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CADTH Reimbursement Recommendation

Ravulizumab (Ultomiris)

Indication: Ultomiris (ravulizumab for injection) is indicated for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)

Sponsor: Alexion Pharma Canada Corp.

Final recommendation: Reimburse with conditions

CADTH

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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

CADTH

What Is the CADTH Reimbursement Recommendation for Ultomiris?

CADTH recommends that Ultomiris should be reimbursed by public drug plans for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Ultomiris should only be covered to treat patients who meet existing reimbursement criteria for a similar drug, eculizumab, for the treatment of PNH. Patients already receiving eculizumab for treatment of PNH are eligible to switch to Ultomiris as long as they still have a good response to treatment with eculizumab.

What Are the Conditions for Reimbursement?

Ultomiris should be reimbursed in a similar way to eculizumab for PNH. Also, the cost of treatment with Ultomiris should not be more than the cost of treatment with eculizumab.

Why Did CADTH Make This Recommendation?

- Evidence from 2 clinical trials showed that Ultomiris is no worse than eculizumab in controlling hemolysis (destruction of red blood cells) within blood vessels and removing the need for blood transfusions.
- Although IV infusions of Ultomiris are less frequent than for eculizumab (every 8 weeks instead of every 2 weeks), there was not enough evidence to show that health-related quality of life is better with Ultomiris than with eculizumab.
- There is no evidence to suggest Ultomiris is more effective than eculizumab in treating PNH. Therefore, Ultomiris should be priced so that the cost of treatment is no more than the cost of treatment with eculizumab.
- If the actual price of eculizumab for the participating drug plans is 1% less than the current public list price, Ultomiris would be more costly than eculizumab, and a price reduction would be required.
- Based on public list prices, the 3-year budget impact is $13,180,849.

Additional Information

What Is Paroxysmal Nocturnal Hemoglobinuria?

PNH is an extremely rare disease in which the bone marrow produces abnormal red blood cells 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 of per year per 100,000 persons.

Unmet Needs in Paroxysmal Nocturnal Hemoglobinuria

Some patients treated with eculizumab do not have a good treatment response or their treatment causes hemolysis outside of blood vessels. Intravenous infusions of eculizumab every 2 weeks are burdensome to patients.

How Much Does Ultomiris Cost?

Treatment with Ultomiris is expected to cost the public drug plans between $569,140 and $685,887 in year 1 and between $474,284 and $569,140 in subsequent years, depending on patient weight.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ravulizumab be reimbursed for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two randomized controlled trials (RCTs) demonstrated that treatment with ravulizumab resulted in similar clinical benefit for adult patients with PNH compared with eculizumab. Results from Study 301 (N = 246) in treatment-naive patients and Study 302 (N = 197) in patients with adequately controlled intravascular hemolysis while on the labelled dosage of eculizumab showed that ravulizumab was noninferior to eculizumab in percentage of patients achieving transfusion avoidance (noninferiority margin of 20% for the mean difference), proportion of patients with lactate dehydrogenase (LDH) normalization (noninferiority margin of 0.39 for the odds ratio in Study 301 and not part of the statistical testing hierarchy in Study 302), and mean percent change in LDH level (noninferiority margins of 20% in Study 301 and 15% in Study 302 for the mean difference) over 26 weeks of treatment, with maintenance of efficacy up to 52 weeks of treatment in the extension periods of the studies. Evidence regarding symptom control, such as improvement of fatigue, was supportive of noninferiority of ravulizumab versus eculizumab. There is a need for treatments that are effective in patients who have insufficient control of intravascular hemolysis despite treatment with eculizumab, treatments that address the issue of extravascular hemolysis (an iatrogenic effect of eculizumab in some patients), and treatments that are less burdensome to patients (e.g., less frequent administration or improved ease of administration). The latter unmet need was emphasized in the patient input to CADTH. Given the evidence and the same mechanism of action for ravulizumab as for eculizumab, there is insufficient evidence to suggest that ravulizumab meets the first 2 unmet needs. Although ravulizumab may meet the third unmet need based on its less frequent administration, it was not possible to conclude whether ravulizumab treatment was associated with better health-related quality of life versus eculizumab treatment due to the lack of statistical testing for health-related quality of life outcomes, the open-label study design of both studies, and the lack of evidence in patients with PNH for the validity of the health-related quality of life scale used in the studies.

Using the sponsor-submitted price for ravulizumab and publicly listed price for eculizumab, ravulizumab was equally as effective and less costly compared with eculizumab for adult patients with PNH in the CADTH base case reanalysis. However, these results are extremely sensitive to the assumptions around the price of eculizumab. If the reimbursed price of eculizumab is 1% less than the list price, ravulizumab is more costly. The available clinical evidence suggests that ravulizumab is noninferior to eculizumab; as such, there is no evidence to support a price premium for ravulizumab.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation, renewal, discontinuation, and prescribing	
1. List in a similar manner to eculizumab for initiation, renewal, discontinuation, and prescribing, with the addition of condition 2 for initiation and condition 3 for prescribing.	Given the lack of evidence for superior efficacy of ravulizumab compared with eculizumab, CDEC considered it appropriate to align the reimbursement conditions for ravulizumab with current Canadian public drug plan reimbursement criteria for eculizumab.
Initiation	
2. Patients with insufficient initial response or who have failed treatment with eculizumab at the Health Canada–recommended dosage are not eligible for reimbursement of ravulizumab.	There is insufficient evidence to demonstrate that patients who do not respond or lose response to treatment with eculizumab will benefit from ravulizumab treatment.
Prescribing	
3. Ravulizumab should only be prescribed at the Health Canada–recommended dosage.	Patients treated with ravulizumab in Study 301 and Study 302 received the labelled dosage of ravulizumab with no allowance for an increase in dose or frequency. Currently, there is no evidence to inform the usage of ravulizumab beyond the labelled dosage.
Pricing	
4. Ravulizumab should be negotiated so that it does not exceed the drug program cost of treatment with eculizumab reimbursed for the treatment of adult patients with PNH.	There is no clinical evidence to suggest that ravulizumab is superior in efficacy to eculizumab nor is there any long-term comparative effectiveness data. As such, there is insufficient evidence to justify a cost premium for ravulizumab over eculizumab for adult patients with PNH.
Feasibility of adoption	
5. The feasibility of adoption of ravulizumab 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 CADTH's estimate.

PNH = paroxysmal nocturnal hemoglobinuria.

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by CDEC and the drug plans are summarized in Table 2.

Table 2: Implementation Guidance From CDEC

Condition no. from Table 1	Implementation considerations and guidance
1	Patients already receiving eculizumab treatment with adequate treatment response should be eligible to directly switch to ravulizumab treatment without having to meet the initiation criteria.
4	Due to the incremental cost of ravulizumab loading doses, drug programs will incur additional costs in the first year of treatment for both treatment-naive patients initiating ravulizumab and patients switching from eculizumab to ravulizumab. Such costs will likely take years to recoup when comparing the total costs of ravulizumab vs. eculizumab, which should be taken into consideration should ravulizumab be reimbursed.

Discussion Points

- CDEC heard from the clinical expert that up to 20% of patients treated with eculizumab for PNH require the higher dose of eculizumab (1,200 mg) to achieve complete complement blockade. There is no evidence to inform the efficacy of ravulizumab in these patients specifically because they were likely to be excluded from Study 302 and patients in Study 301 were treatment naive. Therefore, ravulizumab should not be considered as a second-line treatment for patients who do not have an adequate response to eculizumab treatment at the Health Canada–recommended dosage.
- It is possible that biosimilars of eculizumab will enter the market in the future and appropriate formulary management strategies for the optimal use of innovator biologics and biosimilars alike will become increasingly important. Although the comparative efficacy or cost-effectiveness of such biosimilars versus ravulizumab is unknown at the time of this review, CDEC considered there to be a risk of ravulizumab not being cost-effective versus a biosimilar of eculizumab should such a product enter the market.

Background

Ravulizumab has a Health Canada indication for the treatment of adult patients with PNH. Ravulizumab is a terminal complement inhibitor that specifically binds to the complement protein C5 and inhibits terminal complement–mediated intravascular hemolysis. It is available as a 10 mg/mL concentrate for solution for infusion; the Health Canada–recommended dosing regimen consists of a single loading dose followed 2 weeks later by the first maintenance dose, with maintenance doses administered every 8 weeks. The loading and maintenance doses are weight-based according to 3 different body weight ranges.

Sources of Information Used by the Committee

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

- a review of 2 RCTs in adults with PNH, 2 long-term extension studies of the 2 RCTs, and 1 patient preference substudy
- patients' perspectives gathered by 1 patient group: the Canadian Association of PNH Patients
- input from public drug plans that participate in the CADTH review process
- one clinical specialist with expertise diagnosing and treating patients with PNH
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient group submission was received from the Canadian Association of PNH Patients. Information was gathered through one-on-one interviews with 6 individuals living with PNH in Canada and from the scientific literature. The following negative impacts of PNH were described: dependence on frequent transfusions and difficulty in maintaining school attendance or employment for patients and caregivers due to frequent clinic visits, blood transfusions, and hospitalizations. According to the patient input, patients want treatment options and the less-burdensome treatment regimen of ravulizumab (every 8 weeks) compared with eculizumab (every 2 weeks) represents an improvement in quality of life and the opportunity to travel for longer periods of time. It was also noted that patients with PNH, who are immunocompromised, would prefer to visit the clinic for infusions less frequently in the context of the current pandemic.

Clinician Input

Input From Clinical Experts Consulted by CADTH

The following input was provided by 1 clinical specialist with expertise in the diagnosis and management of PNH.

One unmet need of patients with PNH is that the quality of life of patients being treated with eculizumab could be improved by modifying the treatment schedule or ease of treatment administration. Additionally, at the Health Canada–approved product monograph–recommended dosage for eculizumab in PNH, approximately 20% of patients do not have complete control of signs and symptoms associated with incomplete pharmacologic C5 inhibition though this can be addressed by administering higher doses of eculizumab. Finally, patients who have clinically significant anemia secondary to eculizumab treatment have an unmet need for extravascular hemolysis control; however, extravascular hemolysis would not be expected to improve with ravulizumab treatment.

Ravulizumab has the same mechanism of action as eculizumab and, if funded, would be considered first-line therapy in place of eculizumab for most patients. Patients in need of anti-complement therapy include those with evidence of a PNH clone (usually white blood cell clone size > 10%), hemolysis (i.e., LDH > 1.5 × the upper limit of normal [ULN]), and symptoms. Almost all, if not all, patients with hemolytic PNH who would qualify for eculizumab would similarly be expected to respond to ravulizumab. Neither treatment would be effective in the small proportion of patients of Japanese (approximately 3%) and Han Chinese (approximately

1%) descent who have a polymorphism which negates the effect of eculizumab as there is no effective target on C5. Currently, eculizumab may be preferred over ravulizumab during pregnancy given the available efficacy and safety data for eculizumab though this may change as more clinical experience with ravulizumab accumulates.

A clinically meaningful response to treatment would include improved symptoms and signs (e.g., fatigue, dyspnea, kidney function, abdominal pain, erectile dysfunction) and/or reduced transfusion demands. Response is assessed by review of the signs or symptoms and mapping onto biochemical evidence of reduced intravascular hemolysis (LDH < 1.5 × ULN) and improved counts (e.g., hemoglobin), and other parameters (e.g., creatinine, echocardiogram). Discontinuation of anti-complement therapy would rarely be considered, and relevant situations would include nonresponse (almost always associated with the polymorphism that negates the effect of C5 inhibition); persistent, severe adverse reactions (very rare); progression to severe bone marrow failure requiring bone marrow transplant; and regression of PNH clone to less than 10%, if associated with resolution of clinically significant hemolysis.

Drug Program Input

Table 3: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
Soliris (eculizumab) is listed on most public drug plans; however, the criteria are not publicly available for most plans. The clinical trials for ravulizumab required that diagnosis of PNH be confirmed by flow cytometry with a granulocyte or monocyte clone size of at least 5% before initiation. Current criteria for Soliris require a granulocyte clone size of greater than or equal to 10%. For consistency, alignment with initiation criteria for Soliris should be considered. **Question for the clinical expert:** What is the appropriate cut-off for clone size for the diagnosis of PNH?	According to the clinical expert, a threshold of 10% for PNH clone size is likely appropriate as long as either a granulocyte or monocyte clone size of at least 10% is accepted. The current criteria in Ontario only allow for granulocyte clone size to be considered and occasionally there are patients with active disease and with monocyte clone size of well over 10% but granulocyte clone size of around 9%. Therefore, clone type should be considered along with clone size for the initiation criteria. Based on the clinical expert's input, CDEC agrees with the use of a clone size of at least 10% as a cut-off for the diagnosis of PNH.
Considerations for continuation or renewal of therapy	
Consider alignment with renewal criteria for Soliris.	CDEC agrees that the renewal criteria for ravulizumab should be aligned with the renewal criteria for Soliris.
Considerations for discontinuation of therapy	
Consider alignment with discontinuation criteria for Soliris.	CDEC agrees that the discontinuation criteria for ravulizumab should be aligned with the discontinuation criteria for Soliris.

Implementation issues	Response
Considerations for prescribing of therapy	
The recommended dose of Soliris is 900 mg IV every 2 weeks. However, if breakthrough hemolysis occurs the sponsor noted that the dose could be escalated to 1,200 mg or more every 2 weeks. Ravulizumab is dosed by weight and given IV every 8 weeks. **Question for the clinical expert:** Could dose escalation occur with ravulizumab?	According to the clinical expert, there is very limited experience with ravulizumab in Canada, but experience in the US suggests that there are some patients who experience persistent breakthrough hemolysis with the recommended dosage. In such cases, ravulizumab is dosed every 7 weeks or even every 6 weeks if necessary. Although the tendency with eculizumab is to increase the dose to maintain the same dosing schedule, it is unclear whether the dose for ravulizumab can be increased. CDEC defers to the clinical expert with respect to dose escalation or reduction of dosing interval with ravulizumab and notes that it is outside the mandate of CDEC to make recommendations beyond the Health Canada–recommended dosing regimen for the drug under review.
System and economic issues	
The submitted price for ravulizumab is $7,296.67 per vial, and the annual cost is $561,841. It is expected that patients will transition from Soliris to Ultomiris. Patent expiry for Soliris is 2027 and for ravulizumab 2035. If patients transition to the new, more convenient C5 inhibitor, then savings that could be obtained by the entry of biosimilars will be lost. **Question for CDEC:** The budget impact analysis report estimates that Ultomiris would be cost saving from year 4 onward. Is this accurate given that biosimilars could enter the market in the future?	CDEC acknowledges that biosimilars for eculizumab and/or ravulizumab may enter the market at some point; however, presently there is no information available on the comparative efficacy or costs of any biosimilar products.

CDEC = CADTH Canadian Drug Expert Committee; PNH = paroxysmal nocturnal hemoglobinuria.

Clinical Evidence

Pivotal Studies and Protocol-Selected Studies

Description of Studies

Two relevant studies, the ALXN1210-PNH-301 and ALXN1210-PNH-302 studies (referred to here as Study 301 and Study 302, respectively), were selected for inclusion in the CADTH systematic review. Both studies were open-label, active-controlled, parallel-group, noninferiority RCTs. Both studies were sponsored by Alexion Pharmaceuticals, Inc., and the primary evaluation periods of both studies took place from 2016 to 2018. Study 301 (N = 246) enrolled adult patients with PNH who were treatment naive, whereas Study 302 (N = 197) enrolled adult patients with PNH who had been receiving eculizumab. Patients were randomized 1:1 to ravulizumab or eculizumab. Noninferiority of ravulizumab compared with eculizumab was assessed for transfusion avoidance, fatigue, breakthrough hemolysis, LDH normalization, and hemoglobin stabilization during a 26-week primary evaluation period.

Patients in both studies had to have a PNH diagnosis confirmed by flow cytometry (granulocyte or monocyte clone size of at least 5%); patients in Study 301 had to have an LDH

level of at least 1.5 × ULN and at least 1 PNH-related sign or symptom in the past 3 months. Patients in Study 302 had to have received eculizumab and have controlled LDH for at least the 6 months before the study. Across both studies, approximately half of patients were male, most were either Asian or White, and the mean age was 45 years to 49 years. In Study 301, most patients had an LDH level of 3 × ULN or greater and had received at least 1 transfusion in the past year. Patients in Study 302 had a mean LDH of 228 U/L to 235 U/L (with ULN for LDH considered to be 246 U/L), with 12.2% to 13.4% of patients having received at least 1 transfusion in the past year. Patients in Study 301 had a shorter mean disease duration (6.4 years to 6.7 years) than patients in Study 302 (11.9 years to 12.4 years), who had been receiving eculizumab for a mean of 5.6 years to 6.0 years. There were lower percentages of patients in Study 301 who had experienced a major adverse vascular event (13.6% to 20.7%) than in Study 302 (22.4% to 28.9%).

Efficacy Results

The results for transfusion avoidance, LDH normalization, and percent change in LDH level, which were the primary and co-primary end points in the studies, are presented in this summary. Results for other clinically important outcomes — health-related quality of life and fatigue — are also presented. The results for the per-protocol analyses for all primary and key secondary end points were consistent with the primary analyses.

Transfusion Avoidance

Transfusion avoidance was a co-primary end point in Study 301 and a key secondary end point in Study 302 that was tested for noninferiority in both studies according to the closed testing procedure. In Study 301, 73.6% of the ravulizumab group and 66.1% of the eculizumab group achieved transfusion avoidance throughout the 26-week primary evaluation period; the mean difference for ravulizumab versus eculizumab was 6.8% (95% confidence interval [CI], −4.66% to 18.14%). In Study 302, 87.6% of the ravulizumab group and 82.7% of the eculizumab group achieved transfusion avoidance throughout the 26-week primary evaluation period; the mean difference for ravulizumab versus eculizumab was 5.5% (95% CI, −4.27% to 15.68%). Noninferiority was met in both studies as the lower bounds of the 95% CIs were higher than −20%.

Intravascular Hemolysis

LDH normalization was a co-primary end point in Study 301 and a secondary end point in Study 302. In Study 301, the proportion of patients achieving LDH normalization from day 29 to day 183 was 0.536 (95% CI, 0.459 to 0.612) in the ravulizumab group and 0.494 (95% CI, 0.417 to 0.570) in the eculizumab group, with an odds ratio of 1.187 (95% CI, 0.796 to 1.769) for ravulizumab versus eculizumab. Noninferiority was met as the lower bound of the 95% CI was greater than 0.39. In Study 302, the proportion of patients achieving LDH normalization from baseline to day 183 was 0.660 (95% CI, 0.561 to 0.747) in the ravulizumab group and 0.708 (95% CI, 0.613 to 0.788) in the eculizumab group, with an odds ratio of 0.801 (95% CI, 0.500 to 1.282) for ravulizumab versus eculizumab (the outcome was not part of the statistical testing hierarchy).

Mean percent change in LDH level from baseline to day 183 was the primary end point in Study 302 and a key secondary end point in Study 301. It was tested for noninferiority in both studies and for superiority in Study 302 in accordance with the closed testing procedure. In Study 302, the least mean squares difference in percent change in LDH level was −9.21% (95% CI, −18.84% to 0.42%) for ravulizumab versus eculizumab. Noninferiority was met as the upper bound of the 95% CI was lower than 15%. Percent change in LDH was the first

outcome in the Study 302 testing hierarchy for superiority. The significance level was not met for superiority and no further testing was performed. In Study 301, the least mean squares difference in percent change in LDH level was −0.83% (95% CI, −5.21% to 3.56%) for ravulizumab versus eculizumab. Noninferiority was met as the upper bound of the 95% CI was lower than 20%.

Health-Related Quality of Life

Change in the European Organisation for Research and Treatment of Cancer Questionnaire (EORTC QLQ-C30) global health status score from baseline to week 26 was a secondary end point and not part of the closed testing procedure in either study. Increase in global health status score corresponds to improvement. In Study 301, patients in the ravulizumab and eculizumab groups had a change in global health status score of 13.17 (standard deviation [SD] = 21.44) and 12.85 (SD = 21.83), respectively. In Study 302, baseline and week 26 scores were similar to each other within each group, with a change in global health status score of 1.15 (SD = 16.51) in the ravulizumab group and −1.93 (SD = 15.34) in the eculizumab group

Symptoms of PNH

The change in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) total score was a key secondary end point and was tested for noninferiority in accordance with the closed testing procedure in both studies. Lower FACIT-Fatigue scores correspond to greater fatigue. In Study 301, least squares mean (LSM) change from baseline to week 26 in total score was 7.07 (standard error of the mean [SEM] = 0.77) in the ravulizumab group and 6.40 (SEM = 0.79) in the eculizumab group, with a mean difference for ravulizumab versus eculizumab of 0.67 (95% CI, −1.21 to 2.55). In Study 302, LSM change from baseline to week 26 in total score was 2.01 (SEM = 0.697) in the ravulizumab group and 0.54 (SEM = 0.704) in the eculizumab group, with a mean difference for ravulizumab versus eculizumab of 1.47 (95% CI, −0.21 to 3.15). Noninferiority was met in both studies as the lower bounds of the 95% CIs were higher than −5 and −3 in Study 301 and Study 302, respectively.

Harms Results

Most patients (86.8% to 88.0%) in both treatment groups in both studies reported at least 1 adverse event (AE). The most common AE was headache; there were no notable imbalances in AEs. Serious AEs were reported in 4.1% to 8.8% of each treatment group in both studies. The most common serious AEs were hemolysis and pyrexia, which occurred in 3.1% of patients or less in each treatment group. There were no withdrawals due to AE in either study. One patient in the eculizumab group in Study 301 died due to lung adenocarcinoma during the extension phase of the study.

In terms of notable harms, serious infections were reported in 1.0% to 3.3% of each treatment group in both studies. Infusion reactions were reported in 3.1% to 8.8% of patients across each treatment group in both studies. As for treatment-emergent anti-drug antibody–positive samples, there was 1 in each treatment group in Study 301 and 1 in the eculizumab group in Study 302 and titres were considered to be low.

Critical Appraisal

The prespecified noninferiority margins for the primary and key secondary end points (aside from percent change in LDH, potentially) were based on a magnitude of loss of benefit that may not be clinically acceptable. However, there are several factors that mitigate the risk of unacceptable loss of benefit with ravulizumab versus eculizumab. All the primary and key secondary end points met their respective noninferiority margins, there was minimal missing

data, the per-protocol analyses were consistent with the primary analyses for all end points, and a more conservative margin would have been met for all end points.

The open-label nature of the studies means that outcomes relying on subjective reporting, such as the EORTC QLQ-C30 and the FACIT-Fatigue, could have been biased with potential for bias in favour of ravulizumab. Additionally, the reliability, validity, and responsiveness of the EORTC QLQ-C30 and the FACIT-Fatigue have yet to be characterized in patients with PNH. Statistical testing was only performed for the FACIT-Fatigue score and not for other symptom assessments or for the EORTC QLQ-C30 scales.

The criteria for Study 302 were chosen in such a way that patients requiring a higher dose or more frequent dosing of eculizumab beyond the product monograph–recommended dosage would have been excluded. Although these patients were included in Study 301, the studies did not allow for deviation from the labelled dosage of eculizumab (900 mg maintenance dose) and this may have biased the efficacy results in favour of ravulizumab relative to how eculizumab is dosed in clinical practice.

Other Relevant Evidence

Description of Studies

Safety and efficacy results from the respective extension periods for Study 301 (N = 243) and Study 302 (N = 191), when all patients received ravulizumab, were also submitted by the sponsor and are presented in this report for the 26-week period following the randomized treatment period. Also included in the sponsor's submission was a patient preference substudy (N = 95) in which patients from Study 302 who enrolled in the extension period and had received at least 2 doses of ravulizumab during the extension period were eligible to enrol. A novel patient preference questionnaire was developed for the study and the objective of the study was to assess patient preferences for ravulizumab or eculizumab and to identify the key factors influencing preference.

Efficacy Results

The results from the extension periods of Study 301 and Study 302 were reported as summary statistics and indicated that efficacy, as assessed through transfusion avoidance, FACIT-Fatigue score, breakthrough hemolysis, LDH normalization, and hemoglobin stabilization, was generally maintained with ravulizumab treatment for another 26 weeks following the randomized treatment period.

According to the results from the questionnaire administered in the patient preference substudy, 93% of patients preferred ravulizumab overall with 43% of patients choosing frequency of infusions and 23% of patients choosing overall quality of life as the most important treatment factor when decided preference.

Harms Results

The AE profiles in the extension periods of Study 301 and Study 302 were similar to those in the randomized treatment periods, with no new safety signals identified. The frequency of headaches numerically decreased between the 2 periods in both treatment groups in both studies.

Critical Appraisal

The extension periods of Study 301 and Study 302 do not provide evidence for the comparative efficacy of ravulizumab versus eculizumab because all patients who continued in the extension periods received ravulizumab. As well, reductions in sample size in periods beyond the first 52 weeks of study treatment precluded the ability to assess results beyond 1 year of treatment, which is a concern given the chronic nature of the disease.

There were several limitations identified in the patient preference substudy that introduce substantial uncertainty in the results. These include the lack of evidence for the reliability and responsiveness of the questionnaire, the potential for recall bias given that ravulizumab was the most recent treatment for all patients, the small sample size relative to the population of Study 302, and uncertainty surrounding reasons for the reduction in sample size.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov cohort model
Target population	Adult patients with paroxysmal nocturnal hemoglobinuria, stratified by those who are treatment naive to complement inhibitor therapy and those who are stable on eculizumab
Treatment	Ravulizumab
Submitted price	Ravulizumab, 10 mg/mL, 30 mL vial: $7,296.67
Treatment cost	Assuming patients receive 6.5 administrations annually beyond the first year, the estimated annual costs of ravulizumab treatment ranges between $474,284 and $569,140, depending on patient weight
Comparator	Eculizumab
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (up to 100 years of age)
Key data source	Clinical studies 301 for patients who are treatment naive (cohort 1) and 302 for patients who are stable on the labelled recommended dose for eculizumab for at least 6 months (cohort 2).

Component	Description
Key limitations	• The CADTH clinical review concluded that ravulizumab was noninferior to eculizumab, for all outcomes, including those used in the sponsor's model, and that no conclusions may be made with regards to superiority. The sponsor's model, however, suggests that patients receiving ravulizumab will experience better outcomes than patients on eculizumab; for example, they will never experience incomplete C5 inhibition breakthrough hemolysis events over the entire model horizon. • Health states used in the model did not capture all important aspects of the condition affecting patient quality of life, health care resource utilization, and/or mortality, such as thrombosis. • The sponsor used treatment-specific utilities values, which is inappropriate because utility values should reflect health states, not specific treatments. Additionally, the sponsor incorporated a utility increment related to the frequency of administration visits with ravulizumab, which was not appropriately implemented in the submitted model, and the increment itself was based on assumption and is associated with uncertainty. • The likelihood of up-dosing associated with both eculizumab and ravulizumab is highly uncertain because the relationship between a higher dose and drug efficacy has not been established in clinical studies. Additionally, how patients receiving ravulizumab or eculizumab may be up-dosed (e.g., higher doses at the same administration frequency, or reducing administration frequency, or up-dosing ravulizumab patients with a dose of eculizumab) is uncertain.
CADTH reanalysis results	• CADTH undertook reanalyses to address limitations, which included assuming equal efficacy of ravulizumab and eculizumab, making health-state utility values equal for ravulizumab and eculizumab, and removing the utility increment due to frequency of health care visit for patients receiving ravulizumab. • When assuming equal clinical efficacy, ravulizumab compared with eculizumab is associated with lower total costs, resulting in cost savings of $13,386. Whether cost savings will be realized is highly uncertain as cost savings are only realized much later in the time horizon (i.e., higher first year or loading doses costs with ravulizumab are only offset by lower maintenance dose costs only after 26 and 34 years in the treatment-naive and treatment-experienced populations, respectively) and, should the actual cost of eculizumab be even 1% less than current list price, ravulizumab would be more costly.

LY = life-year; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis.

- The budget impact analysis (BIA) population reflects the size of the current eculizumab reimbursement population, not the population based on the Health Canada indication for eculizumab or ravulizumab.
- Uptake of ravulizumab is expected to be higher than that estimated by the sponsor.
- The sponsor assumed that no new PNH patients would initiate complement inhibitor therapy upon ravulizumab becoming available, which was deemed to be inappropriate. Among the new patients, a greater proportion are expected to initiate ravulizumab than estimated by the sponsor.
- The sponsor's approach to incorporating treatment discontinuation led to a different number of patients eligible for treatment in the reference and new drug scenarios, which is not expected. The discontinuation rate of complement inhibitor therapy was also deemed to be higher than expected.
- The BIA assumed 10% of eculizumab patients would be continuously up-dosed, which was not aligned with the sponsor's or CADTH's base case pharmacoeconomic analysis.

- The number of ravulizumab maintenance dose administrations in the first year of treatment was underestimated.
- The distribution of patient weights used in the BIA to determine drug costs are uncertain.

CADTH reanalyses included increasing the uptake of ravulizumab, changing the number of new patients eligible for complement inhibitor therapy from 0 to 14 each year, increasing the proportion of new patients who initiate ravulizumab, using the discontinuation rate for ravulizumab observed in Study 302, assuming no up-dosing with eculizumab, and assuming that ravulizumab patients receive 7 maintenance dose administrations in the first year of treatment. Based on the CADTH reanalyses, the estimated budget impact from reimbursing ravulizumab is expected to be $6,956,164 in year 1, $3,259,336 in year 2, and $2,965,349 in year 3 for a 3-year total of $13,180,849. Note that the there is uncertainty in the budget impact estimate as CADTH's 3-year budget impact is greater than double that estimated by the sponsor ($1,055,670 over 3 years). If a proportion of patients receiving eculizumab are continuously receiving a higher than 900 mg dose, the expected budget impact associated with reimbursing ravulizumab will be less. This scenario also assumes no up-dosing is required for patients receiving ravulizumab.

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, 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: December 15, 2021

Regrets: One expert committee member did not attend

Conflicts of interest: None