatrombopag or any of the TPO receptor agonists. However, in general, patients who at an earlier stage of disease tend to respond more favourably to treatment. This may be especially true for TPO receptor agonists as these medications may be more likely to induce remission in patients with early-stage disease.

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

In ITP, patients are monitored regularly with bloodwork (CBC that includes platelet counts) and clinically in a healthcare setting

(clinics, hospital). Platelet count response criteria have been published and are commonly used in clinical trials and in practice (Rodeghiero F et al. Blood. 2009). These criteria are:

- Complete response: platelet count ≥ 100 × 10^9/L and absence of bleeding
- Response: platelet count ≥ 30 × 10^9/L and at least 2-fold increase the baseline count and absence of bleeding
- Time to response: time from starting treatment to time of achievement of complete response or response
- No response: platelet count < 30 × 10^9/L or less than 2-fold increase of baseline platelet count or bleeding
- Loss of Complete response or response: platelet count below 100 × 10^9/L or bleeding (from CR) or below 30 × 10^9/L or less than 2-fold increase of baseline platelet count or bleeding (from R)

Although the platelet count is strictly speaking a surrogate marker, it is well accepted as the principal indicator of disease activity and has been shown to predict clinical outcomes including bleeding, the need for rescue therapies and quality of life once platelet count levels drop significantly.

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)
- Attainment of major motor milestones
- Ability to perform activities of daily living
- Improvement in symptoms
- Stabilization (no deterioration) of symptoms

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

A clinically meaningful response would be to achieve and maintain a platelet count above 30 x10^9/L. This would translate to a negligible risk of serious bleeding for nearly all patients. A separate goal of therapy is remission, which would be indicated by a platelet count above 100 x10^9/L (or the achievement of a normal platelet count) off therapy. The achievement of a platelet count above 30 x10^9/L also translates to improved quality of life for most patients, less fatigue which can be debilitating for patients, avoidance of hospitalizations and fewer clinic visits.

6.10. How often should treatment response be assessed?

Typically, adult patients with ITP require weekly bloodwork and/or assessments that can gradually be reduced in frequency once a response is achieved. There is no specific guideline for how often to assess based on platelet levels. The frequency and type of assessments will depend on the severity of the ITP presentation, patient factors such as willingness and availability to attend these investigations and assessments, and clinician factors of availability and comfort with managing ITP.

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- Disease progression (specify; e.g., loss of lower limb mobility)
- Certain adverse events occur (specify type, frequency, and severity)
- Additional treatment becomes necessary (specify)

ITP treatments are often discontinued if there is disease progression (worsening drop in platelets, increased bleeding), adverse side effects, or if “rescue” treatments are frequently required. This should take into account the variability in patient preferences and clinician practices.

Due to the high costs of TPO receptor agonists, and the possibility of remission induction with these medications, clinicians often will gradually taper these medication once a stable platelet count is achieved after 6 – 12 months of treatment. Similar to romiplostim and eltrombopag, this would be an expected practice with avatrombopag.

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

The drug under review would be mostly applied to the outpatient setting (patients seen in community setting or outpatient hospital clinic). The drug may also be useful in the emergency room or for hospitalized patients if the clinical presentation is severe and if the patient is failing other treatments. The time to response with avatrombopag is within 1 week.

The drug is anticipated to be more widely applicable compared with other TPO receptor agonists including the other oral agent, eltrombopag. This is because avatrombopag has the added benefit of better bioavailability with no dietary restrictions and a lower risk of hepatotoxicity. Unlike eltrombopag, no dose adjustment is required for avatrombopag for individuals of east Asian descent. Our American colleagues tell us that avatrombopag tends to be their first choice of TPO receptor agonist medication for most patients.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Typically, ITP patients who relapse after first line therapy or ITP patients with resistant disease are referred to a Hematologist for diagnosis, treatment, monitoring and long term management.

Additional Information

Is there any additional information you feel is pertinent to this review?

The drug under review is an active agent that works best when used early in the course of the ITP disease. It can spare patients from an invasive surgery, such as a splenectomy and the associated immune suppression with splenectomy or rituximab. The therapy is taken orally, thus it is easy to administer, plus it does not interact with other drugs or food. Avatrombopag is well tolerated and effectively increases platelet production in most patients with ITP. Hematologists view the data for the class of TPO receptor agonist medications as applicable to Avatrombopag. Thus, while we acknowledge that the number of patients in phase II-III trials treated with avatrombopag is relatively low, we consider the totality of the data from all TPO receptor agonists for ITP (including romiplostim and eltrombopag) directly applicable.

Collectively, we strongly support the need for avatrombopag (Doptelet) as a second-line treatment option for patients with ITP. Compared to other countries, including those with similar health care systems such as the UK, Canadian patients are being disadvantaged because of severely limited access to TPO receptor agonists in Canada. Both romiplostim and eltrombopag received negative decisions from CADTH in the past. Avatrombopag has advantages over those because it is an oral drug with good bioavailability and less risk of hepatotoxicity.

Conflict of Interest Declarations

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 clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

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. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Jason Berman
Position: President, CHS
Date: February 16, 2022

☒ **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.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Paladin			X	
Pfizer			X	
Hoffman La Roche			X	
Seagen Canada Inc.	X			
CSL Behring	X			

SOBI		X		
AstraZeneca Canada			X	
Janssen J&J	X			
Dr. Reddy's Laboratories	X			
Alnylam			X	
Astellas			X	
Incyte			X	
Novartis	X			
Grifols	X			
Bristol Myers Squibb			X	
Takeda	X			
Scientific Advisory Board – Oxford Immune Algorithmics	X			

* Place an X in the appropriate dollar range cells for each company.