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CADTH Reimbursement Recommendation

Pegcetacoplan (Empaveli)

Indication: For the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have an inadequate response to, or are intolerant of, a C5 inhibitor

Sponsor: Sobi Canada Inc.

Final recommendation: Reimburse with conditions

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

What Is the CADTH Reimbursement Recommendation for Empaveli?

CADTH recommends that Empaveli should be reimbursed by public drug plans for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have an inadequate response to, or are intolerant of, a C5 inhibitor if certain conditions are met.

Which Patients Are Eligible for Coverage?

Empaveli should only be covered to treat patients with PNH who have met existing reimbursement criteria used by public drug plans for initiating C5 inhibitor treatment (e.g., eculizumab or ravulizumab). While receiving C5 inhibitor treatment, patients should have had persistently low hemoglobin levels, likely due to red blood cell (RBC) destruction occurring outside of blood vessels (known as extravascular hemolysis [EVH]), or intolerable side effects.

What Are the Conditions for Reimbursement?

Empaveli should only be reimbursed if prescribed by or in consultation with a hematologist with experience managing PNH. It should not be used with other C5 inhibitors beyond the first 4 weeks of treatment. Also, the cost of Empaveli should be reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Empaveli improved hemoglobin levels in patients with PNH who were taking eculizumab and had a low hemoglobin level and signs of EVH.
- Empaveli treatment could meet some needs important to patients, including increasing hemoglobin levels and reducing the need for blood transfusions.
- Based on CADTH's assessment of the health economic evidence, Empaveli does not represent good value to the health care system at the public list price. A price reduction is therefore required. The modelled population reflected only adult patients with PNH with an inadequate response to C5 inhibitor treatment.
- Based on public list prices, Empaveli is estimated to result in cost savings to public drug plans of approximately $863,569 over the next 3 years for the treatment of adult patients with PNH who have inadequate response to, or are intolerant of, a C5 inhibitor. However, Empaveli may increase public drug plan budgets if eculizumab up-dosing is not publicly funded.

Summary

Additional Information

What Is Paroxysmal Nocturnal Hemoglobinuria?

PNH is an extremely rare disease in which the bone marrow produces abnormal RBCs that are prematurely destroyed by the immune system, leading to a wide range of symptoms and complications, including life-threatening blood clots. It is estimated that there are approximately 0.13 new cases per year per 100,000 persons based on a study in the UK.

Unmet Needs in Paroxysmal Nocturnal Hemoglobinuria

Some patients treated with eculizumab or ravulizumab do not have a good response to treatment or their treatment causes EVH.

How Much Does Empaveli Cost?

Treatment with Empaveli is expected to cost between $516,880 to $566,932 in the first year (depending on the C5 inhibitor prescribed during the first 4 weeks) and $516,880 thereafter per patient.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that pegcetacoplan be reimbursed for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have an inadequate response to, or are intolerant of, a C5 inhibitor only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, open-label, randomized controlled trial (RCT) demonstrated that treatment with pegcetacoplan resulted in added clinical benefit for patients with PNH with clinically significant anemia and signs of extravascular hemolysis (EVH) despite eculizumab treatment. The PEGASUS trial (N = 80) demonstrated that treatment with pegcetacoplan was associated with a statistically significant and clinically meaningful improvement in change in hemoglobin level from baseline at week 16 compared with eculizumab (mean difference = 3.84 g/dL; 95% confidence interval [CI], 2.33 g/dL to 5.34 g/dL; P < 0.001). Transfusion avoidance, an important outcome according to patients and the clinical experts, was more commonly observed in the pegcetacoplan arm (85.4% versus 15.4% of patients; adjusted risk difference = 62.5%; 95% CI, 48.3% to 76.8%). Patients expressed a need for treatments that can effectively control intravascular hemolysis (IVH), reduce EVH, improve anemia, reduce or eliminate transfusion requirements, and improve fatigue and quality of life. CDEC concluded that pegcetacoplan treatment met some of the needs identified by patients in terms of improving anemia and reducing transfusion needs.

Without a head-to-head trial between pegcetacoplan and ravulizumab, the pharmacoeconomic model assumed equivalent clinical efficacy between eculizumab and ravulizumab. Using the sponsor-submitted price for pegcetacoplan and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for pegcetacoplan was $62,144 per quality-adjusted life-year (QALY) gained compared with ravulizumab. At this ICER, pegcetacoplan is not cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per QALY for adult patients with PNH who have an inadequate response to C5 inhibitors. A price reduction is required for pegcetacoplan to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Patients must have a confirmed diagnosis of PNH with all of the following: 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 either have	Evidence from the PEGASUS trial demonstrated that pegcetacoplan treatment resulted in a clinically meaningful improvement in hemoglobin levels in a study population representative of patients with PNH with a hemoglobin level < 10.5 g/dL and signs of extravascular hemolysis despite eculizumab treatment. Patients with intolerable adverse events from a C5 inhibitor were not specifically studied in	Based on clinical expert opinion, a minimum treatment duration of C5 inhibitor of 6 months at a stable dose is adequate for assessing eligibility for pegcetacoplan treatment.

Reimbursement condition	Reason	Implementation guidance
persistent anemia with hemoglobin levels < 10.5 g/dL despite an adequate trial of C5 inhibitor treatment and causes other than extravascular hemolysis have been excluded, or have intolerable adverse events from C5 inhibitor treatment.	the PEGASUS trial. However, CDEC considered it reasonable to reimburse pegcetacoplan treatment in these very rare occurrences.	
Renewal		
2. Pegcetacoplan should be renewed in a similar manner to other complement inhibitors currently reimbursed for the treatment of patients with PNH.	There is no evidence that pegcetacoplan should be held to a different standard than other complement inhibitor treatments currently reimbursed 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 complement inhibitors.
Discontinuation		
3. Pegcetacoplan should be discontinued in a similar manner as other complement inhibitors currently reimbursed for the treatment of patients with PNH.	There is no evidence that pegcetacoplan should be held to a different standard than other complement inhibitor treatments currently reimbursed when considering discontinuation.	—
Prescribing		
4. Pegcetacoplan should be prescribed by or in consultation with a hematologist with experience managing PNH.	This is to ensure that pegcetacoplan is prescribed only for appropriate patients.	—
5. Pegcetacoplan should not be used in combination with other complement inhibitors except in the first 4 weeks of treatment.	There is no evidence supporting concomitant use of complement inhibitors except in the first 4 weeks of pegcetacoplan treatment.	—
Pricing		
6. A reduction in price.	Based on the sponsor-submitted price for pegcetacoplan and publicly listed prices for C5 inhibitors, the ICER for pegcetacoplan is $62,144 per QALY gained compared with ravulizumab. A price reduction of at least 0.9% would be required for pegcetacoplan to achieve an ICER of $50,000 per QALY gained compared with C5 inhibitors. Given limitations in the model structure that could not be addressed in CADTH reanalyses, the estimated QALY gains are highly uncertain. Furthermore, the analysis is sensitive to drug acquisition costs of C5 inhibitors, and the use of confidential negotiated pricing in	—

Reimbursement condition	Reason	Implementation guidance
	the analysis is expected to produce different conclusions. Together, these suggest a higher price reduction may be required.	

CDEC = CADTH Canadian Drug Expert Committee; ICER = incremental cost-effectiveness ratio; PNH = paroxysmal nocturnal hemoglobinuria; QALY = quality-adjusted life-year.

Discussion Points

- CDEC affirmed that the place in therapy for pegcetacoplan is as a second-line treatment for patients who have received treatment with a C5 inhibitor for PNH and have either persistent anemia, likely due to EVH, or intolerance to C5 inhibitors due to adverse events. The PEGASUS trial population was representative of the former group of patients; therefore, the trial evidence does not support first-line use of pegcetacoplan for PNH. In addition, the Health Canada–approved indication specifies use as a second-line treatment for PNH.
- Although noninferiority was not demonstrated in the PEGASUS trial for lactate dehydrogenase (LDH) level (a marker of IVH), CDEC, in consultation with the clinical experts, considered there to be sufficient evidence of acceptable IVH control with pegcetacoplan.
- Results from the PEGASUS trial suggested treatment with pegcetacoplan could improve fatigue and health-related quality of life. Due to a lack of superiority testing, no definitive conclusions could be drawn regarding the efficacy of pegcetacoplan versus eculizumab for these outcomes. However, the clinical experts expected that the mean change in hemoglobin levels observed with pegcetacoplan treatment would translate into noticeable improvements in fatigue, ability to perform activities of daily living, and overall health-related quality of life.
- Results from the PEGASUS trial also suggested treatment with pegcetacoplan could reduce EVH. However, due to a lack of superiority testing, no definitive conclusions could be drawn regarding the efficacy of pegcetacoplan versus eculizumab for markers of EVH other than the noninferiority of pegcetacoplan in terms of absolute reticulocyte count (ARC).
- Although the results of the extension of the PEGASUS trial suggested that the benefits of pegcetacoplan are sustained through 48 weeks of treatment, the duration of follow-up may not fully capture the incidence of breakthrough IVH because these events can occur due to specific situations such as infection or surgery. As well, long-term outcomes, such as thrombotic events and survival, could not be adequately evaluated in the 48-week study period.
- One indirect treatment comparison, an anchored matching-adjusted indirect comparison (MAIC) submitted by the sponsor, evaluated the comparative efficacy of pegcetacoplan versus ravulizumab for the treatment of adult patients with PNH previously treated with eculizumab. Although the results favoured pegcetacoplan for transfusion avoidance, hemoglobin level stabilization, and fatigue (with no difference in change in LDH levels), there is uncertainty in the estimated treatment effects due to limitations of the MAIC, including the lack of matching of some effect modifiers and heterogeneity in the study design and population. The committee acknowledged that, given the uncertainties in

the MAIC, the assumption of clinical equivalence between ravulizumab and eculizumab within their submitted economic model may be appropriate.

- The economic analysis was highly sensitive to the drug acquisition cost of C5 inhibitors, which were based upon the publicly available list prices. CDEC discussed that the required price reduction for pegcetacoplan to be cost-effective at a WTP threshold of $50,000 per QALY gained may be higher under the confidential negotiated price for C5 inhibitors.
- A biosimilar for eculizumab is currently under review by Health Canada. CDEC discussed that, at the time of this review, the comparative efficacy and cost-effectiveness of pegcetacoplan relative to this biosimilar is unknown. CDEC considered that there is potential for pegcetacoplan to not to be cost-effective versus a C5 inhibitor biosimilar should such a product enter the market.
- All QALYs gained in the economic analysis were a result of improved hemoglobin levels and transfusion avoidance, based on results from the PEGASUS trial. Given the duration and limitations of that trial, there is uncertainty if this benefit will be maintained despite the model's assumption of lifelong relative effectiveness. There is further uncertainty associated with the validity in the hemoglobin level cut-off that dichotomized the modelled health states and the utility values associated with these states. CDEC noted that it remains unclear if the estimated QALY gains would be realized. In a CADTH reanalysis, when the utility value was identical across both hemoglobin health states, the ICER associated with pegcetacoplan increased from $103,441 to $313,336 per QALY gained.
- CDEC discussed that pegcetacoplan is delivered through a specialized pump that requires specialized training. Within the PEGASUS trial, there were 14 treatment interruptions due to pump malfunction or user error. There may be substantial unanticipated costs depending on who is responsible for coverage of replacement doses arising from treatment interruptions.
- CDEC noted that the savings observed within the budget impact results were sensitive to assumptions on dose escalation and whether drug costs associated with dose escalation are covered by public drug plans. In the CADTH reanalyses, pegcetacoplan provided cost savings relative to C5 inhibitors based on publicly available list prices, the assumption that observed trial dose escalation reflects real-world practice, and that dose escalation would be publicly reimbursed. CDEC noted that pegcetacoplan may increase budget impact if these assumptions do not hold.

Background

PNH is an extremely rare, chronic disease characterized by IVH and heterogenous signs and symptoms, such as hemoglobinuria, anemia, abdominal pain, dyspnea, and fatigue, and could lead to complications including thrombosis, chronic kidney disease, and pulmonary hypertension. PNH is a consequence of an acquired genetic mutation leading to clonal expansion of hematopoietic stem cells that produce abnormal blood cells that are susceptible to complement-mediated IVH. The annual incidence of clinical PNH was estimated to be approximately 0.13 per 100,000 persons based on a study in the UK.

Approximately 20% to 30% of patients with PNH have ongoing clinically significant anemia despite first-line standard of care (SOC) with terminal complement component C5 inhibitor treatments (e.g., eculizumab, ravulizumab). Causes of inadequate treatment response include breakthrough IVH, C3-mediated EVH, development of human-anti-human or eculizumab-neutralizing antibodies, and C5 genetic polymorphism. The SOC for patients with C3-mediated EVH is to provide best supportive care (e.g., red blood cell [RBC] transfusion, steroids, splenectomy, danazol, epoetin alfa) while continuing C5 inhibitor treatment, or referral to clinical trials; however, many best supportive care therapies are associated with toxicities.

Pegcetacoplan has been approved by Health Canada for the treatment of adult patients with PNH who have an inadequate response to, or are intolerant of, a C5 inhibitor. Pegcetacoplan is a proximal complement C3 inhibitor. It is available as a 54 mg/mL solution for subcutaneous infusion use; the dosage recommended in the product monograph is 1,080 mg subcutaneous infusion twice weekly via a syringe system infusion pump. Dosage increase to 1,080 mg every third day may be considered if the LDH level is greater than 2 times the upper limit of normal on twice weekly dosing.

Sources of Information Used by the Committee

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

- a review of 1 RCT in adults with PNH, 1 long-term extension of the RCT, and 1 indirect treatment comparison
- patients' perspectives gathered by 2 patient groups: the Canadian Association of PNH Patients and the Aplastic Anemia & Myelodysplasia Association of Canada
- input from public drug plans that participate in the CADTH 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.

Stakeholder Perspectives

Patient Input

The Canadian Association of PNH Patients and the Aplastic Anemia & Myelodysplasia Association of Canada submitted 1 joint input for this review. Information was gathered from the scientific literature and one-on-one interviews with 6 individuals diagnosed with PNH living in Canada. The patient group expressed the following negative impacts of PNH: persistent anemia (manifested as fatigue or extreme fatigue), hemolysis leading to thrombosis, employment absenteeism for patients and caregivers, dependence on frequent blood transfusions, and reduced quality of life. According to the input, patients with PNH, particularly those experiencing EVH, need alternative treatment options because of the inability of available therapies with eculizumab or ravulizumab to thoroughly control IVH and prevent EVH. They also expressed

the need for therapies to improve anemia, reduce or eliminate transfusion requirements, and improve fatigue and quality of life. Among 3 patients who had used pegcetacoplan, all noted an immediate normalization of hematological parameters, easier administration (self-administered subcutaneous injection twice weekly at home) compared with eculizumab or ravulizumab (visits for IV transfusions), reduced blood transfusions, and improved physical functioning and quality of life. Some patients stated the importance of proper injection training.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The clinical experts noted there is a need for treatments that are effective in patients who have insufficient control of IVH despite treatment with eculizumab, address the issue of C3-mediated EVH, and can be used in patients with intolerance to C5 inhibitors or poor venous access. The clinical experts noted that pegcetacoplan is a C3 inhibitor with a mechanism of action in addition to C5 inhibitors because it inhibits a more upstream effector in the complement activation pathway. They anticipated that the drug would serve as a second-line treatment for PNH.

The clinical experts noted that suitable candidates for pegcetacoplan treatment include patients with PNH who have persistent anemia (with or without history of ongoing blood transfusion needs) and evidence of EVH despite an adequate trial of C5 inhibitor treatment, patients with intolerance to a C5 inhibitor, or patients with a rare C5 genetic polymorphism (which prevents eculizumab from binding to its target molecule; mainly present in patients of Japanese descent). The clinical experts noted that pegcetacoplan could potentially be considered in patients who are geographically isolated or have poor venous access. Patients with a PNH clone size (i.e., proportion of blood cells deficient in complement system regulatory protein) of less than 10% should not receive pegcetacoplan.

The clinical experts noted that a clinically meaningful treatment response would include improvement in hemolytic parameters (LDH, bilirubin) and hemoglobin level, reduced transfusion need, and improved quality of life. In general, follow-up assessments are conducted every 3 months and treatment response is determined per clinical judgment by the treating physician based on a global assessment of all patient parameters, chronology of symptoms, and laboratory results. The clinical experts noted that treatment discontinuation is not considered unless any of the following occurs: treatment failure (persistent anemia and ongoing transfusion needs) necessitating a switch to a more effective treatment, intolerance to pegcetacoplan, or resolution of disease following bone marrow transplant. The clinical experts noted that patients with PNH should be managed by hematologists in consultation with PNH specialists.

Clinician Group Input

One clinician group, the Canadian PNH Network, submitted input for this review based on contributions from 11 clinicians. The group noted that the current SOC for PNH is C5 inhibitors (i.e., eculizumab and ravulizumab), which act via terminal complement blockade. They noted that although C5 inhibitors are not curative treatment, these treatments have been shown to be effective in controlling IVH, leading to significant improvement in fatigue, quality of life, transfusion dependence, thrombosis, and overall survival.

The only curative treatment for PNH is allogeneic hematopoietic stem cell transplant, which is available for patients with predominant or progressive bone marrow failure or for eligible patients with evidence of clonal evolution. However, the group highlighted 3 unmet needs: some patients do not have access to SOC due to highly restrictive reimbursement criteria, there is high treatment burden with eculizumab due to administration every 2 weeks requiring venous access and nurse visits, and despite treatment, approximately one-third of patients remain anemic due to EVH and possibly transfusion-dependent. The group expressed that drugs that exploit proximal complement blockade, such as C3 inhibitors, address the EVH risk, significantly increase hemoglobin, and improve quality of life. Regarding place in therapy, the group stated pegcetacoplan is the first C3 inhibitor that protects against EVH, and it would fit into the current treatment landscape as an alternative (i.e., switch) option in patients with no or inadequate response or who are intolerant to eculizumab or ravulizumab. These would include patients with persistent anemia (hemoglobin < 10.5 g/dL or could be higher if symptomatic) despite stable doses of eculizumab or ravulizumab and have other causes of ongoing anemia (e.g., breakthrough hemolysis or bone marrow failure) ruled out. The group indicated that a clinically meaningful response to treatment would be sustained control of LDH level (i.e., less than 1.5 times the upper limit of normal), increase in hemoglobin (or possibly hemoglobin stabilization without further needs of transfusion), and improvement in anemia-related symptoms. Treatment discontinuation should be considered in patients who have adverse events that preclude ongoing therapy (e.g., recurrent breakthrough hemolysis, issues with effective self-administration, intolerable pain from injection). The group indicated that treatment and monitoring of patients should ideally be done by clinicians who specialize in the area, although patients can self-administer pegcetacoplan at home or anywhere they prefer.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially affect the implementation of a CADTH recommendation for pegcetacoplan:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

The clinical experts consulted by CADTH 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	
Eculizumab was used as the comparator in the pivotal trial (PEGASUS) and is an appropriate comparator. Although eculizumab is covered by most provincial and federal drug programs, the reimbursement information is not publicly available for most. Another relevant comparator is ravulizumab, which was not used in the PEGASUS trial. At the time of trial initiation, ravulizumab was not available. Likewise, it is still in negotiations and is not yet listed on any jurisdiction's formulary.	This is a comment from the drug programs to inform CDEC deliberations.
Consideration for initiation of therapy	
As pegcetacoplan is indicated for second-line treatment of PNH, it is presumed that patients have already met any diagnostic criteria that would have made them eligible for a C5 inhibitor such as the comparator, eculizumab. 1. **Question for clinical experts:** Would there be any scenario in which a patient gained access to treatment with a C5 inhibitor without having met drug program criteria? 2. **Question for CDEC:** In the hypothetical scenario that a patient started C5 inhibitor treatment without going through a drug program's criteria process, and the patient has intolerance or inadequate response, would the patient be eligible for consideration of treatment with pegcetacoplan?	1. The clinical experts noted that some patients who participated in clinical trials of C5 inhibitors continue to access a C5 inhibitor treatment via a compassionate access program after completion of the clinical trials. The clinical experts noted the provincial funding criteria differ from the eligibility criteria of the clinical trials; therefore, it is possible that these patients may not have met the provincial funding criteria for C5 inhibitors. 2. CDEC noted that there is insufficient information to provide guidance regarding patients who may have initiated C5 inhibitor treatment without going through a public drug plan's reimbursement process. Reimbursement criteria are not published for all jurisdictions funding eculizumab for PNH, and clinical parameters before eculizumab treatment are unknown for these patients as well as patients in the PEGASUS trial.
The inclusion criteria for PEGASUS required the patient to have been on a stable dose of eculizumab for at least 3 months before screening. In addition, patients were required to have a Hb < 10.5 g/dL at time of screening, showing ongoing anemia despite C5 inhibitor treatment. As noted in the submission, there is no universally accepted method to determine response to C5 inhibitor treatment. Assessment can include clinical improvement in signs and symptoms of PNH as well as biochemical evidence of reduced IVH (i.e., LDH < 1.5 × ULN) and improved blood parameters (e.g., Hb). Another inclusion criterion from PEGASUS was that patients (or caregivers) be willing and able to self-administer pegcetacoplan. **Questions for clinical experts:** 1. Is it sufficient to look at a single test result from 1 point in time when assessing C5 inhibitor treatment response? How likely is it that an inadequate lab value is not accurately reflective of the treatment, but influenced by circumstantial factors at the time of testing?	1. The clinical experts noted that a switch from a C5 inhibitor to pegcetacoplan would only be pursued after careful consideration and would not be considered by clinicians unless patients are unsatisfied with treatment or physicians believe that a change is in favour of the patient's health. According to the clinical experts, the decision to switch to pegcetacoplan would not be based on a single episode of anemia but on clinical judgment of all patient parameters, chronology of symptoms, and laboratory results to assess the cause of ongoing anemia. The clinical experts noted that hemolysis can be chronic and low grade or it can be acute in response to infection, stress, pregnancy, or other situations; as such, hemolytic parameters and hemoglobin level, can vary widely. 2. The clinical experts noted that although 3 months is a reasonable time frame for assessing response to C5 inhibitor treatments in patients on a stable dose of C5 inhibitor, most clinicians would not be ready to undertake a switch in therapy to pegcetacoplan at 3 months because additional investigations are generally required to rule out other

Implementation issues	Response
2. Is 3 months a sufficient duration to see an adequate response to C5 inhibitor treatment if a patient only stabilized on the dose 3 months before enrolling in the study? 3. What other specific indicators of inadequate response would be appropriate to document to support a patient's need for second-line treatment with pegcetacoplan? 4. In terms of intolerance to C5 inhibitor treatment, what would constitute an intolerance that would require a switch to pegcetacoplan and what documentation would be reasonable to expect in support of this scenario? **Question for CDEC:** 5. In the event of a positive recommendation with conditions, would it maintain consistency with the PEGASUS inclusion criteria for lab parameters or would consideration be given to requiring evidence of inadequate lab parameters over time (i.e., a visible decline in Hb over the previous 3 month period)?	contributors of treatment failure (e.g., bone marrow failure, polymorphism) and ascertain EVH as the cause of treatment failure. Accounting for the additional turnaround time for these investigational tests, a switch to pegcetacoplan would most likely take place after at least 6 months of C5 inhibitor treatment at a stable dose in clinical practice as per the clinical experts. 3. The clinical experts commented that the indicators included in the inclusion criteria of the PEGASUS trial were adequate to support a patient's need for second-line treatment with pegcetacoplan. 4. The clinical experts noted that intolerance to C5 inhibitors is rare in clinical practice and most likely manifests as infusion-related reactions if it does occur. The clinical experts commented that the need for specific supporting documentation for intolerance is unnecessary since the decision to switch from a C5 inhibitor to pegcetacoplan upon intolerance is made at the discretion of the treating physician and will not be made lightly. The clinical experts added that some latitude should be given to allow patients to switch back to a C5 inhibitor in the event that pegcetacoplan is less tolerated by patients compared with the original C5 inhibitor treatment. 5. CDEC noted that the determination of whether a patient has had an inadequate response to C5 inhibitor treatment (i.e., persistent anemia caused by EVH) should largely be left to the treating clinician's judgment and that evidence of inadequate lab parameters over time would not specifically be necessary.
Question for CDEC: Pegcetacoplan is indicated for second-line therapy, with prior treatment being a C5 inhibitor. If granted a positive recommendation with conditions, would the required duration of C5 inhibitor treatment be consistent with the inclusion criteria from PEGASUS (i.e., a duration greater than or equal to 3 months on a stable dose)?	CDEC noted that it would be appropriate to reimburse pegcetacoplan in patients who have inadequate response after at least 6 months of C5 inhibitor treatment because this aligns with the clinical experts' input and the publicly available C5 inhibitor assessment criteria for eculizumab set by the jurisdictions.
Considerations for continuation or renewal of therapy	
With regards to assessment of response, the primary end point was change in Hb from baseline to the end of the 16-week randomized controlled period. LDH was monitored too and influenced dose modification in 2 patients. Secondary end points included transfusion avoidance, change from baseline to week 16 in the ARC, the LDH, and the FACIT-Fatigue score. Depending on individual circumstances and location, there may be challenges with frequent blood monitoring and other follow-up.	This is a comment from the drug programs to inform CDEC deliberations.
To facilitate implementation of a recommendation to reimburse with conditions, consider whether renewal conditions can be aligned with the criteria for eculizumab and ravulizumab.	This is a comment from the drug programs to inform CDEC deliberations.

Implementation issues	Response
Considerations for discontinuation of therapy	
The submission noted that patients with an inadequate response to pegcetacoplan would most likely return to their original C5 inhibitor treatment, based on a survey in Canadian physicians. **Question for clinical experts:** 1. Would you agree with this statement and, if not, how would you approach this scenario? 2. What would constitute an inadequate response significant enough to discontinue therapy?	The clinical experts noted the decision to continue a patient on pegcetacoplan or to return to their original C5 inhibitor treatment should be determined on a case-by-case basis taking factors such as treatment tolerance, ease of administration, side effects, and efficacy into consideration, with the goal to maintain quality of life. The clinical experts noted that treatment discontinuation should be considered in patients with persistent anemia with ongoing transfusion needs despite an adequate trial of pegcetacoplan.
To facilitate implementation of a recommendation to reimburse with conditions, consider whether discontinuation conditions can be aligned with the criteria for eculizumab and ravulizumab.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for prescribing of therapy	
Patients should be monitored closely for signs and symptoms of hemolysis, including LDH concentration. If the LDH rises to > 2 × ULN, the dosing regimen may be modified to 1,080 mg every third day (vs. standard dose of twice weekly). **Question for clinical experts:** Would you expect the percentage of patients requiring an increased dosing frequency to align with what was seen in the PEGASUS trial? If not, would it be more or less? Two of 41 patients in the trial (4.9%) required a dose increase to every third day.	The clinical experts noted an increased dosing frequency of pegcetacoplan will likely be required in some patients in case of hemolysis; however, it is difficult to predict the proportion of patients requiring a dose increase given the short duration of follow-up and small sample size of patients in the pivotal trial.
Question for CDEC: Pegcetacoplan is administered by self-subcutaneous infusion. In the rare circumstance that a patient and/or caregiver is unwilling or unable to self-administer, would treatment with pegcetacoplan be initiated and, if yes, under what conditions (i.e., where would administration occur and who would cover the cost of this)?	CDEC considered it important for the sponsor to clarify how the costs for administering pegcetacoplan under such a circumstance would be covered because this may affect the budget impact of reimbursing pegcetacoplan.
Question for CDEC: Given the PSP is expected to train patients on how to self-administer the medication, would there be any anticipated issues for training patients outside of metro areas?	The clinical experts did not anticipate issues providing self-administration training for such patients. CDEC did not have any further comment.
Question for clinical experts: Although not analyzed in the PEGASUS trial, what would the likelihood be of a patient being treated with both a C5 inhibitor and pegcetacoplan due to inadequate response on pegcetacoplan alone?	The clinical experts noted that most hematologists are reluctant to prescribe C5 and C3 inhibitors concurrently and they have limited experience with this treatment approach.
To facilitate implementation of a recommendation to reimburse with conditions, if the diagnostic criteria are to be included, consider whether these conditions can be aligned with the criteria for eculizumab and ravulizumab.	This is a comment from the drug programs to inform CDEC deliberations.
Generalizability	
Question for CDEC: Patients matching the indication but who had certain cardiovascular factors that would potentially confound cardiac safety outcomes were excluded from the trial. Would this patient population still be eligible for treatment with pegcetacoplan?	CDEC agreed with the clinical experts that pegcetacoplan treatment could be considered in patients with cardiovascular disease or receiving QT-prolonging medications.

Implementation issues	Response
Care provision issues	
Considerations for CDEC: As pegcetacoplan is self-administered by subcutaneous infusion, there is training involved and specialized pump supplies. As per the submission, the FreedomEdge pump system will be available at no charge to patients through the PSP. The training will also be via the PSP. If a patient starts on treatment with pegcetacoplan and, in time, is unable or unwilling to continue to self-administer for any reason, or likewise have a caregiver do so, how would this be approached in terms of who will administer it, where will it be administered, and who would provide coverage of the administration should it require private services? The submission also noted that there were 14 treatment interruptions during the trial, mainly due to pump malfunction or user error. In similar situations, would the PSP be providing replacement doses? If the FreedomEdge pump system supplies become short-stocked, are there alternative pump systems available that can be used in its place and would they be provided by the PSP? Switching from a C5 inhibitor to pegcetacoplan requires a 4 week overlap period during which the patient receives both pegcetacoplan and their C5 inhibitor for the first 4 weeks of pegcetacoplan treatment. This is to minimize the risk of hemolysis with abrupt discontinuation of C5 inhibitor treatment. As this 4-week period would require the provision of 2 medications, it may have a significant impact on cost if drug plans reimburse this initial period.	The CADTH review team noted that the costs of both pegcetacoplan and eculizumab in the first 4 weeks of pegcetacoplan initiation were accounted for in the budget impact analysis submitted by the sponsor, while the costs related to services to administer drug when patient or caregiver is unable to perform SC injection and replacement doses due to pump malfunction were not. It is unclear if alternative pump systems can be used and if they will be provided by the PSP based on the information submitted by the sponsor. CDEC considered it important for the sponsor to clarify information on these costs (aside from the cost of eculizumab during the first 4 weeks) because this may affect the budget impact of reimbursing pegcetacoplan.
Question for clinical experts: Although the submission noted most TEAEs were mild or moderate in severity, if a patient develops intolerance to pegcetacoplan, would it be expected the patient return to treatment with the previously discontinued C5 inhibitor and discontinue the pegcetacoplan? If they had likewise been intolerant to the C5 inhibitor, would they discontinue all therapy or continue with the pegcetacoplan?	The clinical experts noted that discontinuation of both C3 and C5 inhibitor treatments would be unlikely, and patients would continue with the better tolerated treatment.
At times, prophylactic antibiotics may be clinically indicated given the risk of serious infections with encapsulated bacteria.	This is a comment from the drug programs to inform CDEC deliberations. The CADTH review team noted that the cost of prophylactic antibiotics was not accounted for in the budget impact model based on the assumption that that all patients would be vaccinated against encapsulated bacteria at least 2 weeks before the initiation of pegcetacoplan and would not require treatment with prophylactic antibiotics.
Although the indication is for inadequate response or intolerance to C5 inhibitors, it could be anticipated that jurisdictions might see requests indicating that infusion clinics and/or hospitals are not readily accessible to a patient and argue for initiation of treatment with pegcetacoplan in the first line in this situation. Given that treatment with pegcetacoplan will require regular	The clinical experts noted that, in their experience, access to infusion support could be a challenge for patients receiving eculizumab treatment living in rural areas (e.g., Northwest Territories). They would prefer prescribing ravulizumab as the first-line treatment in these patients.

Implementation issues	Response
follow-up and blood work, and possibly transfusions, it would be a difficult argument to make against the accessibility to use C5 inhibitor infusions. However, hypothetically, can CDEC address how this type of request might be approached?	CDEC noted that pegcetacoplan should not be reimbursed for first-line use as there is no evidence to support this use.
System and economic issues	
The drug cost is significant and has the potential to create a high budget impact.	This is a comment from the drug programs to inform CDEC deliberations.
It's unclear whether the cost of the required vaccinations will be picked up by the PSP or fall on the drug programs.	This is a comment from the drug programs to inform CDEC deliberations. The CADTH review team noted that vaccination costs were included in the budget impact analysis, but not in the pharmacoeconomic model. In the budget impact analysis, the costs of vaccines against *S. pneumoniae* and *H. influenzae* were accounted for although the costs of meningococcal vaccines were not based on the assumption that patients would have already received this vaccine while receiving prior eculizumab or ravulizumab treatment. The sponsor noted that the PSP will provide logistical support to assist physicians and patients with the coordination of pretreatment vaccination but will not provide coverage for the cost of pretreatment vaccination.
For most drug plans, reimbursement information is not publicly available. Likewise, PLAs exist with confidential negotiated prices. Ravulizumab is currently undergoing pCPA negotiations, the outcome of which would impact price comparisons. Both concerns make it difficult to assess budget impact and any potential cost savings.	This is a comment from the drug programs to inform CDEC deliberations.

ARC = absolute reticulocyte count; CDEC = CADTH Canadian Drug Expert Committee; EVH = extravascular hemolysis; FACIT = Functional Assessment of Chronic Illness Therapy; Hb = hemoglobin; IVH = intravascular hemolysis; LDH = lactate dehydrogenase; pCPA = pan-Canadian Pharmaceutical Alliance; PLA = product listing agreement; PNH = paroxysmal nocturnal hemoglobinuria; PSP = patient support program; SC = subcutaneous; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

The CADTH systematic review identified 1 relevant study, PEGASUS, which was a pivotal phase III, open-label RCT comparing pegcetacoplan (1,080 mg twice weekly via subcutaneous infusion) versus eculizumab (at patients' established dosage regimen via IV infusion) in adult patients with PNH who continued to have hemoglobin levels of less than 10.5 g/dL despite treatment with eculizumab at a stable dosage for at least 3 months (N = 80). After receiving both interventions concurrently in a 4-week run-in period, patients were randomized to either pegcetacoplan or eculizumab monotherapy on a 1:1 ratio in a 16-week randomized controlled period. The primary outcome was change from baseline (before the run-in period) at week 16 in hemoglobin (primary end point), and the key secondary end points were transfusion avoidance, change

in baseline at week 16 in ARC, LDH, and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score.

At baseline, the mean age of patients was 48.8 years (standard deviation [SD] = 16.0 years), with the majority of patients being female and white (both 61.3%). Mean time since diagnosis was 10.2 years (SD = 8.6 years); patients received eculizumab for a mean duration of 1,808.7 days (SD = 1,447.6 days) before the study and 30% of patients received eculizumab at a dose higher than the maintenance dose approved for PNH by Health Canada. The study population had a mean hemoglobin level of 8.7 g/dL (SD = 1.0 g/dL), reasonable control of IVH (mean LDH = 282.4 U/L; SD = 211.0 U/L), elevated mean ARC (216.9 × 10^9 cells/mL; SD = 71.7 × 10^9 cells/mL) and indirect bilirubin (mean = 33.8 µmol/L; SD = 25.8 µmol/L) levels, and low haptoglobin (mean = 0.135 g/L; SD = 0.121 g/L), consistent with the signs of EVH.

Efficacy Results

Survival

Survival was not assessed in the efficacy analysis.

Hemoglobin Outcomes

Change from baseline at week 16 in hemoglobin level was the primary end point. The mean hemoglobin level at baseline was 8.69 g/dL (SD = 1.08 g/dL) in the pegcetacoplan arm and 8.68 g/dL (SD = 0.89 g/dL) in the eculizumab arm. The least square (LS) mean change from baseline at week 16 in hemoglobin level (censored for transfusion) was 2.37 g/dL (standard error [SE] = 0.36 g/dL) in the pegcetacoplan arm and −1.47 g/dL (SE = 0.67 g/dL) in the eculizumab arm, with a between-group difference of 3.84 g/dL (95% confidence interval [CI], 2.33 g/dL to 5.34 g/dL) in favour of pegcetacoplan (P < 0.0001). Results of the sensitivity analyses (controlled-based pattern imputation and tipping point analyses) and supportive analysis using all patient data (uncensored for transfusion) were consistent with the primary analysis.

Hemoglobin response (i.e., at least 1 g/dL increase) in the absence of transfusion (secondary end point) was achieved in 75.6% of patients in the pegcetacoplan arm and 0 patients in the eculizumab arm, with an adjusted risk difference of 67.5% (95% CI, 54.5% to 80.4%). Hemoglobin normalization in the absence of transfusion at week 16 (secondary end point) was achieved in 34.1% of patients in the pegcetacoplan arm, and 0 patients in the eculizumab arm, with an adjusted risk difference of 30.4% (95% CI, 14.9% to 45.9%). The differences between treatments for both outcomes were not tested for statistical significance.

Transfusion

Transfusion avoidance was a key secondary end point and was tested for noninferiority according to the hierarchal testing procedure. Transfusion avoidance was achieved in 85.4% of patients in the pegcetacoplan arm, and 15.4% in the eculizumab arm, with an adjusted risk difference of 62.5% (95% CI, 48.3% to 76.8%) in the intention-to-treat (ITT) analysis. The lower bound of the 95% CI for risk difference was greater than the noninferiority margin (NIM) of −20% in both the ITT and per-protocol (PP) analysis sets, supporting noninferiority of pegcetacoplan versus eculizumab.

The mean number of packed RBC units transfused (secondary end point) was 0.6 units (SD = 2.03 units) in the pegcetacoplan arm and 5.1 units (SD = 5.6 units) in the eculizumab arm. The difference between treatments was not tested for statistical significance.

Thrombotic Events

Thrombotic events were not assessed in the efficacy analysis.

Symptoms of PNH

Change from baseline at week 16 in the FACIT-Fatigue score was a key secondary end point but was not tested for inferiority nor superiority due to prior failure in the testing hierarchy. The LS mean change from baseline at week 16 in the FACIT-Fatigue score in the ITT set (censored for transfusion) was 9.22 points (SE = 1.61 points) in the pegcetacoplan arm and −2.65 points (SE = 2.82 points) in the eculizumab arm, with a between-group difference in LS means of 11.87 points (95% CI, 5.49 to 18.25 points).

A responder analysis assessing the proportion of patients with at least a 3-point increase in the FACIT-Fatigue score from baseline at week 16 (censored for transfusion) was conducted; the proportion was 73.2% in the pegcetacoplan arm and 0% in the eculizumab arm. The differences between treatment arms were not tested for statistical significance.

Health-Related Quality of Life

Change from baseline at week 16 in Linear Analogue Scale Assessment (LASA) and European Organisation for Research and Treatment of Cancer Quality of life Questionnaire Core 30 (EORTC QLQ-C30) scores were secondary end points. The LS mean between-group difference in change from baseline at week 16 in LASA score (censored for transfusion) was 59.1 points (95% CI, 16.9 to 101.3 points). The LS mean between-group difference in LS mean change from baseline at week 16 in EORTC QLQ-C30 global health status, fatigue, pain, and dyspnea scale scores (censored for transfusion) was 18.62 points (95% CI, 0.12 to 37.13 points), −20.74 points (95% CI, −35.29 to −6.19 points), −2.76 points (95% CI, −20.36 to 14.85 points), and −14.57 points (95% CI, −29.90 to 0.76 points), respectively. The differences between treatment arms for all health-related quality of life outcomes were not adjusted for multiplicity.

Breakthrough Hemolysis

Breakthrough hemolysis was not assessed in the efficacy analysis.

Complications of PNH Other Than Thrombotic Events

Complications of PNH were not assessed in the efficacy analysis.

Hemolytic Parameters

Change from baseline at week 16 in LDH and ARC were key secondary end points and were tested for noninferiority according to the hierarchal testing procedure.

The mean LDH level at baseline was 257.5 U/L (SD = 97.6 U/L) in the pegcetacoplan arm and 308.6 U/L (SD = 284.8 U/L) in the eculizumab arm. The LS mean change from baseline at week 16 in LDH level (censored for transfusion) was −14.8 U/L (SE = 42.7 U/L) in the pegcetacoplan arm and −10.1 U/L (SE =

71.0 U/L) in the eculizumab arm, with a between-group difference in LS means of −4.6 U/L (95% CI, −181.3 to 172.0 U/L). Noninferiority was not met since the upper bound of the 95% CI of the between-group difference was not less than the NIM of 20 U/L in both the ITT and PP sets. Results of a supportive analysis based on data uncensored for transfusion were consistent with the primary analysis (between-group difference in LS means for ravulizumab versus eculizumab = −85.2 U/L; 95% CI, −192.9 U/L to 22.6 U/L).

The mean ARC at baseline was 217.5 × 10^9 cells/L (SD = 75.0 × 10^9 cells/L) in the pegcetacoplan arm and 216.2 × 10^9 cells/L (SD = 69.1 × 10^9 cells/L) in the eculizumab arm. The LS mean change from baseline in ARC at week 16 in the ITT set (censored for transfusion) was −135.8 × 10^9 cells/L (SE = 6.5 × 10^9 cells/L) in the pegcetacoplan arm and 27.9 × 10^9 cells/L (SE = 11.9 × 10^9 cells/L) in the eculizumab arm, with a between-group adjusted mean difference of −163.6 × 10^9 cells/L (95% CI, −189.9 × 10^9 cells/L to −137.3 × 10^9 cells/L). Noninferiority was met because the upper bound of the 95% CI of the adjusted mean difference was less than the prespecified NIM of 10 × 10^9 cells/L in the ITT set and the results were consistent in the PP set. Results of a supportive analysis based on data uncensored for transfusion were also consistent with the primary analysis.

LDH normalization in the absence of transfusion (secondary end point) was achieved in 70.7% of patients in the pegcetacoplan arm and 15.4% of patients in the eculizumab arm, with an adjusted risk difference of 48.8% (95% CI, 32.3% to 65.3%). LDH normalization (uncensored for transfusion) was achieved in 73.2% of patients in the pegcetacoplan arm and 59.0% in the eculizumab arm, with a risk difference of 12.3% (95% CI, 7.0% to 31.5%). The difference between treatment arms was not tested for statistical significance.

Reticulocyte normalization in the absence of transfusion (secondary end point) was achieved in 78.0% of patients in the pegcetacoplan arm and 2.6% of patients in the eculizumab arm, with a risk difference of 66.4% (95% CI, 53.1% to 79.7%). Reticulocyte normalization (uncensored for transfusion) was 80.5% in the pegcetacoplan arm and 17.9% in the eculizumab arm, with a risk difference of 54.8% (95% CI, 38.8% to 70.7%). The difference between treatment arms was not tested for statistical significance.

Health Care Resource Utilization

Health care resource utilization was not assessed in the study.

Harms Results

In the run-in period, treatment-emergent adverse events (TEAEs) were reported in 69 patients (86.3%), but none led to death or discontinuation of study treatment or study. A serious TEAE was reported in 1 patient due to sepsis, which resolved during the run-in period despite continued treatment with pegcetacoplan and eculizumab.

TEAEs were reported in 87.8% of patients in the pegcetacoplan arm and 87.2% of patients in the eculizumab arm. The most common TEAE of pegcetacoplan (in at least 10% of patients) were diarrhea, injection site erythema, injection site reaction, and abdominal pain. There was a similar incidence of serious TEAEs in both arms (pegcetacoplan: 17.1%; eculizumab 15.4%). Withdrawal from study treatment due to TEAE occurred in 3 (7.3%) patients in the pegcetacoplan arm, all due to breakthrough hemolysis. No patients in the eculizumab withdrew from study treatment due to a TEAE. No deaths were reported in either arm.

The incidence of injection site–related TEAEs (36.6%) was notably higher in the pegcetacoplan arm than the eculizumab arm (2.6%). Breakthrough hemolysis was less frequently reported in the pegcetacoplan arm (9.8%) relative to the eculizumab arm (23.1%). In the pegcetacoplan arm, there was no report of thrombosis or anti-pegcetacoplan peptide antibody response; 1 patient reported a serious treatment-emergent bacterial infection, but it was unrelated to encapsulated organism. There was no report of pulmonary hypertension or chronic kidney disease.

Critical Appraisal

Appropriate methods of randomization were used. Imbalances in some baseline characteristics between treatment groups were noted; however, none were expected to cause confounding. The open-label design could introduce reporting bias for subjective efficacy end points (i.e., FACIT-Fatigue, LASA, EORTC QLQ-C30) in favour of pegcetacoplan. The high number of major protocol deviations related to study assessment or schedule noncompliance could compromise the completeness and reliability of study data and introduce uncertainties to the results, although the direction or extent of bias is unclear. The statistical analyses were generally well-designed, with adequate sample size and appropriate multiplicity adjustments for all key secondary outcomes. Other secondary outcomes were either not tested for statistical significance or not adjusted for multiplicity. No justification was provided for the chosen NIMs, although NIMs were considered reasonable by the clinical experts. Supportive PP analysis were conducted for end points tested for noninferiority and results were consistent with the primary ITT analysis. There was a high amount of missing data due to censoring for transfusion. Nonetheless, with respect to the primary end point (change in hemoglobin), results from the sensitivity analyses and supportive analysis using different imputation methods and censoring rules were consistent the primary analysis, increasing certainty of the findings. It is unclear if improvement in hemoglobin level is a predictor of long-term clinical outcomes given that long-term studies are scarce for this rare disease. The reliability, validity, and responsiveness of the FACIT-Fatigue, LASA, EORTC QLQ-C30 scales have not been previously characterized in patients with PNH, which limits conclusions that can be made on these outcomes.

There was no major concern with the generalizability of the study population because the inclusion and exclusion criteria and patient baseline characteristics were consistent with clinical practice. Patients with intolerance to eculizumab were not included; however, this represents a very small population of patients in clinical practice per clinical expert input. Eculizumab was considered a representative comparator, and the distribution of eculizumab dosing aligns with clinical practice. The follow-up duration was adequate for assessing the efficacy outcomes included in the study but inadequate for other clinically important outcomes, such as breakthrough hemolysis, survival, thrombosis, and other complications of PNH. The clinical relevance of the FACIT-Fatigue, EORTC QLQ-C30, and LASA instruments is uncertain because they are not used in clinical practice, although they did capture some common symptoms of PNH (e.g., fatigue, dyspnea, pain) reported by patients.

Indirect Comparisons

Description of Studies

The sponsor submitted an anchored MAIC to evaluate the relative efficacy of pegcetacoplan to ravulizumab in adult patients with PNH previously treated with eculizumab. The MAIC did not report a systematic literature review to identify relevant studies for inclusion. Two studies were included in the analysis: patient level data from the PEGASUS study, comparing pegcetacoplan and eculizumab, and aggregate patient data from the ALXN study, comparing ravulizumab and eculizumab. Outcomes analyzed were transfusion avoidance, number of packed RBCs transfused, hemoglobin level stabilization, change from baseline in LDH level and LDH level normalization, fatigue and fatigue symptoms, global health status, and physical functioning. A propensity score model using logistic regression was used to account for between study differences in patient baseline characteristics. Effect modifiers were matched in the weighting process separately for clinical and hematological outcomes and fatigue and quality-of-life outcomes. Compared with patients who received ravulizumab, a greater proportion of patients who received pegcetacoplan had a history of transfusions during the year before the study (72.2% versus 13.4%) and mean hemoglobin was lower for patients who received pegcetacoplan (8.7 g/dL versus 11.1 g/dL). Transfusion history and mean hemoglobin were not adjusted for in the analysis.

Efficacy Results

After matching and anchoring on eculizumab, treatment with pegcetacoplan compared with ravulizumab was associated with more transfusion avoidance (adjusted difference = 71.4%; 95% CI, 53.5% to 89.3%), greater stabilization of hemoglobin levels (adjusted difference = 75.5%; 95% CI, 56.4% to 94.6%), greater normalization of LDH level in the absence of transfusions (adjusted difference = 64.0%; 95% CI, 41.8% to 86.1%), and fewer mean number of units of packed RBCs transfused (adjusted difference = −5.7 units; 95% CI, −7.2 to −4.2 units). In addition, treatment with pegcetacoplan compared with ravulizumab was associated with improvements in adjusted difference in mean change from baseline in fatigue (adjusted mean difference = 8.2 points; 95% CI, 3.8 to 12.6 points), global health status (adjusted mean difference = 9.6 points; 95% CI, 0.1 to 19.0 points), physical functioning (adjusted mean difference = 11.5 points; 95% CI, 3.6 to 19.5 points), and fatigue symptoms (adjusted mean difference = −13.3 points; 95% CI, −23.7 to −3.0 points). There was no difference in the mean change from baseline in LDH levels (adjusted mean difference = 0.3 U/L; 95% CI, −154.5 U/L to 155.1 U/L).

Critical Appraisal

The anchored MAIC has several limitations, including the inability to adjust for 2 clinically important effect modifiers (hemoglobin level and history of transfusions), which differed substantially between the 2 studies at baseline, and heterogeneity between studies regarding duration of follow-up (i.e.,16 weeks for PEGASUS versus 26 weeks for ALXN), treatment administration schedule, and dosing regimen. These limitations may introduce unmeasurable confounding in the relative treatment effect estimates, although the direction or extent of bias is unclear. Overall, there is uncertainty in the relative treatment effect estimates favouring pegcetacoplan versus ravulizumab.

Other Relevant Evidence

Description of Study

Safety and efficacy results from the 32-week single-arm extension period (following the randomized controlled period) for the PEGASUS trial (N = 77), during which all patients received pegcetacoplan, were also submitted by the sponsor and are presented in this report.

Efficacy Results

The results were reported as summary statistics, which indicated that efficacy as assessed through hemoglobin level, transfusion avoidance, ARC, LDH level, FACIT-Fatigue scale score, LASA scores, EORTC QLQ-C30 scores, as well as the number of packed RBC units transfused was generally maintained in the pegcetacoplan to pegcetacoplan group for another 32 weeks following the randomized controlled period. In the eculizumab to pegcetacoplan group, improvement was consistently observed across all outcomes after initiation of pegcetacoplan, and the group achieved similar benefits from pegcetacoplan as the pegcetacoplan to pegcetacoplan group.

Harms Results

The TEAE profile of pegcetacoplan was generally consistent with the randomized controlled period. Hemolysis was reported in 15 (19.5%) patients, which led to treatment discontinuation in 2 patients. Thrombosis was reported in 2 (2.6%) patients, but neither was deemed related to pegcetacoplan by the sponsor. There was no report of serious bacterial infection or renal failure. The incidence of pulmonary hypertension was not reported.

Critical Appraisal

The noncomparative design of the extension period precludes conclusions about the comparative efficacy of pegcetacoplan and eculizumab beyond 16 weeks. It is difficult to ascertain if the observed effects can be attributed to pegcetacoplan alone due to lack of control for confounding in a nonrandomized study. No formal statistical testing was conducted, and results were presented using descriptive statistics. The open-label design can influence reporting of subjective outcomes (FACIT-Fatigue, LASA, EORTC QLQ-C30, harms), introducing uncertainties to the results. Although the study results seem to suggest that the efficacy and safety of pegcetacoplan can be maintained long term, outcomes such as survival, thrombosis, and other complications of PNH require a much longer duration of follow-up to gain certainty in the results.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov cohort model
Target population	Adult patients with PNH who have an inadequate response to a C5 inhibitor. The population does not align to the full anticipated Health Canada indication, which also includes patients who are intolerant to a C5 inhibitor.
Treatment	Pegcetacoplan in addition to the patient's current C5 inhibitor treatment during the first 4 weeks of treatment.
Submitted price	Pegcetacoplan, 1,080 mg (54 mg/mL) solution for infusion: $4,970.00 per single-dose vial
Treatment price	First year costs: $516,880 to $556,932 Subsequent year costs: $516,880
Comparators	• Eculizumab • Ravulizumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALY, LYs
Time horizon	Lifetime (51.2 years)
Key data source	• PEGASUS trial: clinical efficacy and safety of pegcetacoplan vs. eculizumab • Assumption of equivalent clinical efficacy between eculizumab and ravulizumab
Key limitations	• The model structure did not capture all important clinical aspects of the diseases as it was based on Hb levels and transfusion status. There is further uncertainty regarding the validity of the hemoglobin level cut-off (Hb < 10.5 g/dL vs. Hb ≥ 10.5 g/dL) that drives majority of the utility benefits. • The sponsor's estimation of health state utility values based on mapping from cancer patients is inappropriate because the characteristics of PNH patients differ from those of cancer patients. This introduces uncertainty to the magnitude of the estimated incremental QALYs gains associated with pegcetacoplan. • Eculizumab and pegcetacoplan dosing escalations were modelled based on the PEGASUS trial but were noted by the clinical expert consulted by CADTH for the review to be uncertain. Given that the main cost driver in the model is drug acquisition costs, alternative assumptions on dose escalation can impact the expected cost difference and the cost-effectiveness of pegcetacoplan compared with a C5 inhibitor. • The sponsor used different transition probability matrices for the first and subsequent cycles of eculizumab and ravulizumab. CADTH clinical expert feedback noted that such difference is unexpected given patients would have simply stayed on C5 inhibitor treatment. • Uncertainty exists in the rate of treatment discontinuation and PNH-related complications. According to clinical expert feedback, treatment waning is anticipated over time and would continue to be observed beyond 1 year of treatment which was not modelled.
CADTH reanalysis results	• CADTH conducted reanalyses to address some of the key limitations, which included assuming identical transition probability matrices for the first and subsequent cycles of eculizumab and ravulizumab, and selecting discontinuation rate of pegcetacoplan based on the inclusion of more patient observations. • In CADTH's base case, pegcetacoplan dominated eculizumab (i.e., less costly, more effective). The ICER of

Component	Description
	pegcetacoplan compared with ravulizumab was $62,144 per QALY gained (incremental costs = $110,807; incremental QALYs = 1.78) in adult patients with PNH who have an inadequate response to a C5 inhibitor. A price reduction of 0.9% would be needed for pegcetacoplan to be cost-effective at a WTP threshold of $50,000 per QALY gained. • The model was highly sensitive to the cost of eculizumab and ravulizumab. CADTH conducted a series of 2-way price reduction analyses to highlight where pegcetacoplan would no longer be considered cost-saving compared with eculizumab. Furthermore, given limitations in the model structure that could not be addressed, the estimated QALY gains are highly uncertain. If the QALY gains between pegcetacoplan compared with C5 inhibitors are expected to be less than modelled, or if treatment waning is expected, this would increase the ICER of pegcetacoplan and a higher price reduction would be required.

Hb = hemoglobin; ICER = incremental cost-effectiveness ratio; LY = life-year; PNH = paroxysmal nocturnal hemoglobinuria; QALY = quality-adjusted life-years; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's budget impact analysis: the size of the target population may have been overestimated, uncertainties in the uptake of pegcetacoplan, and inappropriate assumptions of continuous up-dosing of eculizumab that misalign with its product monograph. Furthermore, the prices of eculizumab and ravulizumab were based on publicly accessible list prices and do not reflect any confidential pricing that may have been negotiated by public plans. CADTH reanalyses reduced the proportion of patients who had inadequate response to, or intolerance for, C5 inhibitor treatment and revised the market share of pegcetacoplan. Based on the CADTH reanalyses, the estimated budget impact from reimbursing pegcetacoplan is expected to result in increased costs of $39,833 in year 1 but lead to budget savings of $461,559 in year 2 and $441,843 in year 3 for a 3-year total incremental savings of $863,569. Scenario analyses to explore the sensitivity of the budget impact model to the limitations noted found that pegcetacoplan may increase the drug budget depending on whether drug up-dosing is publicly reimbursed.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting date: January 25, 2023

Regrets: One expert committee member did not attend

Conflicts of interest: None