CADTH REIMBURSEMENT REVIEW

Patient and Clinician Group Input

iptacopan (TBC)

(Novartis Pharmaceuticals Canada Inc.)

Indication: The treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

August 23, 2024

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.

Patient Group Input

Name of Drug: Iptacopan

Indication: Paroxysmal Nocturnal Hemoglobinuria

Name of Patient Group: The Canadian Association of PNH Patients & Aplastic Anemia

Author of Submission: Barry Katsof & Cindy Anthony

1. About Your Patient Group

The Canadian Association of PNH Patients

Established in 2009, this patient advocacy group is a non-profit Canadian organization dedicated to serving individuals affected by Paroxysmal Nocturnal Hemoglobinuria (PNH). Its mission is twofold: to connect Canadians impacted by PNH and to advocate for optimal patient care, ensuring access to the latest tools and information for managing the condition effectively. Additionally, the organization offers support to caregivers and endeavors to raise awareness and understanding of PNH.

The Canadian Association of PNH Patients was initiated by Barry Katsof, a PNH patient, driven by his recognition of the inadequate support available to individuals in need of life-sustaining medications. Barry's own journey, characterized by successful self-advocacy in accessing the first biologic treatment, inspired him to extend his knowledge and support to all Canadians affected by PNH. Today, he channels his experiences to assist every Canadian PNH patient facing similar challenges to those he encountered back in 2007. The website is: http://www.pnhca.org

Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC)

AAMAC was established in 1987 by a parent deeply affected by their child's aplastic anemia diagnosis. Among its primary objectives was advocating for the creation of a national bone marrow donor registry in Canada. Today, AAMAC stands as a federally incorporated and registered national charity with a bold mission: to offer comprehensive support to every Canadian affected by aplastic anemia, myelodysplasia, or PNH, including patients, family members, friends, and healthcare providers. The website: https://aamac.ca/

About PNH

PNH is a rare, chronic, and serious blood disorder caused by complement-mediated destruction of red blood cells (RBCs). Individuals with PNH have an acquired mutation in some of their hematopoietic stem cells, located in the bone marrow, which develop into RBCs, white blood cells, and platelets. This mutation results in the production of RBCs that are vulnerable to premature destruction by the complement system, leading to both intravascular hemolysis (within

blood vessels) and extravascular hemolysis (primarily in the spleen and liver). These processes cause anemia, thrombosis (blood clots), fatigue, and other debilitating symptoms that significantly impact quality of life.

Anemia, resulting from the destruction of RBCs, leads to a deficiency in the oxygen-carrying capacity of the blood. This can cause severe fatigue, weakness, and shortness of breath, making it difficult for individuals to engage in everyday activities. The ongoing need for blood transfusions to manage anemia can be both physically exhausting and emotionally challenging, as it requires frequent hospital visits and constant medical supervision.

Thrombosis, or the formation of blood clots, is a serious complication of PNH and can occur in unusual sites such as the veins in the abdomen, liver, brain, and skin. These clots can lead to life-threatening conditions such as stroke, pulmonary embolism, or Budd-Chiari syndrome, significantly increasing morbidity and mortality in PNH patients. Managing thrombosis often requires anticoagulant therapy, which carries its own risks and complications.

Extravascular hemolysis (EVH), primarily occurring in the spleen and liver, contributes to further complications. The breakdown of RBCs in these organs can lead to jaundice (yellowing of the skin and eyes), dark urine, and abdominal pain. Chronic hemolysis also results in the release of free hemoglobin into the bloodstream, which can damage the kidneys and other organs over time.

Intravascular hemolysis, the destruction of red blood cells within blood vessels, significantly impacts patients by causing severe anemia, which leads to fatigue, weakness, and shortness of breath due to reduced oxygen delivery to tissues. This process releases hemoglobin into the bloodstream, resulting in dark urine (hemoglobinuria) and potential kidney damage from the toxic effects of free hemoglobin. Additionally, patients may develop jaundice due to increased bilirubin levels, experience pain and discomfort, and face a heightened risk of thrombosis, which can lead to serious complications such as deep vein thrombosis or stroke. The condition also weakens the immune system, increasing susceptibility to infections, and imposes substantial psychological burdens, including anxiety and depression, due to its chronic nature and the complexity of its treatment regimen. Effective management is essential to alleviate these impacts and improve the quality of life for patients.

Approximately 10-20 people per million worldwide live with PNH. While it can develop at any age, it is most commonly diagnosed in individuals between the ages of 30 and 40. The diagnosis of PNH often follows a period of unexplained symptoms and significant health deterioration, as the condition can be challenging to identify due to its rarity and the variability of its presentation.

The chronic nature of PNH means that patients must manage their condition over a lifetime, dealing with the physical, emotional, and financial burdens associated with the disease. The impact on quality of life is profound, as patients must cope with the unpredictability of symptoms, the side effects of treatments, and the constant threat of serious

complications. Regular monitoring and supportive care are essential to managing the disease and improving patient outcomes.

In summary, PNH is a complex and multifaceted disorder that requires comprehensive management to address the various aspects of the disease and improve the quality of life for those affected. Advances in understanding the pathophysiology of PNH and the development of new therapeutic options hold promise for better management and potential future cures.

2. Information Gathering

Unfortunately, the clinical trial size for Iptacopan was limited, allowing us to gather personal experiences from only one Canadian patient receiving this treatment. Consequently, our submission will primarily focus on illustrating the study's findings and highlighting Iptacopan's potential efficacy in addressing the critical need for therapies that control both EVH and IVH in adult patients diagnosed with PNH. Additionally, we will include insights and experiences from patients in the USA to provide a more comprehensive overview.This need is particularly important as Iptacopan offers an oral administration route, which can significantly enhance patients' quality of life by providing a more convenient and less invasive treatment option. Although the sample size was small and the trial duration was short, the insights gained from this single patient's perspective provide valuable firsthand information. These insights contribute significantly to our understanding of Iptacopan's impact and benefits, emphasizing the importance of a therapy that not only addresses both EVH and IVH but also supports improved quality of life for individuals living with PNH in the Canadian context.

3. Disease Experience

PNH is a rare, chronic, and serious blood disorder caused by complement-mediated destruction of red blood cells (RBCs). Individuals with PNH have an acquired mutation in some of their hematopoietic stem cells, located in the bone marrow, which develop into RBCs, white blood cells, and platelets. This mutation results in the production of RBCs that are vulnerable to premature destruction by the complement system, leading to both intravascular hemolysis (within blood vessels) and extravascular hemolysis (primarily in the spleen and liver). These processes cause anemia, thrombosis (blood clots), fatigue, and other debilitating symptoms that significantly impact quality of life.

Approximately 10-20 people per million worldwide live with PNH. While it can develop at any age, it is most diagnosed in individuals between the ages of 30 and 40.

Physical Impact

The chronic anemia caused by the destruction of red blood cells (RBCs) leads to severe fatigue, weakness, and shortness of breath. These symptoms can make it challenging for patients to perform daily activities, maintain

employment, and engage in social interactions. The ongoing need for blood transfusions to manage anemia can be exhausting and time-consuming, requiring frequent hospital visits and medical procedures. The persistent risk of thrombosis (blood clots) adds to the physical burden, as clots can lead to life-threatening complications such as stroke, pulmonary embolism, and organ damage.

Emotional and Psychological Impact

Living with PNH often involves coping with the unpredictability of symptoms and the constant threat of complications. This uncertainty can lead to significant emotional distress, anxiety, and depression. Patients may experience fear and worry about their health and future, compounded by the stress of managing a chronic illness. The emotional burden can be exacerbated by feelings of isolation, as the rarity of PNH means that patients often lack a support network of others who understand their condition. Psychological support, including counseling and therapy, can be crucial in helping patients manage these emotional challenges.

Social Impact

The physical limitations and emotional toll of PNH can strain relationships with family, friends, and colleagues. Patients may withdraw from social activities due to fatigue or the fear of experiencing symptoms in public. The need for frequent medical appointments and hospitalizations can disrupt social plans and lead to a sense of isolation. Patients may feel disconnected from their peers, leading to a reduced sense of belonging and community. Support from patient advocacy groups and connections with others living with PNH can provide much-needed social support and reduce feelings of isolation.

Economic Impact

The financial burden of PNH is considerable. The cost of ongoing treatments, including blood transfusions and anti-C5 therapies (SOLIRIS® or ULTOMIRIS®), can be substantial. Additionally, the need for regular medical monitoring, potential hospitalizations due to complications, and the management of comorbid conditions add to the overall healthcare costs. Patients may face loss of income due to their inability to work or maintain consistent employment, further exacerbating financial stress. The economic impact extends to families, who may need to provide financial and caregiving support.

Impact on Daily Life and Activities

PNH affects patients' ability to engage in daily activities and pursue personal goals. The fatigue and physical weakness associated with anemia can make it difficult to perform household tasks, participate in recreational activities, or maintain an active lifestyle. Patients may need to make significant adjustments to their daily routines, including

prioritizing rest and managing energy levels. This can limit their ability to enjoy life and achieve personal aspirations, leading to frustration and a diminished sense of purpose.

Impact on Mental Health

The chronic nature of PNH and the constant management of symptoms can take a toll on mental health. Patients may experience chronic stress, which can lead to burnout and exacerbate symptoms. The psychological impact of living with a rare and serious condition can lead to feelings of hopelessness and helplessness. Mental health support, including access to mental health professionals and peer support groups, is essential for helping patients cope with the mental health challenges associated with PNH.

Quality of Life

Overall, PNH severely impacts the quality of life. The physical symptoms, combined with the emotional, social, and economic burdens, can significantly diminish a patient's well-being. Continuous management of the disease and its complications requires a comprehensive approach that includes medical treatment, psychological support, and social services. Improving awareness and understanding of PNH among healthcare providers and the general public is essential to provide better support and care for those affected.

In summary, PNH affects nearly every aspect of a patient's life. While current treatments can help manage some symptoms, there is a crucial need for more effective therapies and comprehensive support systems to improve the overall quality of life for PNH patients. Advances in medical research, increased awareness, and a greater emphasis on holistic care approaches hold promise for alleviating the burdens associated with this challenging condition.

4. Experiences with Currently Available Treatments

PNH presents a significant unmet need not fully addressed by current anti-C5 therapies (SOLIRIS® or ULTOMIRIS®). Despite these treatments, many PNH patients continue to experience anemia, fatigue, and dependence on blood transfusions. This persistent burden highlights the need for new therapeutic approaches that can more effectively target the underlying causes of PNH and improve patient outcomes.

Current anti-C5 therapies work by inhibiting the complement system to prevent the destruction of red blood cell (RBCs), but they do not fully address extravascular hemolysis or the ongoing bone marrow failure seen in many patients. Extravascular hemolysis, which occurs primarily in the spleen and liver, leads to the continuous breakdown of RBCs despite treatment. This ongoing hemolysis can result in chronic anemia, which significantly impacts a patient's quality of life.

Chronic anemia can cause severe fatigue, reducing a patient's ability to perform daily activities and participate in social and professional life. The constant need for blood transfusions to manage anemia can be physically and emotionally draining, contributing to a diminished sense of well-being. Patients often experience additional symptoms such as jaundice, dark urine, and abdominal pain due to the breakdown of hemoglobin from destroyed RBCs.

The psychological impact of living with PNH and managing chronic anemia can also be profound. Patients may suffer from anxiety, depression, and feelings of isolation due to their condition and the rigorous treatment regimen it requires. The need for frequent medical appointments and treatments can disrupt personal and professional life, leading to financial strain and a reduced overall quality of life.

New research and emerging therapies aim to provide more comprehensive solutions by targeting different pathways involved in PNH, including those responsible for extravascular hemolysis. These advancements hold promise for reducing the need for frequent blood transfusions, alleviating fatigue, and improving overall health and well-being for PNH patients. Addressing these unmet needs is crucial, as improved treatment options can lead to better disease management, enhanced patient quality of life, and potentially reduced healthcare costs associated with the complications of PNH.

In addition to developing more effective therapies, there is a need for increased awareness and understanding of PNH among healthcare providers and the general public. Early diagnosis and timely intervention are critical for managing PNH and preventing severe complications. Enhanced screening protocols and diagnostic tools can help identify PNH cases sooner, allowing for prompt and appropriate treatment.

Moreover, patient support and education play a vital role in the management of PNH. Providing patients with comprehensive information about their condition, treatment options, and lifestyle adjustments can empower them to take an active role in their care. Support groups and counseling services can also help patients cope with the emotional and psychological challenges associated with living with a chronic and serious blood disorder.

The future of PNH treatment looks promising with ongoing clinical trials and research efforts focused on innovative therapies, such as oral therapy. As the medical community continues to advance its understanding of PNH and develop new treatment strategies, there is hope for significantly improving the lives of those affected by this debilitating condition.

Unmet Need: A treatment that controls both EVH and IVH. Iptacopan is to be the first treatment capable of effectively managing both EVH and IVH, addressing this critical unmet need. We understand from patients that it is crucial for a drug to control both EVH and IVH because it provides comprehensive relief from a wide range of symptoms, significantly improving their overall well-being. Effective management of both types of hemolysis leads to better health outcomes, reducing the severity and frequency of complications, and allowing patients to maintain their

daily activities and responsibilities with fewer disruptions. Addressing both conditions can also alleviate pain and discomfort, lower the risk of organ damage caused by free hemoglobin, and result in fewer medical crises and hospital visits, lessening the physical and emotional toll on patients. Additionally, a single drug that targets both EVH and IVH simplifies the treatment regimen, making it easier for patients to adhere to their medication schedule, which in turn increases the likelihood of consistent health benefits. This comprehensive management can alleviate anxiety and stress, improve mental health, and provide substantial psychological and emotional benefits. Economically, it reduces overall medical expenses and decreases the indirect costs associated with lost workdays and the need for additional medical care, ultimately lowering the financial burden on patients.

5. Improved Outcomes

Iptacopan targets Factor B of the alternative complement pathway, thereby modulating the cleavage of C3, the generation of downstream effectors, and the amplification of the terminal pathway. In paroxysmal nocturnal hemoglobinuria (PNH), intravascular hemolysis (IVH) is driven by the membrane attack complex (MAC), while extravascular hemolysis (EVH) is facilitated by C3b opsonization. Iptacopan intervenes early in the alternative pathway of the complement cascade, effectively controlling both C3b-mediated EVH and terminal complement-mediated IVH. This dual action helps to mitigate the underlying mechanisms that contribute to hemolysis in PNH.

We do believe that an important goal in clinical practice is for patients to have higher hemoglobin levels. Higher hemoglobin levels are crucial for patients because they ensure adequate oxygen transport from the lungs to the rest of the body, which is essential for the proper functioning of tissues and organs. This improved oxygen delivery enhances energy levels, physical endurance, and overall vitality, allowing patients to engage more effectively in daily activities and exercise. Additionally, sufficient oxygen supply supports cognitive functions such as concentration and memory, boosts immune function, and promotes faster wound healing. Higher hemoglobin levels also alleviate symptoms of anemia, such as fatigue and shortness of breath, thereby improving the overall quality of life. Furthermore, maintaining healthy hemoglobin levels supports cardiovascular health by reducing the workload on the heart and decreasing the risk of heart-related complications. Overall, higher hemoglobin levels significantly enhance a patient's well-being and contribute to better health outcomes. According to the clinical trial, it was demonstrated that higher hemoglobin levels could be achieved. According to the study, most people taking Iptacopan achieved normalized hemoglobin levels of ≥12 g/dL without the need for RBC transfusions after 24 weeks.

The need for less blood transfusions is also important for patients and their caregivers. Avoiding blood transfusions is crucial for patients with PNH and their caregivers due to the significant health risks and complications associated with transfusions. These include the potential transmission of infections, severe transfusion reactions, iron overload, and

immune system complications like alloimmunization. Frequent transfusions necessitate regular hospital visits, which can be time-consuming, physically and emotionally draining, and financially burdensome. Moreover, transfusions can mask underlying symptoms, delay effective treatments, and create long-term dependency. By minimizing the need for transfusions through alternative therapies such as Iptacopan, patients can achieve better disease management, improved health outcomes, and an enhanced quality of life, ultimately reducing the physical, emotional, and financial strain on both patients and caregivers. The clinical trial demonstrated that this was also possible. Almost all who switched to Iptacopan did not receive an RBC transfusion. In the 6 months before the trial:

- 57% (n=35/62) of people in the Iptacopan group had at least one RBC transfusion
- 60% (n=21/35) of people in the C5i group had at least one RBC transfusion

APPLY-PNH:

An impressive 94.8% of participants treated with Iptacopan achieved transfusion independence, meaning they did not require blood transfusions, compared to only 25.9% of participants treated with C5 inhibitors, representing a significant difference of 68.9%. Furthermore, during the trial extension period, 94.1% of participants who switched from C5 inhibitors to Iptacopan also achieved transfusion independence. These results highlight the superior efficacy of Iptacopan in reducing the need for blood transfusions in patients with PNH.

APPOINT-PNH

An outstanding 97.6% of participants treated with Iptacopan achieved transfusion independence.

The following is important to consider as it has the most impact on patients' quality of life: the primary endpoints of the drug Iptacopan for the treatment of PNH are centered around its efficacy in increasing hemoglobin levels and reducing the need for blood transfusions. Specifically, the Phase III APPLY-PNH study demonstrated:

1. A significant increase in the proportion of patients achieving a hemoglobin level increase of at least 2 g/dL from baseline without the need for blood transfusions at 24 weeks.
2. A significant increase in the proportion of patients reaching hemoglobin levels of 12 g/dL or more without requiring blood transfusions at 24 weeks.

We believe these endpoints indicate the drug's effectiveness in managing anemia associated with PNH and reducing the reliance on transfusions, thereby improving the overall quality of life for patients.

A caregiver in the United States shared that her husband began treatment with Iptacopan in May 2024. On July 23rd, they received the remarkable news that, for the first time, his hemoglobin levels were within the normal range. They described Iptacopan as a 'miracle drug'.

A patient from the USA shared their experience: 'I started Iptacopan three weeks ago, and the improvement has been faster than I anticipated. My hemoglobin levels increased more significantly than they had in months while I was on Soliris, rising from 7.6 to 9, which is quite high for me. For the first time in over ten years, my LDH levels are now within the normal range. I was amazed by this progress."

One patient from the USA shared that after just one week on Iptacopan, her hemoglobin levels were the highest they had been since 2015, and her bilirubin levels significantly decreased.

Another USA patient mentioned starting Iptacopan on February 7th, after 12 years on Soliris and nearly five years on Ultomiris. She had her blood counts checked on February 6th before beginning Iptacopan, with follow-up tests at 4 weeks and 6 weeks. Her results have been remarkable: her hemoglobin increased from 10.0 to 13.2, and then to 14.3 over the 6-week period. Additionally, her fatigue has greatly improved, and she has more energy.

6. Experience With Drug Under Review

"When I was diagnosed last year with PNH, it was going to be hard to predict the impact this condition would have on my life physically, emotionally and financially. The initial treatment of Solaris did not have enough of an impact to feel normal or have a decent quality of life. A few months ago I started Iptacopan and the benefits were more immediate and after a year of alternative treatments this was the first time I started to feel normal again. Having some freedom from injection type infusions is a huge benefit. PNH is not that understood and the few people that are impacted are feeling the same, are hopeful for not only a cure but a medication that will help us to feel normal again. Having treatment in a pill form to help manage symptoms will also be less stress on our already overburden medial system." Patient S.

Individuals with PNH receiving C5 inhibitors commonly report fatigue as the most prevalent and bothersome symptom, affecting 52% of patients. Other self-reported symptoms include anemia, headache, shortness of breath, and anxiety.

Fatigue significantly impacts daily life, with individuals having trouble in performing usual activities, participating in social engagements, and requiring daytime naps due to exhaustion. Additionally, cognitive problems such as memory loss, confusion, brain fog, difficulty concentrating, and trouble focusing on tasks have also been reported.

In the APPOINT-PNH and APPLY-PNH clinical trials, individuals treated with Iptacopan experienced significant and sustained improvements in fatigue throughout the study duration. These improvements were notable within just one

week of starting Iptacopan treatment, and by the end of the 24-week treatment period, fatigue levels had decreased to levels comparable to those of the general population without PNH.

At the conclusion of the 24-week treatment period, 39 participants were interviewed regarding their experience with fatigue. They were asked to assess whether their fatigue symptoms and their impact on daily life had changed during the trial, and if these changes were perceived as meaningful. Participants consistently reported meaningful improvements in both their fatigue symptoms and their overall quality of life related to fatigue after receiving Iptacopan.

Similar to pegcetacoplan, Iptacopan is a proximal complement inhibitor that can reduce or stop the destruction of blood cells both within and outside blood vessels. Pegcetacoplan targets a protein in the complement system called C3, while Iptacopan targets a different protein called Factor B. By blocking Factor B, Iptacopan has been shown to reduce the destruction of red blood cells.

Furthermore, Iptacopan 's mechanism of action provides a distinct therapeutic option for patients with PNH who may not respond adequately to other treatments. Clinical studies have demonstrated that Iptacopan not only alleviates hemolysis but also improves overall hemoglobin levels and reduces the need for blood transfusions. This can significantly enhance the quality of life for patients, addressing both hematologic and extravascular complications associated with PNH.

The introduction of Iptacopan adds to the growing arsenal of therapies available to manage PNH, offering hope for better disease control and improved patient outcomes. Continued research and patient monitoring will be essential to fully understand the long-term benefits and optimal use of this promising treatment.

The impact of oral treatments versus injections on patients' quality of life is significant, offering several advantages:

1. Convenience and Comfort:

- **Ease of Use:** Oral medications are generally easier and more convenient to take compared to injections, which require more preparation and sometimes assistance from healthcare providers.
- **Reduced Pain and Discomfort:** Oral treatments eliminate the pain and discomfort associated with needles and injections. This can be particularly beneficial for patients who have a fear of needles or experience pain from frequent injections.

2. Adherence to Treatment:

- **Improved Compliance:** Patients are more likely to adhere to their treatment regimens when taking oral medications compared to injections, leading to better health outcomes. Oral administration is less intrusive and can be more easily incorporated into daily routines.

- **Fewer Interruptions:** Oral treatments can be taken at home without the need for regular visits to healthcare facilities, reducing disruptions to daily life and work.

3. Psychological Benefits:

- **Reduced Anxiety:** For many patients, the anticipation and act of receiving injections can cause significant anxiety and stress. Oral medications can help alleviate this mental burden, contributing to better overall mental health.
- **Greater Sense of Normalcy:** Oral treatments can help patients feel more in control of their lives and maintain a sense of normalcy, as they can avoid the clinical setting associated with injections.

4. Economic and Practical Benefits:

- **Cost Savings:** Oral medications can be more cost-effective for patients by reducing the need for healthcare professional administration and travel expenses associated with regular clinic visits.
- **Accessibility:** Oral treatments are easier to store and transport, making them more accessible, especially in remote or resource-limited settings.

Overall, oral treatments provide significant benefits over injections in terms of convenience, comfort, adherence, psychological well-being, and economic factors. These advantages contribute to an improved quality of life for patients, making oral treatments a preferred option when available.

Sources:

1. **Convenience and Comfort:** Harvard Health Publishing
2. **Adherence to Treatment:** Journal of Clinical Pharmacy and Therapeutics
3. **Psychological Benefits:** American Psychological Association
4. **Economic and Practical Benefits:** National Center for Biotechnology Information

7. Companion Diagnostic Test

N/A

8. Anything Else?

Patients with residual anemia despite an adequate trial of C5 inhibitors (C5i) are candidates for treatment switch to proximal inhibition. This new management approach is particularly relevant in the current era of

paroxysmal nocturnal hemoglobinuria (PNH) treatment, where optimizing patient outcomes is paramount. For patients who are inadequate responders to C5 inhibitors, proximal inhibitors offer a promising alternative, targeting upstream components of the complement pathway to more effectively control hemolysis and improve anemia.

We strongly urge the Canadian Drug Agency (CDA) to provide a positive recommendation for this product and prioritize patient access over pharmacoeconomic concerns. We firmly believe that placing a monetary value on patients' lives is unacceptable, as every individual diagnosed with PNH deserves access to biologic therapies. Despite the approval of treatments such as Soliris, Ultomiris, and Pegcetacoplan, many Canadian patients still lack access to these vital therapies, which is unacceptable.

Based on the robust clinical evidence presented by the company, we encourage the CDA to immediately offer this therapy to patients who either have not received prior treatment with existing complement inhibitors for PNH or have received such treatment but continue to suffer from anemia (and there should not be any range number dictated by the CDA). Timely access to effective treatments is crucial for improving patient outcomes and quality of life.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, 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.

Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.
Yes, consultant (Hanzo Pharma & Biotech Consultant)

1. 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. Yes, consultant (Hanzo Pharma & Biotech Consultant)
2. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.
3. Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Alexion			X (direct interest)	
Novartis			X	
Roche		X		
Sobi			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Barry Katsof

Position: President & Founder
Patient Group: The Canadian Association of PNH Patients
Date:

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Abbvie		X		
Alexion				X
BMS			X	
Sobi			X	
Regenron			X	
Taiho		X		
Roche		X		
Novartis			X	

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Cindy Anthony
Position: Executive director
Patient Group: AAMAC
Date:

Clinician Group Input

CADTH Project Number: **SR0851-000**

Generic Drug Name (Brand Name): **IPTACOPAN**

Indication: **Patients with PNH who remain anemic despite C5 inhibition**

Name of Clinician Group: **Canadian PNH Network**

Author of Submission: **Drs Marc Bienz, Monika Oliver, and Christopher Patriquin, with contribution and editorial support by the cosignatories of this document**

1. About Your Clinician Group

The Canadian PNH Network is a group of Canadian hematologists with a special interest and expertise in the care of patients with paroxysmal nocturnal hemoglobinuria (PNH). Members represent centres of excellence from Newfoundland, Nova Scotia, Quebec, Ontario, Alberta, and British Columbia. The Canadian PNH Network sites follow the vast majority of PNH patients in Canada, either directly or as part of shared-care relationships with community physicians. We also set consensus for diagnosis and management of PNH in the country (Patriquin CJ et al. [2019] Eur J Haematol) and serve as sites for ongoing observational and interventional research activities both nationally and internationally (https://www.pnhnetwork.ca).

2. Information Gathering

Information for this submission was obtained via publicly available documents, congress abstracts, and the published literature (including data from the APPLY-PNH trial – Peffault de Latour et al. [2024] NEJM). Standard of care data were similarly obtained, and the members of the Canadian PNH Network were invited to contribute to the various segments.

3. Current Treatments and Treatment Goals

The current standard of care (SOC) for patients with hemolytic PNH is terminal complement inhibition with C5 blockade. Eculizumab, and more recently ravulizumab, remain the only first-line therapies across the country. To be approved for eculizumab or ravulizumab in Canada, patients must have evidence of a PNH clone ≥ 10%, lactate dehydrogenase (LDH) > 1.5 x the upper limit of normal (ULN), and at least one significant clinical manifestation such as thrombosis, anemia, transfusion-dependence, renal or respiratory failure without other explanation, and smooth muscle dystonic symptoms requiring either hospitalization or opioid analgesia.

The only curative treatment for PNH is allogeneic hematopoietic stem cell transplant. It should be noted, however, that this is reserved for patients with predominant or progressive bone marrow failure (e.g. aplastic anemia or myelodysplastic syndrome), which can coincide with, precede, or follow a diagnosis of PNH. Transplant is not recommended for all patients given the increased risk of complications and transplant-related mortality compared to C5 inhibition. Though complement inhibition does not address the underlying marrow mutations which cause PNH, complement blockade and associated control of intravascular hemolysis (IVH) leads to significant improvement in quality of life, fatigue, transfusion-dependence, thrombosis, and overall survival. Supportive therapies for PNH patients, if needed, include hematinic support (folate, iron), analgesia, and anticoagulation either to treat or protect against thrombosis. It should be noted, however, that anticoagulation alone does not protect against thrombosis in PNH, which is the leading cause of death in untreated patients (40-67%).

Treatment with C5 inhibition, such as with eculizumab/ravulizumab, is highly effective at controlling intravascular hemolysis. This is measured by targeting an LDH <1.5 x ULN. Associated with this, we aim for improvement in hemoglobin, reduced transfusion needs, and absence of other end-organ complications like thrombosis, renal failure, and pulmonary hypertension. With C5 inhibition, PNH red cells are now able to survive and circulate where previously they would have been exquisitely sensitive to terminal complement-mediated IVH. Now that red cells survive, they can have more and more C3 split products (e.g. iC3b, C3dg) bind to their membranes. As cell-bound complement inhibitors are missing, the dense C3 deposits drive extravascular hemolysis (EVH), mostly via receptors on Kupffer cells in the liver. Because of this, about a third of PNH patients remain symptomatically anemic and possibly still transfusion-dependent (Debureaux P et al. [2021] Bone Marrow Transplant), with increasing rates of extravascular hemolysis

coinciding with reduced levels of hematologic response. Due to the underlying disease phenotype, any C5 inhibitor can drive this extravascular hemolysis.

Treatment goals of proximal inhibitors are to minimize EVH and improve hemoglobin, transfusion dependance and symptoms/complications, by blocking the complement at the C3 level or upstream. Pegcetacoplan has been recently approved in Canada and is currently publicly available in several provinces as the only second-line treatment for PNH. By blocking the complement more proximally at the C3 level, the EVH is also blocked, allowing for increased hemoglobin. In the PEGASUS trial (Hillmen et al. [2021] NEJM), patients receiving pegcetacoplan had a significant improvement in change-from-baseline hemoglobin, which has been sustained now out to 3 years of follow-up (de Castro et al. [2023] ASH abstract / Patriquin et al. [2024] Advances in Therapy). Pegcetacoplan is a twice-weekly subcutaneous infusion (typically self-administered) which is indicated for patients with persistent anemia despite a trial of C5 inhibitor-based therapy or should they be intolerant to C5 inhibitors.

Please note that a general therapeutic approach to patients with PNH with a Canadian focus can be found in our consensus guidelines (Patriquin CJ et al. [2019] Eur J Haematol) and recent review (Oliver M & Patriquin CJ [2023] J Blood Medicine).

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Not all patients respond to available treatment

Breakthrough hemolysis (BTH) is a complication of PNH therapy in which (due to insufficient dosing, exposure to complement-amplifying conditions, or both) there is a return of IVH, typically detected by elevated LDH, anemia, return/exaggeration of symptoms, and possibly significant drops in hemoglobin. This can occur with incomplete complement blockade due to improper dosage or lack of compliance, or by overwhelming the complement inhibitor due to an underlying complement-amplifying condition (CAC) with both terminal and proximal complement inhibitors. With proximal complement inhibitors however, the pool of vulnerable circulating PNH red cells naturally increases with treatment as they avoid both intravascular and extravascular hemolysis, thus theoretically increasing the potential for a more significant and brisker drop in hemoglobin in case of BTH. Indeed, if there is incomplete *proximal* complement blockade, complement activation can occur in a massive enzymatic cascade (i.e. each unblocked molecule can lead to activation of significant downstream complement activity/formation of multiple membrane attack complexes), leading to severe hemolytic anemia. For this reason and other mechanisms outlined by Notaro and Luzzatto (NEJM 2022), outcomes of BTH with proximal complement inhibitors may be more severe than episodes on terminal complement inhibitors, a finding supported by trial data and anecdotal clinical experience. Massive BTH has been seen in some patients on pegcetacoplan. Moreover, a clinical trial assessing a twice-daily anti-Factor D drug (vemircopan) as monotherapy was terminated early due to concerns over higher reported rates of BTH compared to other trials, despite promising results from phase II data (Browett et al., [2022] ASH poster). As the pegcetacoplan data mature, with now 3 years of follow-up for the PEGASUS data, approximately 30% of patients will have reported BTH. As was seen in the PEGASUS trial supplementary data, some patients on pegcetacoplan have had massive BTH with LDH values 10-15x ULN and dramatic drops in hemoglobin from hemolysis. Danicopan (oral factor D inhibitor) administered in combination with eculizumab/ravulizumab is under evaluation by CADTH as an alternative second line option offering dual complement blockade to counteract the risk of IVH. The additional proximal blockade would provide patients with the same benefits of improved hemoglobin, with a lower risk of complications (as was seen in the ALPHA trial by Lee et al. [2023] in Lancet Haematology) though still requiring regular parenteral intervention.

Treatments are needed that are better tolerated

With ravulizumab now available in Canada, the patient treatment burden can also be reduced significantly by switching from fortnightly to every-8-week intravenous dosing. In patients on Danicopan, the superior dosing schedule of Ravuliziumab to Eculizumab helps to off-set the thrice daily danicopan oral therapy. However, a subset of patients still struggle with adequate venous access or needle phobias requiring insertion of peripheral or central venous catheters which come with their own risk of thrombosis, infection and procedural risk.

The delivery mechanism for pegcetacoplan, as mentioned, is a self-administered subcutaneous infusion that can take 30-60 minutes. Most patients take this twice weekly, though if they have incomplete control, some require escalation to every-3-day or even thrice-weekly dosing. This can be challenging for some, including patients with needle phobia, vision problems, poor skin integrity, and/or

issues with manual dexterity, and the product must also be kept refrigerated (including in the context of travel). While support doses exist for patients to travel to infusion clinics for drug delivery, this is not logistically feasible twice or thrice weekly for most patients.

Formulations are needed to improve convenience and compliance

Geographically, Canada is vast and thus a small but still significant proportion of PNH patients live remotely. These patients may not have access to specialized nurses who have the comfort and expertise to administer IV anti-C5 therapies (eculizumab or ravulizumab) and thus must travel by plane, car, or boat in challenging winter climates to receive their life-sustaining therapies. As above, some patients lack the competence to self-administer pegcetacoplan or access to reliable refrigeration. Thus, an oral monotherapy, namely iptacopan, would allow patients in these remote areas to easily administer their PNH therapy. In patients who do not live locally, an oral monotherapy allows for patients to have increased control over their treatments including freedom to travel for longer periods and longer distances without a product that needs to be refrigerated and without the hassle of packing syringes, sterile administration supplies, sharps disposal, medication pump etc. In the correctly selected patient, oral monotherapy may help improve treatment compliance, giving patients the autonomy to self-administer their therapy without discomfort from their own home.

No treatments are available to reverse the course of disease

Ultimately, a large unmet need is that no currently available PNH therapies (outside of allogenic transplantation, see above) reverse the course of the disease, thus necessitating life-long treatment.

5. Place in Therapy

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

Iptacopan is a twice-daily oral Factor B (proximal complement) inhibitor which has shown significant improvements in hemoglobin in patients with suboptimal response to C5 inhibition alone (i.e. eculizumab, ravulizumab). In the APPLY-PNH trial which evaluated adult patients with PNH who had clinically significant extravascular hemolysis despite terminal complement inhibitors (mean hemoglobin <100 g/L, reticulocytes ≥100 x 10^9/L). Patients were randomized to iptacopan monotherapy (n=62) or to stay on C5 inhibitor (n=35) for 24 weeks. At 24 weeks, iptacopan was superior in regard to increase in hemoglobin by at least 20 g/L from baseline without transfusions (51/60 evaluable patients vs 0/35). Of the 60 evaluable patients on iptacopan, 42 reached a hemoglobin of at least 120 g/L without transfusions compared to 0/35 in the control arm (both P<0.0001) (Peffeault de Latour et al. [2024] NEJM). This drug would be used in patients as per the APPLY-PNH protocol, for those with persistent anemia despite C5 inhibition in whom EVH is suspected. It would be expected to work for any such patient with symptomatic and/or transfusion-dependent anemia felt to be related to EVH, even with higher hemoglobin values that those used in the trial (i.e. the same patient population as approved for pegcetacoplan). It could also provide another option for patients who may receive proximal inhibition monotherapy (e.g. pegcetacoplan) who may not tolerate it or who would rather use oral drugs.

Given the absence of data comparing second-line therapeutic options in PNH to each other, there is no evidence to support one second line treatment over another based on their efficacy. The choice of second line therapy resides mainly in patient preference. Some patients may prefer oral options given ease of administration. Other patients may prefer pegcetacoplan as the drug itself can be used for the treatment of BTH and extra doses can be brought with them when traveling. Iptacopan will not in itself cause a shift in the current treatment paradigm, but instead will provide well-needed diversity to the available treatments to best suit the needs and lifestyle of each patient.

The APPOINT-PNH trial (Peffeault de Latour, NEJM, 2024) also provides data to support the use of iptacopan in complement inhibitor-naïve patients with hemoglobin increases of at least 20 g/L in 31 of 33 patients tested without red cell transfusion.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As described above, and as seen in APPLY-PNH, the patients most likely to benefit from iptacopan and most in need of an intervention are those who have persistent anemia despite stable-dose eculizumab or ravulizumab and meet the APPLY-PNH clinical trial eligibility criteria including: Age ≥18 years, PNH diagnosis (RBC and WBC clone size ≥10%), clinically significant extravascular hemolysis despite treatment, mean hemoglobin <100 g/L and reticulocytes ≥100 x 109/L. For complement naïve patients, patients thought to benefit most from Iptacopan would be those that met the APPOINT-PNH eligibility criteria which include: Adult PNH patients a with confirmed diagnosis of PNH (clone size ≥ 10%) naive to complement inhibitor therapy, mean hemoglobin <10 g/L and

LDH>1.5xULN. As per is standard prior to treatment with any approved complement inhibitor, patients will require an updated vaccination profile, for Iptacopan this includes vaccination against Neisseria meningitidis, Streptococcus pneumoniae, Haemophilus influenzae.

Patients best suited for treatment are those selected by their clinician to meet the above diagnostic and laboratory criteria (which should be easily accessible), in addition to demonstrating that are likely to be compliant with an oral monotherapy. Patients especially suited for Iptacopan are those who are unable or unwilling to continue or initiate other approved therapies (ravulizumab, eculizumab or pegcetacopan) due to issues with needle phobia, poor peripheral venous access, side effect profile or who may live remotely without reliable or easy access to other therapies. Additionally, there is an attractive convenience factor for those patients engaging in frequent long-distance or prolonged duration travel.

Given the high sensitivity and specificity of PNH flow cytometry, the risk of misdiagnosis of PNH is extremely low. However, it is of course important that clinicians assess for other causes of ongoing anemia outside of BTH or EVH but this is easily done with standard history taking and laboratory testing. Pharmacokinetic BTH can be identified in patients with cyclical symptoms leading up to their next C5 inhibitor infusions who may also show increased LDH and CH50 values. Patients with bone marrow failure would likely show evidence of decreasing reticulocyte and platelet counts (this could be confirmed with bone marrow biopsy/aspiration in unclear cases but not required). Extravascular hemolysis is typically suspected in PNH patients on C5 inhibition who have persistent reticulocytosis, indirect hyperbilirubinemia and with minimal LDH elevation. This must all be taken together in the individual patient context, as concomitant marrow failure (not uncommon in PNH) may blunt the reticulocytosis, as example, and obscure EVH. There are some additional findings that may support EVH as a contributor to anemia, such as C3d loading found on direct antiglobulin testing, but this is not yet a validated test for this clinical situation.

PNH patients least suitable for iptacopan would be those who are not anemic, who meet exclusion criteria otherwise as used in the APPLY-PNH and APPOINT-PNH trials, and particularly those planning to get pregnant as do not have safety data (as compared to eculizumab alone, where we have evidence to support its efficacy and safety in this context (Kelly R et al. -2015] NEJM). Finally, patient who have demonstrated poor compliance to physician appointments, suggested laboratory testing, or other therapies may be poor candidates for Iptacopan or other oral monotherapies, given a high risk of BTH with missed doses.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Response to complement blockade in PNH patients primarily focuses on reduction in LDH, which is a consistent surrogate used to identify intravascular hemolysis activity in clinical trials and in practice. The goal is to have patients consistently fall below an LDH ratio of 1.5x the ULN. This not only reduces hemolysis and may improve hemoglobin and transfusion-dependence, but it also reduces the risk of thrombosis and other end-organ complications of PNH. Clinical outcomes related to this, as seen in the landmark eculizumab and ravulizumab trials, are decreased fatigue, transfusion requirements, improved QoL and, given the maturity of eculizumab data available, also improved overall survival. An important outcome of clinical (and clinical trial) interest is an increase in hemoglobin, particularly now that there are proximal inhibitors.

A clinically meaningful response to treatment would be sustained control of LDH but with further hemoglobin increases and improvement in anemia-related symptoms and overall quality of life, including treatment burden. Transfusion-dependence would also be a key parameter to measure, as long-term transfusions can be harmful (by causing iron overload among other) and are also a significant burden on the national blood supply and health care resources in general. The ability for patients to return to full or part-time work and desired hobbies and travel would also be of interest, although more challenging to measure. The increase in hemoglobin in iptacopan-treated patients is objective and not expected to vary across physician treaters. In fact, similar increments around 20-30 g/L have been seen not just in APPLY-PNH and APPOINT-PNH but in trials of other proximal inhibitors trials. Supporting data to show reduced EVH +/- IVH also include a reduction/normalization of reticulocytes and indirect hyperbilirubinemia. Efficacy outcomes would typically be followed every 2-4 weeks initially, but follow-up would be required less often (e.g. every 3-6 months) as a patient becomes established on the drug and does not show evidence of side effects, intolerances or other clinical concerns.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Iptacopan discontinuation should be considered in patients who have adverse events that preclude ongoing therapy. This may include issues with poor compliance or intolerable side effects (this is not common based on the trial data). As per the APPLY-PNH trial data the most commonly reported side effects included headache, nausea, diarrhea, and nasopharyngitis. Elevation in total and

LDL-cholesterol as well as triglycerides has also been reported to the FDA report. However, none of these led to treatment discontinuation in the trials. Other intolerances or side effects would also prompt a discussion about either dose-reduction or discontinuation on a case-by-case basis. The most important feature to watch for is evidence of BTH. It is possible that some patients who take iptacopan will have significant expansion of their circulating red blood cells and, in situations of severe complement-mediated stress, could have increased hemolytic events. In these patients, dual complement inhibition (proximal and distal target) could be considered with the addition of danicopan to terminal complement inhibitors. Lastly, any patient who becomes pregnant and/or was breastfeeding would need to have their iptacopan stopped temporarily, at least for now, as there are no safety data in this context.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

PNH is an ultrarare disease with nuances to diagnosis, treatment, and overall management. Patients likely benefit being followed by clinicians who specialize in the area, particularly once we are considering patients for second/later-line therapeutic strategies. Members of the Canadian PNH Network would certainly be included in this categorization. Monitoring of patients can be done with standard laboratory investigations and clinical visits. Some tests routinely done to monitor patients with PNH require samples to be analyzed in tertiary care centers (ie PNH flow cytometry, CH50/CH100). However, specifically regarding treatment with iptacopan, this is done entirely at the patient's home. Patients can easily travel with their drug.

6. Additional Information

We believe that the submission above addresses the various points, data, and clinical opinions we hope to convey.

7. 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.

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

   We did not.

5. 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.

   We did not.

6. 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 <u>each clinician</u> 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: Marc Bienz

Position: Hematologist, McGill University

Date: 12 August 2024

☒ **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**
Sobi			x	
Novartis	x			
Alexion	x			

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

Declaration for Clinician 2

Name: Monika Oliver

Position: Hematologist, Clinician Investigator, University of Alberta Hospital / Member of the Canadian PNH Network

Date: 05-August-2024

☒ 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 2: Conflict of Interest Declaration for Clinician 2

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Alexion		x		
Sobi		x		
Novartis		x		

Roche	X			

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

Declaration for Clinician 3

Name: Christopher Patriquin

Position: Hematologist, Clinician Investigator, University Health Network / Chair, Canadian PNH Network

Date: 12 August 2024

☒ **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 6

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion			X	
Sobi			X	
Novartis		X		
Roche		X		
Amgen	X			

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

Declaration for Clinician 4

Name: Sue Robinson

Position: Hematologist, Dalhousie University, Nova Scotia

Date: 22-08-2024

☒ 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 4: Conflict of Interest Declaration for Clinician 4

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion	x			
Sobi	x			
Novartis	x			

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

Declaration for Clinician 5

Name: Signy Chow

Position: Hematologist, Sunnybrook Hospital, Toronto

Date: 22-08-2024

☒ 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 5: Conflict of Interest Declaration for Clinician 5

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Sobi	x			

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

Declaration for Clinician 6

Name: Catherine Sperlich

Position: Hematologist, Chief of hematology-oncology, Hôpital Charles-Lemoyne, Greenfield Park, QC; clinical professor, Université de Sherbrooke; member of the Canadian PNH group
Date: 22-08-2024

☒ 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 5: Conflict of Interest Declaration for Clinician 6

Company	**Check appropriate dollar range***			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Alexion		X		
Sobi		X		
Novartis		X		
Roche	X			

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

Declaration for Clinician 7

Name: Brian Leber

Position: Professor of Medicine (Hematology), McMaster University

Date: 22-08-2024

☒ 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 5: Conflict of Interest Declaration for Clinician 7

Company	**Check appropriate dollar range***

	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Novartis		x		
Alexion		x		
Sobi		x		

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

Declaration for Clinician 8

Name: Jennifer Grossman

Position: Hematologist, Foothills Medical Center/ Member of the PNH Network.

Date: 22-08-2024

☒ 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 5: Conflict of Interest Declaration for Clinician 8: None

Declaration for Clinician 9

Name: Danièle Marceau

Position: Laboratory Medical Director, Chaudière-Appalaches, Province de Quebec

Date: 22-08-2024

☒ 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 5: Conflict of Interest Declaration for Clinician 9

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	x			
Alexion		x		
Sobi	x			

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

Declaration for Clinician 10

Name: Kuljit Grewal

Position: Hematologist, Eastern Health, Associate Professor, Memorial University of Newfoundlan

Date: 22-08-2024

☒ 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 5: Conflict of Interest Declaration for Clinician 10

Company	Check appropriate dollar range*			
	$0 to $5,000	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Novartis	x			
Alexion		x		
Sobi		x		
Roche	x			

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