Canadian Journal of Health Technologies

Canada's Drug Agency
L'Agence des médicaments du Canada

March 2025 Volume 5 Issue 3

Drugs Health Technologies Health Systems

Reimbursement Recommendation

Iptacopan (Fabhalta)

Indication: For the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have hemolytic anemia

Sponsor: Novartis Pharmaceuticals Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Fabhalta?

Canada's Drug Agency (CDA-AMC) recommends that Fabhalta be reimbursed by public drug plans for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have hemolytic anemia, if certain conditions are met.

Which Patients Are Eligible for Coverage?

Fabhalta should only be covered to treat adult patients with a diagnosis of PNH who have persistent anemia (lack of red blood cells [RBCs] to carry oxygen), defined as hemoglobin levels less than 10 g/dL (a measure of how much protein is in RBCs that carry oxygen) despite an adequate trial of C5 inhibitor treatment, or who have intolerable adverse events (AEs) from C5 inhibitor treatment.

What Are the Conditions for Reimbursement?

Fabhalta should only be reimbursed if prescribed by or in consultation with a hematologist with experience managing PNH, and should not be used in combination with other complement inhibitors. The cost of Fabhalta should be negotiated so that Fabhalta does not exceed the drug program cost of treatment with pegcetacoplan for the treatment of adult patients with PNH.

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that, compared with C5 inhibitor treatment, treatment with Fabhalta is associated with sustained improvements in hemoglobin levels and a reduced need for blood transfusions.
- Fabhalta meets patients' needs as it improves anemia and reduces blood transfusion needs. Fabhalta also provides an oral treatment option that can be administered in a patient's home.
- Based on the CDA-AMC assessment of the health economic evidence, Fabhalta may not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Fabhalta compared with treatment with pegcetacoplan, reimbursed for the treatment of adult patients with PNH.
- Based on public list prices, Fabhalta is estimated to result in budget savings to the public drug plans of approximately $247,000 over the next 3 years. However, the actual budget impact is uncertain.

Summary

Additional Information

What Is PNH?

PNH is a rare, chronic, and potentially life-threatening blood condition caused by a genetic change that may develop after birth, which leads to the breakdown of RBCs. Ravulizumab or eculizumab (which are C5 inhibitors) are used first-line to treat PNH. However, some patients may still have anemia and may need blood transfusions despite C5 inhibitor therapy and therefore need alternative treatments. The prevalence of PNH in Canada is unknown but is estimated to affect 1.2 to 1.3 per 100,000 people in the US.

Unmet Needs in PNH

There is an unmet need for effective therapies that control hemolysis (the breakdown of RBCs) associated with PNH, improve anemia, decrease the need for blood transfusions, improve symptoms, and provide a more convenient oral route of administration.

How Much Does Fabhalta Cost?

Treatment with Fabhalta is expected to cost approximately $525,916 per patient annually.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that iptacopan monotherapy be reimbursed for the treatment of adult patients with PNH who have hemolytic anemia, if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (RCT), the APPLY-PNH trial, demonstrated that compared to C5 inhibitor treatment at stable regimen, treatment with iptacopan resulted in added clinical benefit in adult patients with PNH who have residual anemia. The APPLY-PNH trial showed that, compared with C5 inhibitor therapy, iptacopan resulted in statistically significant and clinically meaningful improvements in both primary outcomes of hematological response after 24 weeks of treatment. The treatment difference in marginal proportions of patients was 80.2% (95% confidence interval [CI], 71.2 to 87.6; P < 0.0001) for a sustained increase of at least 20 g/L in hemoglobin from baseline, and 67.0% (95%CI, 56.4 to 76.9; P < 0.0001) for achieving sustained hemoglobin levels of at least 120 g/L in the absence of transfusions. The benefits observed in the primary analyses in favour of iptacopan were supported by statistically significant and clinically important improvements in secondary outcomes, change from baseline in hemoglobin levels, and transfusion avoidance. Iptacopan treatment may be associated with improvements in fatigue symptoms and health-related quality of life (HRQoL), based on the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) instruments, respectively; however, these results are of low certainty due to the open-label nature of the analyses, missing data, and small sample sizes. Findings on longer-term efficacy and safety based on the descriptive open-label extension period of the APPLY-PNH study appeared consistent with the randomized controlled period of the trial and suggested ongoing benefit of iptacopan up to 48 weeks.

There was no direct evidence comparing iptacopan with pegcetacoplan, which was identified as the comparator of interest for patients with PNH who have an inadequate response or intolerance to C5 inhibitors. One unanchored matching-adjusted indirect comparison (MAIC) was submitted by the sponsor; however, CDEC was unable to draw definitive conclusions from its results due to the methodological limitations of the MAIC. Thus, the comparative efficacy and safety of iptacopan versus pegcetacoplan remains uncertain. The clinical experts anticipated that iptacopan and pegcetacoplan would have similar efficacy based on how these drugs perform in clinical practice.

Patients expressed a need for treatments that can effectively control intravascular hemolysis (IVH), reduce extravascular hemolysis (EVH), improve anemia, reduce the need for transfusion requirements and disease symptoms, and provide a more convenient oral route of administration. Based on the evidence reviewed, CDEC concluded that iptacopan met some of the needs identified by patients by improving anemia and reducing transfusion needs compared to C5 inhibitor treatment, although the impact of iptacopan relative to other comparators remains uncertain. Iptacopan provides an oral treatment option that can be administered

in a patient's home; however, CDEC noted that there was no evidence assessing the impact of the oral route of administration on patients' HRQoL.

At the sponsor-submitted price for iptacopan and publicly listed price for pegcetacoplan, iptacopan was less costly than pegcetacoplan. As there is no robust evidence to indicate that iptacopan is more effective than pegcetacoplan, the total drug cost of iptacopan should not exceed the total drug cost of pegcetacoplan.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must have a confirmed diagnosis of PNH with the following criteria: 1.1. Patients must have met the public drug plan reimbursement criteria for initiating C5 inhibitor treatment (e.g., eculizumab or ravulizumab) before receiving C5 inhibitor treatment. 1.2. Patients must meet 1 of the following criteria: 1.2.1. persistent anemia with hemoglobin levels < 10 g/dL despite an adequate trial of C5 inhibitor treatment and causes other than EVH have been excluded 1.2.2. intolerable adverse events from C5 inhibitor treatment.	Evidence from the APPLY-PNH trial demonstrated that iptacopan treatment resulted in a clinically meaningful improvement in hemoglobin levels in a study population representative of patients with PNH and residual anemia (mean hemoglobin levels < 10 g/dL) despite at least 6 months of treatment with either eculizumab or ravulizumab. Patients with anemia due to bone marrow failure were excluded, and among those enrolled, the mean ARC levels were elevated, which was consistent with EVH. Patients with intolerable adverse events from a C5 inhibitor were not specifically studied in the APPLY-PNH study; however, CDEC considered it reasonable to reimburse iptacopan treatment in these rare cases.	Based on clinical expert opinion and the clinical trial criteria, a minimum treatment duration with a C5 inhibitor of 6 months, at a stable dose, is adequate for assessing eligibility for iptacopan treatment.
Renewal		
2. Renewal for iptacopan should be based on the criteria used by each of the public drug plans for reimbursement of pegcetacoplan for patients with PNH.	There is no evidence that iptacopan should be held to a different standard than pegcetacoplan when considering renewal.	Evaluation of clinical improvement and/or stabilization of the patient's condition should include hemoglobin level and transfusion history in addition to other markers used to evaluate response to pegcetacoplan and other complement inhibitors.
Discontinuation		
3. Discontinuation for iptacopan should be based on the criteria used by each of the public drug plans for reimbursement of pegcetacoplan for patients with PNH.	There is no evidence that iptacopan should be held to a different standard than pegcetacoplan when considering discontinuation.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
4. Iptacopan should be prescribed by or in consultation with a hematologist with experience managing PNH.	This is to ensure that iptacopan is prescribed only for appropriate patients.	—
5. Iptacopan should not be administered in combination with other complement inhibitors.	Iptacopan was approved by Health Canada for use as monotherapy in adults with PNH who have hemolytic anemia.	—
Pricing		
6. Iptacopan should be negotiated so that it does not exceed the drug program cost of treatment with pegcetacoplan for the treatment of adults with PNH.	The indirect evidence submitted by the sponsor was subject to considerable limitations that challenged interpretation of the evidence, and the committee was unable to reach firm conclusions regarding the comparative efficacy and safety of iptacopan relative to pegcetacoplan. However, clinical expert opinion suggests they are similar proximal complement inhibitor treatments. As such, there is insufficient evidence to justify a cost premium for iptacopan over pegcetacoplan reimbursed for PNH.	—
Feasibility of adoption		
7. The feasibility of adoption of iptacopan must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate.	—

ARC = absolute reticulocyte count; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; EVH = extravascular hemolysis; PNH = paroxysmal nocturnal hemoglobinuria; QALY = quality-adjusted life-year.

Discussion Points

- **Significant unmet need**: CDEC deliberated on iptacopan considering the criteria for significant unmet need that are described in section 11.3.2.3 of the Procedures for Reimbursement Reviews. PNH is a rare and chronic disease with significant mortality and morbidity. C5 inhibitors (e.g., eculizumab, ravulizumab) have improved disease outcomes by controlling IVH; however, C3-mediated EVH may develop in some patients, potentially leading to anemia, associated fatigue, and the need for blood transfusions. Considering the rarity and severity of PNH and the medical need for additional treatment options that control PNH by addressing both IVH and EVH, CDEC concluded that the available evidence reasonably suggests that iptacopan reduces morbidity in patients with residual hemolytic anemia despite treatment with a C5 inhibitor.
- **Efficacy**: The Grading of Recommendations Assessment, Development and Evaluation (GRADE) certainty of evidence assessment resulted in a rating of "moderate" for hematologic outcomes and transfusion avoidance, indicating likely improvement in these measures relative to C5 inhibitor

treatment at stable regimen. The results for the FACIT-Fatigue and EORTC QLQ-C30 instruments were rated as being of “low” certainty using GRADE. Both hematologic and HRQoL outcomes were identified as important to patients and clinicians in demonstrating treatment response. Weighing the uncertainty in the patient-reported outcomes against the rarity of the disease and the notable impact of residual anemia on patients’ quality of life — an impact highlighted by both patients and clinicians — CDEC concluded that the available evidence meets patient needs, based on clinically meaningful improvements in hematologic outcomes and transfusion avoidance. Patients with intolerable AEs from a C5 inhibitor were not specifically studied in the APPLY-PNH trial. However, CDEC considered it reasonable to reimburse iptacopan treatment in these rare cases.

- **AEs**: CDEC discussed the safety profile observed with iptacopan. While the APPLY-PNH trial did not provide direct comparative evidence regarding the AEs of iptacopan versus a relevant comparator (e.g., pegcetacoplan), CDEC noted that, overall, treatment-emergent adverse events (TEAEs) appeared with similar frequency in patients treated with iptacopan compared with C5 inhibitor therapy. The most common AEs in the iptacopan group were headache, diarrhea, nasopharyngitis, and nausea. CDEC heard from the clinical experts that headache is a common adverse reaction in patients with PNH when starting treatment with a complement inhibitor. CDEC noted that the gastrointestinal events were not serious and no deaths or withdrawals due to AEs occurred in either group over the total study duration. CDEC agreed with the clinical experts that, overall, the incidence and severity of AEs appeared manageable; however, uncertainty remains due to the small sample size and limited follow-up duration.
- **Indirect evidence**: CDEC discussed the uncertainty of the comparative efficacy and safety of iptacopan due to the absence of direct comparative evidence. CDEC considered 1 sponsor-submitted unanchored MAIC assessing iptacopan relative to pegcetacoplan. The committee noted several limitations with the submitted comparative analysis, notably heterogeneity across the study designs and populations, risk of residual confounding, small effective sample size, and imprecision. CDEC concluded that the comparative evidence was insufficient to draw definitive conclusions on the relative efficacy (i.e., based on change from baseline in hemoglobin levels, FACIT-Fatigue score, lactate dehydrogenase levels, and transfusion avoidance at week 20) and safety (i.e., serious AEs) of iptacopan versus pegcetacoplan. The clinical experts anticipated iptacopan and pegcetacoplan to have similar efficacy based on how these drugs perform in clinical practice.
- **Long-term extension study**: CDEC considered the data from the 24-week extension period of the APPLY-PNH study, which suggested sustained benefits up to 48 weeks, and a safety profile of iptacopan that was consistent with the randomized controlled period of the trial. However, interpretation of the long-term results was limited by missing data, small sample size, and the open-label and descriptive nature of the extension study, and was considered as supportive evidence by CDEC.
- **Administration method**: CDEC discussed the administration method and schedule of iptacopan and relevant comparator pegcetacoplan. Iptacopan is administered orally twice a day and pegcetacoplan is offered via subcutaneous infusion pump twice weekly. CDEC heard from the clinical experts that

the choice between therapies is guided by availability, route and frequency of administration, patient preference, and contraindications. CDEC concluded that there was no evidence assessing the impact of iptacopan's route and frequency of administration on HRQoL outcomes.

- **Uncertain economic evidence**: The economic evaluation is driven by the treatment costs, which were based on publicly available prices, making all interpretation of economic evidence highly questionable. Combined with the lack of longer-term effectiveness or safety data, and direct comparative evidence relative to relevant comparators, the cost-effectiveness of iptacopan remains uncertain.

Background

PNH is a rare, chronic, and potentially life-threatening condition caused by an acquired genetic defect in hematopoietic stem cells. This defect causes the complement system to recognize RBCs as damaged, triggering hemolysis. Hemolysis occurs through 2 mechanisms in PNH: IVH and EVH, the latter only occurring when a patient is receiving a C5 inhibitor. Persistent IVH results in hemoglobinuria, characterized by dark-coloured urine; anemia and its associated symptoms (e.g., fatigue, dyspnea); and an increased risk of thrombosis, pain, organ damage (e.g., impaired renal function), and underlying bone marrow dysfunction. The clinical manifestations of EVH are heterogeneous, with some patients being asymptomatic with normal hemoglobin levels while others may develop severe clinical symptoms and require blood transfusions to manage ongoing anemia and fatigue. The symptoms of PNH and need for RBC transfusions have a significant impact on patients' daily living, impair their HRQoL, and increase the risk of morbidity and mortality.

The estimated prevalence of PNH is 1.2 to 1.3 per 100,000 persons based on US data, and 1.59 to 3.81 per 100,000 persons based on UK data. Clinical trial and real-world data estimate that approximately 20% of patients with PNH who are clinically stable on C5 inhibitor treatment for IVH develop clinically significant EVH.

In Canada, patients with PNH receive C5 inhibitors, ravulizumab, and eculizumab by IV infusion as standard first-line therapy. Treatment options for patients with EVH and anemia include pegcetacoplan by subcutaneous infusion and danicopan, an oral therapy that is used in combination with C5 inhibitors. Both second-line options, pegcetacoplan and danicopan in combination with C5 inhibitor therapy, require parenteral administration, which may not be acceptable or feasible for all patients. Patients with PNH and EVH require treatments to reduce mortality, inhibit IVH, and improve HRQoL with better hemoglobin support that does not require transfusion, avoids iron overload, and leads to better functional status for patients.

Iptacopan was approved by Health Canada as monotherapy in the treatment of adult patients with PNH who have hemolytic anemia. The sponsor submitted a deviation request for the reimbursement of iptacopan in adult patients with PNH who have an inadequate response to, or are intolerant of, a C5 inhibitor. Per the sponsor's request, this review focuses on the population requested for reimbursement. Iptacopan is available as a 200 mg oral capsule, and the dosage recommended in the product monograph is 200 mg twice daily.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 randomized, active comparator–controlled, open-label study in adult patients with PNH and residual anemia; 1 long-term extension study; and 1 indirect treatment comparison
- patients' perspectives gathered by joint input from 2 patient groups, the Canadian Association of PNH Patients (PNHCA) and the Aplastic Anemia & Myelodysplasia Association of Canada (AAMAC)
- input from public drug plans that participate in the Reimbursement Review process
- 2 clinical specialists with expertise diagnosing and treating patients with PNH
- input from 1 clinician group, the Canadian PNH Network
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Group Input

This section was prepared by the review team based on the input provided by patient groups.

PNHCA and AAMAC submitted a joint input for this review. PNHCA is a nonprofit patient advocacy group that connects individuals with PNH and their caregivers to resources and information on optimal management of PNH. AAMAC is a national charity that provides supportive resources on PNH to patients, caregivers, and health care providers. A clinical summary of PNH was provided and information was gathered through the personal experiences of individuals who had direct experience with iptacopan, including 1 patient living in Canada and 5 patients living in the US.

Input from the patient groups highlighted the diverse and profound ways in which PNH impacts quality of life for both patients and caregivers. Due to the condition's rarity and the variability of presentation, the input noted that patients often experience a period of significant health deterioration before they receive a PNH diagnosis. Thrombosis was emphasized as a serious complication of PNH that can result in life-threatening conditions such as stroke, pulmonary embolism, or Budd-Chiari syndrome, which significantly increases the risk of morbidity and mortality. It was noted that the chronic nature of PNH means that patients must manage their condition over a lifetime, along with the associated physical, emotional, and financial burdens. The need for frequent medical appointments across the patient's lifetime can also result in feelings of isolation, strain on relationships, emotional distress, and decreased quality of life. Patients must also cope long-term with unpredictability of symptoms, treatment side effects, and threat of serious complications.

The patient group input noted that while C5 inhibitor therapies prevent RBC destruction, EVH may not be fully addressed, which can result in chronic anemia despite C5 inhibitor treatment. Chronic anemia can cause severe fatigue, physical weakness, shortness of breath, and transfusion dependence, making it challenging to carry out household tasks, maintain employment, participate in recreational activities, and sustain an active lifestyle. A patient living in Canada who provided input shared that while previous treatment

with eculizumab did not enable a decent quality of life, treatment with iptacopan led to feeling “normal” within months of treatment initiation. This patient also noted valuing the convenience of oral administration, which enabled freedom from injection-type infusions. The 5 patients living in the US reported substantial increases in hemoglobin after initiating iptacopan, with some also experiencing normalization of lactate dehydrogenase (LDH) levels, reductions in bilirubin levels, and improvements in fatigue.

Overall, the patient group input highlighted a need for new therapies that effectively manage IVH and EVH, provide comprehensive relief from a wide range of symptoms, and improve patient well-being. Specifically, the patient group noted the need for new treatments that improve hemoglobin levels and reduce the need for blood transfusions. The patient group noted that oral treatments provide significant benefits over injections in terms of convenience, comfort, adherence, psychological well-being, and economic factors, making oral treatments a preferred option when available.

Input From Clinical Experts Consulted by CDA-AMC

All CDA-AMC review teams include at least 1 clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol, assisting in the critical appraisal of clinical evidence, interpreting the clinical relevance of the results, and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of PNH.

Unmet Needs

The clinical experts noted that C5 inhibitors can provide incomplete control of PNH in some circumstances, including rare genetic polymorphism, inadequate dosing, response to complement-amplifying triggers (e.g., vaccination or infections) leading to breakthrough hemolysis (BTH), or symptomatic EVH related to C5 inhibition. Per the experts, approximately one-third of patients require higher doses of C5 inhibitors, although this may be less likely with ravulizumab because it is dosed by weight. Patients may also develop BTH toward the end of their treatment cycles if they would benefit from more frequent perfusion; per the clinical experts, this last situation is not generally considered a treatment failure. The experts estimated that approximately 40% of patients with PNH will continue to have low hemoglobin despite therapy; approximately 30% will require transfusions; and in 20 to 30% of patients, EVH will contribute to poor HRQoL. Treatment goals for patients with PNH and EVH remain to reduce mortality; inhibit IVH; and improve HRQoL with better hemoglobin support that does not require transfusion, avoids iron overload, and leads to better functional status for patients.

Treatment strategies for a patient diagnosed with EVH include erythropoietin administration and steroids, which the clinical experts stated have questionable efficacy and associated risks such as thrombosis and encapsulated infection predilection. The main nonpharmacologic treatment for EVH and persistent anemia in PNH while on C5 inhibitor treatment is transfusion support. Transfusion is associated with several drawbacks, according to the clinical experts: hospital visits of 2 to 4 hours are required and may be longer if blood typing is not done in advance, and there are risks with transfusion including infection, antibody development, or iron overload, which can lead to heart and liver failure or endocrine disorders including

diabetes, as well as liver cancer if left untreated. In addition, most patients receiving transfusion will have significantly reduced HRQoL and will be unable to maintain regular employment.

Pegcetacoplan is approved as a second-line therapy for patients with PNH who have an inadequate response to, or are intolerant of, a C5 inhibitor. As per the clinical experts consulted for this review, it is currently the primary pharmacologic option offered to patients diagnosed with EVH. Pegcetacoplan is administered as a subcutaneous infusion (over 20 to 40 minutes) with twice-weekly dosing. If BTH occurs, the experts noted that the frequency of pegcetacoplan would usually be increased (every 3 days or up to 3 times weekly). If BTH is severe, doses of ravulizumab or eculizumab would also be added, but the experts noted that C5 inhibitors may not be on formulary in all hospitals. According to the clinical experts, there are patients and caregivers for whom subcutaneous infusions are not possible or are unacceptable, and the treatment burden of administering infusions can be significant. The experts also stated that danicopan, as an add-on therapy to C5 inhibitors, may be available to some patients in Canada via a managed access program, but this therapy can also be problematic as it maintains the need for IV infusions, which can require the installation of a central vein catheter, which is associated with its own risks and need for care. Danicopan is administered orally 3 times daily, and treatment adherence may be challenging for some patients.

Place in Therapy

According to the clinical experts consulted, iptacopan would be used as another second-line option for patients with PNH with an incomplete hematologic response to C5 inhibitors, particularly with ongoing anemia secondary to EVH (either requiring transfusions or not). There is also a place for iptacopan in patients who experience intolerance to C5 inhibition or are no longer able to have IV infusions, either because of long distances to medical care or the inability to maintain IV access.

In patients with genetic polymorphisms in whom C5 inhibitor treatment is ineffective, iptacopan would be a treatment option. As there is currently no test available to detect the polymorphisms, these patients are identified through a trial of C5 inhibitors. Patients with polymorphisms require a switch from the currently approved C5 inhibitors to a more proximal complement blockade to control IVH.

According to the clinical experts, those currently on eculizumab with persistent anemia due to suboptimal control of IVH may be better controlled by switching to ravulizumab, as it uses weight-based dosing, but the experts noted that ravulizumab is unavailable in many provinces. In the absence of ravulizumab or even with suboptimal control on C5 inhibition, a switch to proximal inhibition could be warranted. The experts suggested there may be a role for iptacopan as a third-line option for patients who received pegcetacoplan and experienced adverse effects, were no longer willing to receive subcutaneous infusions, experienced too many episodes of BTH, or had persistently elevated LDH levels even with increased doses of pegcetacoplan. The CDA-AMC review team noted that this review for iptacopan focuses on the population requested for reimbursement (i.e., adult patients with PNH who have an inadequate response or intolerance to a C5 inhibitor). Evidence for the use of iptacopan after pegcetacoplan was not provided in the pivotal trial for iptacopan, the APPLY-PNH trial.

The clinical experts indicated that iptacopan would shift the current treatment paradigm, in that pegcetacoplan and iptacopan would likely be offered in the same line of therapy and for the same indication

as pegcetacoplan. They did not expect that iptacopan would be used as first-line therapy, although there are some data to support this approach (e.g., the APPOINT-PNH study) if there were a situation in which C5 inhibitors could not be used. The clinical experts stated that iptacopan would not be used in combination with other treatments, but as a stand-alone second option after C5 inhibitors.

Patient Population

The clinical experts noted that appropriate candidates for iptacopan treatment include patients with PNH who have persistent anemia (hemoglobin < 100 to 105 g/L, with or without history of ongoing blood transfusion needs, and no known cause for the anemia [e.g., blood loss, bone marrow failure]) and evidence of EVH, despite an adequate trial of C5 inhibitor treatment; patients with intolerance to a C5 inhibitor (uncommon in clinical practice); or patients with a rare C5 genetic polymorphism (mainly in patients of Japanese descent). The clinical experts stated that suitable patients would be accepting of iptacopan's treatment modality and schedule. The clinical experts also highlighted that patients who are potentially undertreated due to not wanting transfusions, whose anemia is not severe enough for transfusion, or for whom currently available therapy is unacceptable or unfeasible, would likely benefit from iptacopan. It would also be suitable for patients who are not willing or not able to use the infusion pump for pegcetacoplan. The experts explained that patients with PNH often have other concurrent causes of anemia, and efforts must be made to control these (e.g., epoetin alpha in patients with chronic kidney disease, or vitamins in the case of deficiencies). The cause of anemia may be multifactorial; for example, patients with concurrent aplastic anemia or myelodysplastic syndromes should not be excluded from receiving iptacopan to control their EVH. For these complex patients, the experts noted that a trial of drug may be necessary to see if there is improvement in the patient's transfusion needs, hemoglobin, and/or quality of life, without necessarily having a fixed laboratory value to be reached, and with the recognition that every effort must be made to continue controlling IVH and preventing its associated mortality.

Iptacopan would also be suitable for patients with no response to C5 inhibition in the case of polymorphisms, according to the clinical experts consulted. The experts indicated that it is not possible to identify in advance which patients will most benefit from 1 therapy over another, and that a trial of therapy may be needed. Further, the clinical experts emphasized the need for fluidity between the therapies, as patients' needs could vary over time and changes between therapies should not be seen as unidirectional.

Iptacopan would not be suitable for patients who are pregnant or who plan to become pregnant, nor those who are not accepting of or are unable to adhere to twice-daily oral dosing, given the risk of BTH with missed doses. As per the FDA product label, iptacopan may not be suitable for patients with uncontrolled dyslipidemia.

Assessing the Response to Treatment

The clinical experts noted that response to therapy is typically an improvement in hemoglobin, a reduction in transfusion requirements, and improvement in symptoms relative to the baseline for a given patient. They noted that ongoing anemia and transfusion needs may or may not be a treatment failure, as it is possible that other concurrent diseases such as bone marrow failure, aplastic anemia, other cancers, bleeding, or comorbidities could be contributing factors. The experts stated that treatment failures or suboptimal

responses emphasize the need for full evaluation of the cause of anemia. Additionally, the experts noted that the hemoglobin outcomes used in the clinical trial (at least 20 g/L hemoglobin improvement, or hemoglobin level of 120 g/L) may not be realistic thresholds in clinical practice, given the complexity and heterogeneity of the condition. The experts stated that a 10 g/L improvement would be meaningful in clinical practice, particularly when combined with other factors such as transfusion independence.

Discontinuing Treatment

According to the clinical experts, discontinuation would be considered in patients who show no improvement in hemoglobin and/or transfusion needs with the use of iptacopan. It would be stopped if there were intolerance, severe and recurrent BTH, or concerns about adherence to the dosing schedule that may place the patient at risk of BTH, or in cases of pregnancy or breastfeeding.

The experts anticipated that a trial of at least 8 weeks would be needed to see improvement. Longer trials may be needed to assess treatment response if the trial period is compromised by a clinical situation leading to BTH or nonadherence to therapy.

Prescribing Considerations

The clinical experts indicated that treatment with iptacopan would need to be initiated by a hematologist, preferably with expertise in PNH, and that consultation with a PNH expert would be warranted if a patient with PNH were being followed in a shared-care model (i.e., a hematologist with expertise in PNH along with a local hematologist).

Clinician Group Input

This section was prepared by the review team based on the input provided by clinician groups.

One clinician group, the Canadian PNH Network, submitted input for this review based on contributions from 10 clinicians. The Canadian PNH Network is a group of hematologists located across Canada who follow the majority of patients with PNH in Canada and set consensus guidelines for the diagnosis and management of PNH. Information was gathered for this input submission through publicly available documents, congress abstracts, and published literature.

Overall, the clinician group input aligned with input provided by the clinical experts consulted for this review. Both the clinician group and clinical experts agreed that, currently, the only curative treatment for PNH is hematopoietic stem cell transplant, which is reserved for patients with predominant or progressive bone marrow failure. For patients who are ineligible for transplant, primary PNH treatment goals highlighted in the input were hemoglobin improvement, reduced transfusion needs, and absence of end-organ complications or other symptoms. Clinical experts also emphasized reducing mortality, avoiding iron overload, and improving HRQoL as important treatment goals.

Key unmet needs identified by the clinician group for patients with PNH included a lack of therapies that reverse the disease course other than allogeneic stem cell transplant, as well as a need for more convenient, tolerable therapies. The input emphasized the importance of therapy convenience for patients living in remote communities that may lack access to an infusion centre or ability to self-inject treatment, and clinical

experts noted that oral therapies would fulfill this need. While danicopan is an oral therapy available through a managed access program, it is an add-on to C5 inhibitor treatment and patients must still access and receive their regular C5 inhibitor infusions.

According to the clinician group, iptacopan will be used as second-line therapy in eligible patients, as per the APPLY-PNH criteria, for those with persistent anemia despite C5 inhibition in whom EVH is suspected. The clinician group noted that it would be reasonable to also use iptacopan as a third-line therapy. The CDA-AMC review team noted that this review for iptacopan focuses on the population requested for reimbursement (i.e., adult patients with PNH who have an inadequate response to, or are intolerant of, a C5 inhibitor). The clinician group noted that iptacopan would provide an additional therapy option besides pegcetacoplan for patients requiring proximal inhibition monotherapy. Given the absence of comparative efficacy data versus pegcetacoplan, the clinician group stated that patient preference will largely drive treatment selection, according to the route of administration that best supports their lifestyle. Patients best suited for iptacopan therapy, as identified by the clinician group, are those with a high likelihood of adhering to oral treatment, frequent travellers, or those who cannot initiate or continue other therapies. Less suitable patients include those who are not anemic, meet APPLY-PNH exclusion criteria, are planning pregnancy, or are unlikely to be adherent with the dosage schedule, given the high risk of BTH with missed doses. The input noted that BTH outcomes are more severe with proximal complement inhibition than terminal, as the pool of vulnerable circulating PNH cells increases with avoidance of both IVH and EVH.

Key outcomes for evaluating treatment response that were identified by clinicians included hemoglobin improvement and reduced transfusion dependence, sustained IVH control (assessed based on LDH levels and BTH events) and improvements in fatigue and quality of life. Treatment discontinuation should be considered in patients with AEs precluding ongoing therapy, who have poor adherence, or who are pregnant or breastfeeding, according to the input. Both the clinician group and consulted experts agreed that patients with PNH benefit from having a clinician involved in their care who specializes in managing and monitoring the disease.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Iptacopan was only compared to C5 inhibitor use and did not include pegcetacoplan use, which is the current option when patients have inadequate response or intolerance to C5 inhibitors. An indirect comparison vs. pegcetacoplan was submitted by the sponsor. All comparators are available in many jurisdictions with	The clinical experts indicated that C5 inhibitors (pegcetacoplan and danicopan) are relevant comparators to iptacopan but may not be accessible in all jurisdictions due to differences in reimbursement. At the time of review initiation for the current iptacopan file, danicopan was under review with CDA-AMC. Danicopan received a final conditional positive CDA-AMC recommendation in November 2024 and is currently under consideration for negotiation at the pCPA.

Implementation issues	Response
criteria, including pegcetacoplan, which is not a C5 inhibitor but has the same reimbursement indication as iptacopan.	Increased doses of C5 inhibitors or more frequent dosing intervals may also be used to improve control of PNH for some patients. The experts noted that access to higher doses of C5 inhibitors is not available in all jurisdictions. CDEC acknowledged the clinical experts' response.
Considerations for initiation of therapy	
The reimbursement indication for iptacopan is for patients with PNH who have an inadequate response or intolerance to a C5 inhibitor. 1. Can an "inadequate response" to C5 inhibitors be clearly defined? 2. Should iptacopan be reimbursed only in the population that was studied (i.e., patients diagnosed with PNH who were treated with a stable regimen of C5 inhibitors [eculizumab or ravulizumab] for at least 6 months before randomization, but still presenting with residual anemia)?	The clinical experts indicated that intolerance to C5 inhibitors is uncommon but there is a rare subset of patients with genetic polymorphisms who have no response to eculizumab or ravulizumab. The clinical experts maintained that C5 inhibitors remain the first-line treatment for patients with PNH. There is no standard definition of inadequate response to C5 inhibitors, and the clinical trials for second-line agents have used different hemoglobin and other criteria to determine enrolment. Further, inadequate response may be related to IVH, EVH, or both, which impacts the second-line options that are most appropriate. CDEC agreed with the clinical experts that alignment with the reimbursement criteria for pegcetacoplan would be reasonable. The experts noted that the hemoglobin thresholds used in the clinical trials were arbitrary, and that patients with anemia but higher hemoglobin levels than used in the clinical trials may also benefit from iptacopan therapy. The experts also noted that patients who have an inadequate response to pegcetacoplan may also be considered for iptacopan in clinical practice. However, evidence for use of iptacopan after pegcetacoplan was not provided in the pivotal trial for iptacopan (the APPLY-PNH trial), and per sponsor request, this CDA-AMC review focused on the population requested for reimbursement (i.e., adult patients with PNH who have an inadequate response to, or are intolerant of, a C5 inhibitor).
Would danicopan be added on to iptacopan for use in patients with signs and symptoms of extravascular hemolysis?	The clinical experts stated that there are currently no data on the use of iptacopan in combination with other treatments for PNH. However, for a patient on iptacopan who experiences an acute episode of BTH, the experts stated that an add-on dose of eculizumab may help control the hemolysis and reduce the need for transfusions. Without further evidence to support combination therapy with iptacopan, the clinical experts stated that iptacopan is unlikely to be used with other drugs, even though mechanistically there is potential for benefit. CDEC agreed with the clinical experts that there is currently insufficient evidence to guide a recommendation on adding danicopan to iptacopan; therefore, iptacopan should be used as monotherapy.
Would patients be considered for iptacopan if they preferred an oral option as opposed to the other available parenteral options?	The clinical experts indicated that C5 inhibitors remain the preferred first-line treatment for PNH and their efficacy and safety are well established. The availability of an oral treatment may be important for patients in very remote areas or for those with conditions where IV or SC infusions are not feasible. Oral therapy may also be preferred if patients need to travel. The clinical experts noted that some patients may find intermittent injections to be more

Implementation issues	Response
	manageable than twice-daily oral administration, which requires strict adherence to avoid potentially serious IVH. CDEC agreed with the clinical experts that the importance of the oral route of administration may depend on clinical and logistical factors, as well as patient preferences.
Considerations for continuation or renewal of therapy	
Should the recommendation be aligned with pegcetacoplan, as they both have the same indication for reimbursement?	CDEC agreed with the clinical experts that alignment with the reimbursement criteria for pegcetacoplan would be reasonable.
Considerations for discontinuation of therapy	
Should the recommendation be aligned with pegcetacoplan, as they both have the same indication for reimbursement?	CDEC agreed with the clinical experts that alignment with the reimbursement criteria for pegcetacoplan would be reasonable.
Considerations for prescribing of therapy	
Should the recommendation be aligned with pegcetacoplan, as they both have the same indication for reimbursement?	CDEC agreed with the clinical experts that alignment with the reimbursement criteria for pegcetacoplan would be reasonable.
Care provision issues	
Vaccinations are required before therapy. Infection risk of encapsulated bacteria is increased with iptacopan.	The clinical experts noted that vaccination is required before initiating PNH therapy for all patients.
System and economic issues	
All 3 comparators (eculizumab, ravulizumab, and pegcetacoplan) have successfully gone through price negotiations; however, only pegcetacoplan is approved for the same indication.	This is a comment from the drug plans to inform CDEC deliberations. Per the sponsor's request, this CDA-AMC review focused on the population requested for reimbursement (i.e., adult patients with PNH who have an inadequate response to, or are intolerant of, a C5 inhibitor).
The price of iptacopan is high at $51,700 per QALY ($719.94 per 200 mg capsule).	This is a comment from the drug plans to inform CDEC deliberations.

BTH = breakthrough hemolysis; CDA-AMC = Canada's Drug Agency; CDEC = Canadian Drug Expert Committee; EVH = extravascular hemolysis; IVH = intravascular hemolysis; pCPA = pan-Canadian Pharmaceutical Alliance; PNH = paroxysmal nocturnal hemoglobinuria; QALY = quality-adjusted life-year; SC = subcutaneous.

Clinical Evidence

Systematic Review

Description of Studies

One phase III, randomized, multicentre, active comparator–controlled, open-label, parallel group study (the APPLY-PNH study) met the inclusion criteria for the systematic review. The objective of the study was to evaluate the efficacy and safety of oral iptacopan monotherapy in adult patients (aged ≥ 18 years) with PNH with residual anemia (hemoglobin < 100 g/L) despite treatment with a C5 inhibitor for at least 6 months before randomization. The APPLY-PNH study included a 24-week randomized treatment period (RTP) and a 24-week open-label, single-arm, iptacopan extension period (details provided in the Long-Term Extension Studies section). During the RTP, 97 patients were randomized at an 8:5 ratio to switch to iptacopan (200

mg twice daily), or to continue with the C5 inhibitor therapy they were receiving before the study (eculizumab or ravulizumab). The co-primary outcomes were the proportion of patients with at least a 20 g/L increase in hemoglobin or who had sustained hemoglobin levels of 120 g/L in the absence of RBC transfusion. Other key outcomes included the mean change from baseline in hemoglobin, transfusion avoidance, fatigue (measured using the FACIT-Fatigue instrument), and BTH.

The mean age of patients enrolled in the APPLY-PNH study was 51.7 years (standard deviation [SD] = 16.9) in the iptacopan group (N = 62), and 49.8 years (SD = 16.7) in the C5 inhibitor group (N = 35). At baseline, the mean hemoglobin value was 89.3 g/L (SD = 7.0) and 88.5 g/L (SD = 8.9), in the iptacopan and C5 inhibitor groups, respectively, with 56.5% and 60.0% of patients having received an RBC transfusion in the past 6 months. Fewer patients in the iptacopan group had a history of major adverse vascular events (MAVEs) than in the C5 inhibitor group (19.4% and 28.6%, respectively). The mean disease duration was 11.9 years (SD = 9.8) and 13.5 years (SD = 10.9) in the iptacopan group and C5 inhibitor groups, respectively. Most patients were receiving eculizumab (65%) at enrolment, with the minority receiving ravulizumab (35%). Before randomization, the mean dose of eculizumab received was numerically lower in the iptacopan than the control group (937.5 mg [SD = 100.5] versus 1,004.3 mg [SD = 171.8], respectively). Among those who received ravulizumab, the mean dose was 3,177.3 mg (SD = 177.1) in the iptacopan group and 3,200.0 mg (SD = 195.4) in the control group.

Efficacy Results

Both primary outcomes in the APPLY-PNH randomized treatment period showed results that favoured iptacopan versus the C5 inhibitor group. The marginal proportion of patients with at least a 20 g/L increase in hemoglobin from baseline (in the absence of transfusion) was 82.3% versus 2.0% in the iptacopan versus C5 inhibitor groups, respectively, with a difference between groups of 80.2% (95% CI, 71.2% to 87.6%; P < 0.0001). With respect to normalization of hemoglobin levels, 68.8% of patients in the iptacopan group reported hemoglobin levels of at least 120 g/L compared with 1.8% of patients in the C5 inhibitor group (difference in marginal proportions of 67.0%; 95% CI, 56.4% to 76.9%; P < 0.0001). Between-group differences in both hemoglobin outcomes were considered clinically important by the clinical experts we consulted.

The change from baseline in hemoglobin levels was a secondary outcome, which showed an adjusted mean change of 36.0 g/L in the iptacopan group and a –0.6 g/L change the C5 inhibitor group. The mean difference between groups was 36.6 g/L (95% CI, 32.0 to 41.2; P < 0.0001) favouring iptacopan versus C5 inhibitors. Based on the threshold of clinically important change that was selected by the clinical experts (10 g/L difference between groups), iptacopan likely results in clinically important improvement in hemoglobin levels versus C5 inhibitors.

Based on observed data, 59 of 62 patients in the iptacopan group and 14 of 35 patients in the C5 inhibitor group did not require a transfusion (i.e., did not receive an RBC transfusion or did not meet the protocol-specified criteria for a transfusion) from day 14 to day 168 in the RTP (marginal proportions of 94.8% and 25.9%, respectively). The difference in marginal proportions of patients avoiding transfusions was 68.9%

(95% CI, 51.4% to 83.9%; P < 0.0001) for the iptacopan group versus the C5 inhibitor group, based on the sponsor's primary analysis.

In the APPLY-PNH study, the definition of clinical BTH was having at least 1 of 2 clinical criteria (≥ 20 g/L decrease in hemoglobin levels or signs and symptoms of hemolysis), and laboratory evidence of IVH (LDH > 1.5 times the upper limit of normal [ULN]). Two patients (3.2%) in the iptacopan group and 6 patients in the C5 inhibitor group (17.1%) met the criteria for a clinical BTH, with an annualized adjusted BTH rate of 0.07% and 0.67%, respectively. The BTH annualized adjusted rate difference was −0.60% (95% CI, −1.24% to 0.04%) for the iptacopan versus C5 inhibitor groups.

Two other secondary outcomes were identified as important surrogate measures of hemolysis: the change from baseline in LDH levels and change in the absolute reticulocyte count (ARC). For the iptacopan versus C5 inhibitor groups, the percent reduction in the LDH change from baseline was 1.14% (95% CI, −10.19% to 11.31%), and the adjusted mean difference in the ARC change from baseline was -116.15×10^9 U/L (95% CI, −132.04 to −100.26; P < 0.0001).

Fatigue was measured using the 13-item FACIT-Fatigue questionnaire, which assesses self-reported tiredness, weakness, and difficulties with daily life activities. The FACIT-Fatigue items are scored such that a high score represents better health outcomes, with the total score ranging from 0 (severe fatigue) to 52 (no fatigue). In patients with PNH, a minimal important difference (MID) of 5 points has been reported in the literature. In the APPLY-PNH study, the change from baseline in FACIT-Fatigue score was a secondary outcome, and was missing data from 4 patients (11%) in the C5 inhibitor group and no patients in the iptacopan group. The mean within-group FACIT-Fatigue scores increased (improved) 8.6 points in the iptacopan group and 0.3 points in the C5 inhibitor group, with an adjusted mean difference of 8.3 points (95% CI, 5.3 to 11.3) favouring the iptacopan group versus the C5 inhibitor group (P < 0.0001).

The change from baseline in the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was an exploratory outcome in the APPLY-PNH study and was not part of the planned statistical testing procedures. The results were based on observed data, with no imputation for missing values, and excluded 2 patients (6%) from the C5 inhibitor group. There was no mean change from baseline in the Global Health Index score in the C5 inhibitor group (0.0 points) and a 15.3-point increase in the iptacopan group. The mean difference was 14.5 points (95% CI, 9.6 to 19.3) for iptacopan versus C5 inhibitor groups at 24 weeks.

Harms Results

Most patients in the APPLY-PNH study experienced at least 1 TEAE, with 82% of those in the iptacopan group and 80% of patients in the C5 inhibitor groups reporting an AE over the 24-week treatment period. The most common events in the iptacopan versus C5 inhibitor group were headache (16% versus 3%), diarrhea (15% versus 6%), nasopharyngitis (11% versus 6%), and nausea (10% versus 3%). Serious adverse events (SAEs) were reported in 9.7% of patients in the iptacopan group and 14.3% of patients in the C5 inhibitor group. No deaths occurred and no patients stopped treatment due to AEs in either group. In the iptacopan group, 3.2% of patients experienced a serious or severe infection, compared with 8.6% of patients in the C5 inhibitor group (risk difference = −5.4%; 95% CI, −15.6% to 4.9%).

No MAVEs were reported in the C5 inhibitor group, but 1 patient (1.6%) in the iptacopan group experienced a MAVE (transient ischemic attack), which was assessed as an SAE. The annualized adjusted rate difference for MAVEs was 0.03% (95% CI, −0.03% to 0.10%) for iptacopan versus C5 inhibitors.

Infections caused by encapsulated bacteria were identified as an important harm for this review. One patient in the iptacopan group (1.6%) and no patients in the C5 inhibitor group reported an infection with encapsulated bacteria. The risk difference for iptacopan versus C5 inhibitors was 1.6% (95% CI, −1.5% to 4.8%).

Critical Appraisal

The APPLY-PNH study was a 24-week open-label RCT. No major concerns were identified with the methods used to conduct the randomization; however, the baseline characteristics showed some imbalances between groups. Considering the small sample size of the study (35 patients in the C5 inhibitor group and 62 patients in the iptacopan group), it may not have been possible to balance all prognostic factors between groups. At baseline, a numerically higher proportion of patients in the C5 inhibitor group than the iptacopan group had received an RBC transfusion in the past 6 months, had a history of MAVE, and had LDH levels greater than 1.5 times the ULN. Also, the mean dose of eculizumab was higher in the C5 inhibitor group than the iptacopan group (1,004.3 mg versus 937.5 mg, respectively). The clinical experts consulted agreed that these factors were indicators of more severe PNH; thus, the differences observed in baseline characteristics potentially biased the results. No major risk of bias was identified due to patient withdrawals.

Patients, investigators, and study personnel were aware of the treatment group assigned; thus, the potential for reporting and performance bias should be considered, particularly when interpreting the results of subjective outcomes, such as FACIT-Fatigue score, EORTC QLQ-C30 score, and harms. The patient-reported outcomes and change from baseline in hemoglobin levels were also potentially biased due to missing data. The C5 inhibitor group was missing data from 2 patients (6%) for the EORTC QLQ C30 Global Health Index, 4 patients (11%) for the FACIT-Fatigue score, and 6 patients (17%) for the change in hemoglobin levels. There were no missing data for the iptacopan group. Given the small sample size, the differential rate of missing data may have biased the results, although the direction and extent of any bias is unclear. The imputation methods used for the transfusion avoidance end point may have impacted the results, adding uncertainty to the magnitude of treatment effects.

With regard to external validity, the study included adults with PNH who had an average age of 51 years and were predominantly female, with low hemoglobin levels (89 g/L). Based on the disease characteristics reported and the low proportion of patients with elevated LDH levels (7% of patients had LDH > 1.5 times the ULN), the clinical experts consulted for this review stated that the patients represented a relatively easy-to-manage and well-controlled population with PNH. The study excluded patients with comorbid conditions such as bone marrow failure or significant cardiac, renal, or hepatic disease; thus, the safety and efficacy of iptacopan in these patients is unclear. The small sample size of the study and potential lack of representativeness in prognostic factors, and the short study follow-up duration (24 weeks) for a life-long condition, contributed to uncertainty in the generalizability of the findings.

The direct evidence was limited to a single open-label RCT comparing iptacopan to C5 inhibitors; however, pegcetacoplan is the key comparator for adults with PNH who have had an inadequate response or intolerance to a C5 inhibitor. The absence of head-to-head studies comparing iptacopan with pegcetacoplan presents an evidence gap.

GRADE Summary of Findings and Certainty of the Evidence

For the RCT identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform the expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e., clinical importance was unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null. The target of the certainty of evidence assessment (presence or absence of an important effect) was based on thresholds identified in the literature (FACIT-Fatigue score and EORTC QLQ-C30 Global Health Index score), thresholds informed by the clinical experts consulted for this review (change from baseline in hemoglobin), or the presence or absence of any (non-null) effect (proportion of patients with an increase in hemoglobin levels of at least 20 g/L or who had hemoglobin levels of at least 120 g/L; proportion who avoided transfusion, had BTH, or experienced infections; and change from baseline in ARC or LDH levels).

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The list of outcomes was finalized in consultation with expert committee members and is shown in Table 3.

Table 3: Summary of Findings for Iptacopan Versus C5 Inhibitors for Patients With PNH

Outcome and follow-up	Patients (studies), N	Relative effects (95% CI) [a]	Absolute effects (95% CI)[a]			Certainty	What happens
			C5 inhibitor	Iptacopan	Difference		
Hemoglobin levels							
Marginal proportion of patients with ≥ 20 g/L increase in hemoglobin from baseline in the absence of RBC transfusions Follow-up: 24 weeks	97 (1 RCT)	OR: 338.25 (25.07 to 4,564.14)	20 per 1,000	823 per 1,000	802 more per 1,000 (712 to 876 more per 1,000)	Moderate[b]	Treatment with iptacopan likely results in a clinically important increase in the proportion of patients with a hemoglobin increase of ≥ 20 g/L in the absence of transfusion when compared with C5 inhibitor therapy.
Marginal proportion of patients with hemoglobin ≥ 120 g/L in the absence of RBC transfusions Follow-up: 24 weeks	97 (1 RCT)	OR: 495.74 (24.41 to 10,066.53)	18 per 1,000	688 per 1,000	670 more per 1,000 (564 to 769 more per 1,000)	Moderate[b]	Treatment with iptacopan likely results in a clinically important increase in the proportion of patients with hemoglobin levels ≥ 120 g/L in the absence of transfusion when compared with C5 inhibitor therapy.
Adjusted mean change from baseline in hemoglobin (g/L) Follow-up: 24 weeks	91 (1 RCT)	NR	−0.6	36.0	36.6 (32.0 to 41.2)	Moderate[c]	Treatment with iptacopan likely results in a clinically important increase in hemoglobin levels when compared with C5 inhibitor therapy.
Transfusion							
Marginal proportion of patients without transfusion Follow-up: 24 weeks	97 (1 RCT)	OR: 108.41 (17.25 to 681.24)	259 per 1,000	948 per 1,000	689 more per 1,000 (514 to 839 more per 1,000)	Moderate[b]	Treatment with iptacopan likely results in a clinically important increase in the proportion of patients who avoided transfusion when compared with C5 inhibitor therapy.
Markers of hemolysis							
Annualized adjusted rate of clinical BTH Follow-up: 24 weeks	97 (1 RCT)	Adjusted rate ratio: 0.10 (0.02 to 0.61)	0.67%	0.07%	−0.60% (−1.24% to 0.04%)	Very low[d]	The evidence is very uncertain about the effect of iptacopan on BTH when compared with C5 inhibitor therapy.

Outcome and follow-up	Patients (studies), N	Relative effects (95% CI) [a]	Absolute effects (95% CI)[a]			Certainty	What happens
			C5 inhibitor	Iptacopan	Difference		
Percent reduction in LDH levels (U/L) Follow-up: 24 weeks	97 (1 RCT)	Geometric mean ratio between groups: 0.99 (0.89 to 1.10)	Geometric adjusted mean ratio to baseline 0.98 (0.89, 1.07)	Geometric adj mean ratio to baseline 0.96 (0.90, 1.03)	1.14% (−10.19% to 11.31%)	Low[e]	Treatment with iptacopan may result in little or no difference in LDH levels when compared with C5 inhibitor therapy. There is some uncertainty about the clinical importance of the estimates.
Adjusted mean change from baseline in ARC (10^9/L) Follow-up: 24 weeks	97 (1 RCT)	NR	0.34	−115.81	−116.15 (−132.04 to −100.26)	Low[e]	Treatment with iptacopan may result in reduced ARC when compared with C5 inhibitor therapy. The clinical importance of the reduction is unclear.
Patient-reported outcomes							
Adjusted mean change from baseline in FACIT-Fatigue score (0 [worst] to 52 [best])[f] Follow-up: 24 weeks	93 (1 RCT)	NR	0.3	8.6	8.3 (5.3 to 11.3)	Low[g,h]	Treatment with iptacopan may result in an clinically important improvement in FACIT-Fatigue scores when compared with C5 inhibitor therapy.
Change from baseline in EORTC QLC-C30 Global Health Index score (0 [worst] to 100 [best])[i] Follow-up: 24 weeks	95 (1 RCT)	NR	0.0	15.3	14.5 (9.6 to 19.3)	Low[g,h,j]	Treatment with iptacopan may result in a clinically important improvement in EORTC QLQ-C30 Global Health Index scores when compared with C5 inhibitor therapy.
Harms							
Number of deaths Follow-up: 24 weeks	97 (1 RCT)	NA	0	0	NA	Very low[j,k,l]	The evidence is very uncertain about the effect of iptacopan on death when compared with C5 inhibitor therapy.
Patients with infections due to encapsulated bacteria Follow-up: 24 weeks	97 (1 RCT)	NA	0	16 per 1,000	16 more per 1,000 (15 fewer to 48 more per 1,000)	Very low[j,k,l]	The evidence is very uncertain about the effect of iptacopan on the occurrence of infection with encapsulated bacteria when compared with C5 inhibitor therapy.

ARC = absolute reticulocyte count; BTH = breakthrough hemolysis; CDA-AMC = Canada's Drug Agency; CI = confidence interval; EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy – Fatigue; HRQoL = health-related quality of life; LDH = lactate dehydrogenase; MID = minimal important difference; NA = not applicable; NR = not reported; OR = odds ratio; PNH = paroxysmal nocturnal hemoglobinuria; RBC = red blood cell; RCT = randomized controlled trial.

Note: Study limitations (which refer to internal validity or risk of bias), indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]All results are reported as unadjusted 95% CIs. The CIs for all efficacy outcomes (except EORTC QLQ-C30 score) are not reflective of the prespecified multiplicity scheme to control type I errors across the primary and secondary end points, and thus should not be interpreted as a basis for claiming statistical significance. EORTC QLQ-C30 score was an exploratory outcome and not part of the multiplicity scheme to control type I error rate; thus, adjusted CIs are not relevant to this end point.

[b]Rated down 1 level for serious concerns about imprecision. No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. Although the point estimate and entire CI excluded the null, the small sample size raises concern for potential overestimation of the true effect and there is evidence of prognostic imbalance. Because the effect appeared plausible, the CDA-AMC review team rated it down only once.

[c]Rated down 1 level due to serious concerns with risk of bias due to missing data. The clinical experts consulted for this review identified a 10 g/L to 15 g/L difference between groups as the threshold for a clinically meaning change.

[d]Rated down 1 level due to serious indirectness. The follow-up duration was insufficient to evaluate the rate of BTH. Rated down 2 levels due to very serious concerns about imprecision. There are a very small number of events captured and the small sample size raises concern for potential overestimation of the true effect as there is evidence of prognostic imbalance. No published between-group MID was identified, and the clinical experts we consulted were unable to estimate a threshold for clinical important effects; therefore, the null was used.

[e]Rated down 1 level due to serious indirectness. LDH and ARC levels are surrogate measures of hemolysis and may be impacted by other factors besides the study drug. Rated down 1 level for serious concerns about imprecision. The small sample size raises concern for potential overestimation of the true effect and there is evidence of prognostic imbalance. No published between-group MID was identified, and the clinical experts consulted by CDA-AMC were unable to estimate a threshold for clinically important effects; therefore, the null was used. For LDH, the CDA-AMC review team considered the 95% CI to include the potential for little to no difference only. No judgments were made on the clinical relevance of the ARC results.

[f]The FACIT-Fatigue is a 13-item, patient-reported questionnaire that assesses tiredness, weakness, and difficulty conducting usual activities due to fatigue over the past week. The scale ranges from 0 (extreme fatigue) to 52 (no fatigue). In patients with PNH, a 5-point increase from baseline was reported as the MID.[31]

[g]Rated down 1 level for serious risk of bias due to missing data and open-label design. The open-label study design and patients' and assessors' knowledge of assigned treatment may lead to biased estimates of subjective outcomes. For the FACIT-Fatigue score, data were missing or excluded from 4 of 35 patients in the C5 inhibitor group (11%) and no patients in the iptacopan group. For the Global Health Index, data were missing for 3 of 35 (6%) of patients in the C5 inhibitor group and no patients in the iptacopan group. Given the small sample size and differential missing data, the potential for bias cannot be ruled out.

[h]Rated down 1 level for serious concerns about imprecision. Although the point estimate and entire CI excluded the threshold of clinical importance, the small sample size raises concern for potential overestimation of the true effect and there is evidence of prognostic imbalance.

[i]The EORTC QLQ-C30 Global Health Index assesses global health status or quality of life with higher scores representing better greater HRQoL. The scores are the sum of the component items, which are then normalized by using the maximum range of values for the subscale and multiplied by 100. The EORTC QLQ-C30 tool has evidence to support its validity and responsiveness in patients with PNH; however, MID values have not been established in the PNH population. In patients with cancer, an increase of at least 10 points in the EORTC QLQ-C30 score is considered moderately large and represents a clinically important improvement.[34]

[j]The change from baseline in EORTC QLQ-C30 Global Health Index score and the safety outcomes were not adjusted for multiplicity in the APPLY-PNH trial and should be considered as supportive evidence.

[k]Rated down 2 levels due to very serious imprecision. There are a very small number of events captured.

[l]Rated down 1 level due to serious indirectness. The follow-up duration was insufficient to evaluate safety of the study drug.

Source: APPLY-PNH Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

The APPLY-PNH treatment extension period was a 24-week open-label extension of the 24-week APPLY-PNH study. The treatment extension period aimed to evaluate long-term efficacy and safety of iptacopan in adult patients with PNH who had residual anemia despite treatment with a C5 inhibitor. All study end points were defined as primary, with no secondary or exploratory end points. Primary efficacy variables included hematological response parameters, transfusion avoidance, hemoglobin, clinical BTH, LDH, ARC, FACIT-Fatigue scores, MAVEs, patient-reported outcomes, C3 fragment deposition on RBCs, PNH clone size, and other PNH-related end points. In the final analysis, the absence of transfusion was not an integral component of the hematological response end points, in contrast to the week 24 primary efficacy analysis, where absence of transfusion between day 14 and day 168 was an end point component. Primary safety end points included AEs, SAEs, safety laboratory parameters, and vital signs. A total of 97 patients were enrolled in the treatment extension period. After completion of the treatment extension period, patients were able to enrol in an ongoing roll-over extension program, which aims to further evaluate the long-term safety, tolerability, and efficacy of iptacopan.

Efficacy Results

Of the original cohort of 97 patients who completed the APPLY-PNH randomized treatment period, all 61 patients allocated to iptacopan continued to the iptacopan arm of the extension period, and 34 of 35 patients in the C5 inhibitor group switched to iptacopan at the beginning of the extension period conducted between September 26, 2022, and March 6, 2023. Overall, efficacy results were consistent with those observed in the pivotal trial and sustained to the end of the treatment extension period.

After 336 days of iptacopan treatment, 86.4% of patients who were randomized to iptacopan had at least a 20 g/L increase in hemoglobin from baseline and 67.8% had sustained hemoglobin levels of at least 120 g/L, both irrespective of RBC transfusions. For patients who switched from a C5 inhibitor to iptacopan, 72.4% had at least a 20 g/L increase in hemoglobin from baseline after 168 days of iptacopan treatment. Additionally, 58.6% had sustained hemoglobin levels of at least 120 g/L at day 168 of iptacopan treatment. Eight patients (12.9%) in the iptacopan randomized group and 3 patients (8.8%) who switched to iptacopan from a C5 inhibitor received at least 1 transfusion while on iptacopan. Among patients who received transfusions, the mean number of transfusions per patient was 1.8 (SD = 1.16) in the iptacopan group and 5.3 (SD = 7.51) in the former C5 inhibitor group. The mean number of RBC units transfused to these patients was 2.9 (SD = 2.59) in the iptacopan group and 6.7 (SD = 8.96) in the former C5 inhibitor group.

During the treatment extension period, 4 patients in the iptacopan group and 1 patient who switched to iptacopan from a C5 inhibitor experienced 1 or more clinical BTH events. Across the entire 48-week study, there were 8 BTH events in 7 patients during treatment with iptacopan, with an adjusted annualized rate of BTH of 0.11 (95% CI, 0.05 to 0.23).

At day 336, the geometric adjusted mean ratio to baseline in LDH was 1.11 (95% CI, 1.02 to 1.22) for the iptacopan group and 0.99 (95% CI, 0.88 to 1.11) for the former C5 inhibitor group, with an adjusted mean ratio to baseline of 1.12 (95% CI, 0.97 to 1.30) between groups. The adjusted mean change from baseline

in ARC at day 336 was −106.26 × 10^9/L (95% CI, −117.57 to −94.96) for the iptacopan group and −107.95 × 10^9/L (95% CI, −123.18 to −92.73) for the former C5 inhibitor group, with an adjusted mean difference of 1.69 × 10^9/L (95% CI, −16.86 to 20.23) between groups. After 7 days of iptacopan treatment, normalization of ARCs (13.5 × 10^9/L to 123 × 10^9/L) occurred in 80.6% of patients in the iptacopan group and was sustained in 80.6% of patients in this group until day 336. In the former C5 inhibitor group, normalization occurred in 61.8% of patients after 7 days of treatment, 85.3% after 28 days, and was consistently seen in 70.6% of participants until day 336.

Both groups demonstrated improvements in fatigue and HRQoL, as measured by FACIT-Fatigue and EORTC QLQ-C30 Global Health Status scores. At day 336, the adjusted mean change from baseline in FACIT-Fatigue score was 9.80 points (95% CI, 8.04 to 11.56) for the iptacopan group and 10.96 points (95% CI, 8.58 to 13.34) for the former C5 inhibitor group, with an adjusted mean difference of −1.17 (95% CI, −4.01 to 1.68) between groups. The mean EORTC QLQ-C30 score was 76.4 (SD = 15.11) for the iptacopan group and 74.4 (SD = 16.98) for the former C5 inhibitor group at day 336, with mean increases from baseline of 16.3 (SD = 17.99) and 15.2 (SD = 22.61), respectively.

Harms Results

Across the entire 48-week study, the most common TEAEs among all patients who received iptacopan were COVID-19 (27.1%), headache (14.6%), diarrhea (12.5%), nasopharyngitis (12.5%), and nausea (11.5%). Most study patients had a TEAE during the 48-week study, with comparable proportions between those randomized to iptacopan (93.5%) and all patients who received iptacopan (88.5%). The majority of TEAEs were mild or moderate, with 9.4% of all iptacopan recipients experiencing severe AEs. Overall, 13.5% of all patients who received iptacopan experienced SAEs: 9 patients who were randomized to iptacopan and 4 patients who switched to iptacopan from a C5 inhibitor in the treatment extension period. No deaths were reported in the study and no patients discontinued the study or iptacopan treatment due to AEs.

Two patients experienced MAVEs during the treatment extension period. One patient was in the iptacopan randomized group and the second had switched to iptacopan from a C5 inhibitor. The events were not considered related to study treatment and no action was taken regarding iptacopan treatment.

Infections caused by encapsulated bacteria were identified as an important harm for this review. Across the entire 48-week study, 3 patients (3.1%) reported an infection with encapsulated bacteria. During the treatment extension period, 1 patient experienced a nonserious TEAE of bilateral otitis media.

Critical Appraisal

Internal Validity

The APPLY-PNH extension period was designed as an open-label extension to assess long-term efficacy and safety of iptacopan in the treatment of adult patients with PNH. This open-label design could bias the magnitude of treatment effect for subjective efficacy outcomes and reporting of safety parameters due to unblinded exposure to the study medication during the treatment period. Statistical hypothesis testing was not part of the design and there was no active comparator or placebo arm.

External Validity

The extension study consisted of patients who took part in pivotal studies, and it is therefore reasonable to expect that the same strengths and limitations related to generalizability apply to the extension period. Given that patients needed to complete the parent study before enrolling, the extension period population is inherently enriched and introduces some selection bias for responders. Additionally, a lack of Canadian study sites limits the ability to generalize these findings to patients living in Canada with PNH.

Indirect Comparisons

Description of Studies

The sponsor submitted an indirect treatment comparison (ITC) that evaluated the efficacy and safety of iptacopan versus pegcetacoplan for the treatment of adult patients with PNH who have residual anemia despite treatment with a C5 inhibitor. The ITC consisted of an unanchored MAIC based on individual patient data (IPD) from the iptacopan group (N = 54) of the APPLY-PNH study and aggregate data for the pegcetacoplan group (N = 41) of the PEGASUS study. The change from baseline in hemoglobin (including and excluding posttransfusion hemoglobin data), transfusion avoidance, change from baseline in LDH, change from baseline in FACIT-Fatigue score, and SAEs were selected as outcomes for the MAIC.

In the first step of the unanchored MAIC, patients from the iptacopan group who did not meet the inclusion criteria of the PEGASUS study were excluded, and then the iptacopan IPD were weighted to balance the 2 treatment groups on baseline hemoglobin levels, sex, and the proportion of patients who were transfusion-free within 12 months before baseline. For continuous outcomes, the iptacopan effect estimates were derived by fitting a mixed model for repeated measures to the weighted IPD, with the comparative effects versus pegcetacoplan derived as the difference between the adjusted mean change from baseline for iptacopan and the published adjusted mean of pegcetacoplan. Binary outcomes estimates were derived with an intercept-only logistic regression model fitted to the weighted IPD for iptacopan. An estimate of the log odds ratio (OR) for iptacopan versus pegcetacoplan was derived as the difference between the weighted log odds for iptacopan and the estimated log odds for pegcetacoplan based on published transfusion events and SAEs from the PEGASUS study.

Efficacy Results

The results of the base case unanchored MAIC were based on 41 patients who received pegcetacoplan, and an effective sample size (ESS) of 16 patients from the iptacopan group. The estimated mean difference in the change from baseline in hemoglobin levels was 13.1 g/L (95% CI, 5.2 to 21.0) censored for transfusion, and 10.5 g/L (95% CI, 4.3 to 16.7) uncensored at transfusion, for iptacopan versus pegcetacoplan.

The MAIC estimated that 85.4% of patients in the pegcetacoplan group and 98.2% of patients in the iptacopan group avoided transfusion, with an OR of 9.17 (95% CI, 1.59 to 52.89), favouring iptacopan.

The mean difference in the change from baseline in LDH levels was 36.68 U/L (95% CI, −62.54 to 135.89) for iptacopan versus pegcetacoplan. For the change from baseline in FACIT-Fatigue score, the unanchored MAIC estimated a mean difference of −2.32 points (95% CI, −6.34 to 1.70) for iptacopan versus pegcetacoplan.

Harms Results

The MAIC estimated that 17.1% and 4.8% of patients in the pegcetacoplan and iptacopan groups, respectively, would experience an SAE, with an OR of 0.24 (95% CI, 0.06 to 0.98), favouring iptacopan.

Critical Appraisal

The unanchored MAIC submitted by the sponsor had serious methodological issues that threaten the validity of the findings. Unanchored MAICs have a high risk of bias, as the underlying assumptions required for valid effect estimates are very difficult to meet. These methods require that all prognostic factors and effect modifiers (measured and unmeasured) be accounted for in the model, which may not be possible. Failure of this assumption leads to an unknown amount of bias in the effect estimates. The sponsor argued that other ITC methods with a lower risk of bias were not feasible due to sparse data available and the heterogeneity in the patient and study characteristics between the APPLY-PNH and PEGASUS trials. The CDA-AMC reviewer agreed that there was significant heterogeneity between the studies and concluded that the MAIC methods used by the sponsor were not able to adequately control for these differences. In the unanchored MAIC, the 2 patient populations were balanced on 3 variables only, and imbalances remained for several clinically important factors (e.g., proportion of patients with at least 4 transfusions in past 12 months, race, history of aplastic anemia, FACIT-Fatigue score, duration of C5 inhibitor therapy, time since diagnosis, platelet count, and body mass index). Other important prognostic factors identified by the clinical experts we consulted were not addressed in the MAIC (i.e., C5 inhibitor dose, LDH levels > 1.5 times ULN, and PNH-related kidney disease). The low ESS of the iptacopan group (16 patients or 30% of the unweighted population) suggests the patients were too dissimilar to warrant valid comparison. In addition, the skewed distribution of weights also suggests the populations were substantially different, and the occurrence of extreme weights may have led to unstable effect estimates. According to the clinical experts we consulted, the population enrolled in the PEGASUS trial was clinically different, with more severe PNH than those in the APPLY-PNH study. Thus, given the underlying differences between the 2 trials and the imbalances in important prognostic factors that remained after matching and weighting, the treatment effect estimates were considered too unreliable to draw any firm conclusions.

Economic Evidence

This is based on second-line treatment, as per the sponsor’s reimbursement request and pre-Notice of Compliance (NOC) proposed indication. Given the change in NOC indication, the budget impact may differ if considered for the full Health Canada indication, and the cost-effectiveness of iptacopan in first-line, third-line, or later-line treatment remains unknown.

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Semi-Markov model
Target population	Adult patients with PNH who have an inadequate response to, or are intolerant of, a C5i (i.e., C5i-experienced patients).
Treatment	Iptacopan
Dose regimen	200 mg twice daily
Submitted price	$719.94 per 200 mg capsule
Submitted treatment cost	$524,116 per patient per year
Comparators	• Eculizumab • Ravulizumab • Pegcetacoplan
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (59 years)
Key data sources	The APPLY-PNH trial informed the efficacy and safety of iptacopan, eculizumab, and ravulizumab. The PEGASUS trial informed the efficacy and safety of pegcetacoplan.
Key limitations	• Pegcetacoplan is the key comparator for patients with PNH and EVH. The comparative clinical efficacy of iptacopan vs. pegcetacoplan is uncertain, as it is based on an MAIC. The MAIC did not allow for firm conclusions on the relative effectiveness or safety of iptacopan vs. pegcetacoplan due to serious methodological limitations that undermine the validity of the findings. • The method used to derive the health state transition probabilities for iptacopan and C5i (MAIC-weighted or unweighted) is potentially at risk of bias and may not be representative of or generalizable to the target population. It is unclear whether all relevant covariates were adjusted for or if the regression model may have overfit the data. As these probabilities directly drive state membership and utilities in the model, this has substantial implications for the validity of the analysis. Also, the use of MAIC-weighted probabilities would distort the comparison between iptacopan and the C5is. • Poor economic modelling practices were employed leading to use of different input values for treatment arms with identical input parameters and making thorough auditing of the sponsor's model impractical. • All-cause discontinuation rate for patients receiving iptacopan was naively compared to that of pegcetacoplan and is highly uncertain. In the submitted model, the probability of discontinuation is a key driver of the results and more than 4 times higher for patients treated with pegcetacoplan compared to those treated with iptacopan. Clinicians expect the discontinuation rates for iptacopan and pegcetacoplan to be relatively similar based on how both drugs perform in clinical practice, the increasing clinical experience with this drug class, and with managing BTH while on C3is. • The submitted model does not align with the indicated population or capture all aspects of the condition and its management (not just inadequate response or prior exposure to C5i). The model does not allow examination of the cost-effectiveness of iptacopan beyond second-line therapy, the impact of subsequent therapies that include switching between C3i drugs or to danicopan plus a C5i,

Component	Description
	and a potential different risk of thrombosis while on treatment with C5is and C3is. • Rates of AEs for iptacopan and C5is were naively compared to pegcetacoplan in the model and although with a small impact, continue to result in different disutilities between the comparators.
CDA-AMC reanalysis results	• CDA-AMC conducted reanalyses to address some of the key limitations, which included assuming equivalent efficacy (i.e., equal health states transition probabilities) and equivalent probability of discontinuation between iptacopan and pegcetacoplan. The CDA-AMC reanalysis attempted to preserve the comparison in efficacy between iptacopan vs. C5i monotherapy by maintaining the data derived from the APPLY-PNH trial. CDA-AMC was unable to explore the cost-effectiveness of iptacopan used beyond second-line therapy, the impact of subsequent therapies besides C5i monotherapy, a potential different risk of thrombosis between C3i and C5i therapies, and confidential prices for the comparators. • Given the available clinical evidence, there is no robust clinical evidence to justify a price premium for iptacopan compared to pegcetacoplan. • In the CDA-AMC base case, the ICER of iptacopan compared to ravulizumab was $62,272 per QALY gained (incremental QALYs gain = 1.53; incremental cost = $95,080) for patients with an inadequate response or intolerance to a C5i. A price reduction of 0.3% would be needed for iptacopan to be cost-effective compared to ravulizumab at a WTP threshold of $50,000 per QALY. Consistent with the sponsor's results, the majority (97%) of the incremental QALY gain of iptacopan accrued beyond the 24-week duration of the trial based on extrapolations and was driven by transfusion avoidance. Although similar to the sponsor's base case, results shifted to iptacopan offering a slightly smaller advantage when compared to both C5is, and subsequent therapy and health care resource use costs are no longer discrepant between iptacopan and pegcetacoplan.

BTH = breakthrough hemolysis; C3i = C3 inhibitor; C5i = C5 inhibitor; CDA-AMC = Canada's Drug Agency; EVH = extravascular hemolysis; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LY = life-year; MAIC = matching-adjusted indirect comparison; PNH = paroxysmal nocturnal hemoglobinuria; QALY = quality-adjusted life-year; WTP = willingness-to-pay.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: the proportion of PNH patients with inadequate response or intolerance to a C5 inhibitor may be overestimated, and market shares in the reference scenario, uptake of iptacopan, coverage rates, and negotiated prices of comparators are uncertain.

CDA-AMC conducted reanalyses of the budget impact analysis (BIA) by decreasing the proportion of patients with an inadequate response or intolerance to C5 inhibitor treatment, changing the market shares in the reference scenario, and the market uptake and source of uptake of iptacopan in the new drug scenario.

Based on the CDA-AMC base case, the estimated budget impact associated with the reimbursement of iptacopan for the treatment of adult patients with PNH who have an inadequate response or intolerance to a C5 inhibitor is expected to decrease the magnitude of the 3-year budget savings to $247,055.

CDA-AMC conducted a scenario analysis to address uncertainty in the coverage rates (assuming 100% coverage), which indicated that the budgetary impact may still be less than 50% of what the sponsor originally estimated.

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: January 22, 2025

Regrets: Two expert committee members did not attend.

Conflicts of interest: One expert committee member did not participate due to considerations of conflict of interest.

Canada's Drug Agency
L'Agence des médicaments du Canada
Drugs. Health Technologies and Systems. Médicaments, technologies de la santé et systèmes.

ISSN: 2563-6596

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.