CADTH

CADTH Reimbursement Review

Patient Input

FOSTAMATINIB (Tavalisse)

Medison Pharma Canada Inc.

Indication: Chronic immune thrombocytopenia

CADTH received patient input from:

Platelet Disorder Support Association

August 16, 2021

Name of the Drug and Indication	Tavalisse (Fostamatinib)
Name of the Patient Group	Platelet Disorder Support Association
Author of the Submission	[redacted]
Name of the Primary Contact for This Submission	[redacted]
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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 70,000 unique visitors to our website per month (www.pdsa.org). In 2020, Canada was one of the top three countries providing unique visitors to the PDSA website. We have 16,414 contacts in our data base (13,461 adults and children; 2,953 physicians) from 130 countries. In Canada alone, we have 635 adults and children in our data base, and 115 physicians. We have 59 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.

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.*

The following patient comments were collected from the PDSA Facebook page. Due to access issues to this drug, to collect enough meaningful experiences for you we had to go back as far as 2018-present. The following (see below) represent people from across the U.S. and Canada and are from adult patients only:

- "Im on Tavalisse for the last 2 years and haven't had any adverse side effects. The good thing is that my platelets are … 160-210K. Never had these numbers. Before I went through every medication/protocol possible and my platelets were 10K or below."
- "Excited to see platelets at 63000! Highest in year since diagnosed. On tavalisse and 10 mg steroids. I normally stay 20-30000. Been on rituximab and Promacta and now tavalisse which none have keep my platelets up."
- "Promacta stopped being effective after many years for me dropping to 2k, Tavalisse has kept me above 70K …"
- "it keeps me around 150,000 – 200,000… I've been on Tavalisse for 2 years."
- "With Tavalisse I am between 55,000-204,000"
- "16 months on Tavalisse, platelets were 467 yesterday 🙏."
- "For me, mine went up to over 200,000 after a week. Not sure what experience others have had but I've never been below 200,000 since I started taking it."
- "I had an immediate response within a week also going into the 200s.. I've had an upset stomach here and there but nothing major."
- "Tavalisse … holding me steady and rising, 188k. Yesterday, I got to kick off 2020 with a bang! 500k for the first count of the year !!!"
- "Yes. Platelets shot up for me and I am also doing Nplate. 13 to 39 to 59 last week. I am usually below 20 for years on Nplate."
- "I've been on Tavalisse for almost 2 years (Nplate and Promacta didn't work for me). A game changer for me! I did come with side effects – elevated blood pressure and chronic diarrhea but both are managed. My numbers have been 80-350K, much better than 20K or lower where they sat for a year."
- "Game changer for me. It gave me my life back – no steroids. The side effects are manageable and so much better than with any of the other drugs I took."

- “I started (Tavalisse) in August. Currently at 127K – tapered off of prednisone 4 weeks ago. This is the longest period of time that counts have remained stable.. have tried it all!”
- “I began taking this at the end of November and it seems to work platelets stay between 89-149K last week 113K. I take 100mg twice a day.”
- “Wish this was in Canada since nothing else works platelets have been under 5K for months.”
- “You guys!!! After 2 weeks on Tavalisse, my patelets are at 189 thousand!!!”
- “I’m on the lowest dose, every other day, no side effects except a rare upset stomach and last count was 370. I was diagnosed 12 years ago. Have tried prednisone, ivig, Promacta, Rituxan, dexamethasone, splenectomy, … and Tavalisse has been the only one I can tolerate and that has worked long term.”
- If you all can get on tavalisse, do it! No side effects for me (yet). It’s been 3 weeks. Can you say 320? I’ve done promacta and n-plate with terrible side effects. This stuff works. So far so good! Took about 2 1/2 weeks to kick in 💪😊😘”
- “I’ve been doing Tavalisse for about 3 months and I am doing great on 300mg my counts have been remaining at 400K since last week.”
- “Ok, Canadians. My doctor said I probably wouldn't be able to get it unless my spleen is removed.”

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 on a daily basis. 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 specialist health care provider in an emergency situation 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 a platelet count where it elevates the risk for bleeding and improves fatigue 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) similar to 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 ensure steroids on a daily basis 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 similar to 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 similar to 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® or 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.

- **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?

Patients often do not have a choice. They may not respond well (or at all) to other therapies or be able to afford other options. 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.

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 of 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 on a daily basis. 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 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. 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?

Currently, access to Fostamatinib in Canada is only through private insurance or self-pay. Fostamatinib is not an up-front therapy for ITP patients, so often this drug is accessed 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, Fostamatinib may be there only hope. Fostamatinib is taken daily orally, 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 Tavalisse.

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 Tavalisse.

9. Anything Else?

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

While there are a number of treatments for ITP, for many with ITP these current therapies do not work. 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 live? ITP patients refractory to steroids and other ITP therapies are at high for critical bleeding. The side-effects that could happen as a result of taking this drug can be successfully managed (such as elevated blood pressure). The trade-off seems simple – treat the side effects because you cannot bring back an ITP patient who has died.

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
Position: Research Program Manager
Patient Group: Platelet Disorder Support Association
Date: 5 July, 2021