Canadian Journal of Health Technologies

CADTH

March 2023 Volume 3 Issue 3

CADTH Reimbursement Recommendation

Ravulizumab (Ultomiris)

Indication: For the treatment of adult and pediatric patients 1 month of age and older with atypical hemolytic uremic syndrome to inhibit complement-mediated thrombotic microangiopathy

Sponsor: Alexion Pharma GmBH

Final recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

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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 be reimbursed by public drug plans for the treatment of adult and pediatric patients at least 1 month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA), if certain conditions are met.

Which Patients Are Eligible for Coverage?

Ultomiris should only be covered to treat adults and children (aged 1 month or older) who: have aHUS, evidence of ongoing and progressing TMA (blood clots forming in small blood vessels), and evidence of at least 1 damaged or dysfunctional organ. Ultomiris may be funded for patients who had a kidney transplant, but not for those who have already tried ravulizumab and it did not work.

What Are the Conditions for Reimbursement?

Ultomiris should only be reimbursed if it is prescribed by or in consultation with a nephrologist or hematologist. Its cost should not be more than the least expensive complement inhibitor that is reimbursed for the treatment of aHUS.

Why Did CADTH Make This Recommendation?

- Based on evidence from 2 clinical trials in which Ultomiris demonstrated clinically meaningful improvements in complete TMA response (certain blood levels returning to normal and improvement in serum creatinine levels) in adult and pediatric patients with aHUS.
- Ultomiris addresses an unmet need as an additional treatment option that is taken less often than the current standard of care.
- Based on the sponsor's submitted price for Ultomiris and publicly listed prices for eculizumab, Ultomiris was less costly than eculizumab.
- Based on public list prices, Ultomiris is estimated to save public drug plans approximately $50 million over the next 3 years. However, potential savings are uncertain across all participating plans as eculizumab is not reimbursed for aHUS by all.

Additional Information

What Is AHUS?

Hemolytic uremic syndrome is a condition that can occur in adults and children when the small blood vessels in the kidney or other organs become damaged and inflamed.

Unmet Needs in aHUS

Not all patients have access to the current aHUS standard of care treatment.

How Much Does Ultomiris Cost?

Treatment with Ultomiris is expected to vary in cost due to weight-based dosing and cost differences between the first and subsequent years. In adult patients, Ultomiris costs between $569,140 and $685,887 in year 1 and between $474,284 and $569,140 in subsequent years. In pediatric patients, Ultomiris costs between $116,747 and $488,877 in year 1 and between $94,857 and $426,855 in subsequent years.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that ravulizumab be reimbursed for the treatment of adult and pediatric patients 1 month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA), only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase III, single-arm open-label studies (i.e., Study 311 for adult patients with aHUS and Study 312 for pediatric patients with aHUS who are complement inhibitor-naive [cohort 1] or previously treated with eculizumab [cohort 2]), demonstrated that treatment with ravulizumab at 26 weeks was associated with clinically meaningful improvements in complete TMA response (53.6%; 95% confidence interval [CI], 39.6% to 67.5% in Study 311 and 77.8%, 95% CI, 52.4% to 93.6% in cohort 1 of Study 312). Complete TMA response was maintained at the median follow-up time of 75.57 weeks (Study 311) and 84.2 weeks (cohort 1 of Study 312). For patients in cohort 2 of Study 312 at week 26, hematologic parameters remained stable. The safety profile of ravulizumab observed in Study 311 and Study 312 appeared consistent with its known safety profile, and no additional safety signals were identified.

CDEC acknowledged that aHUS is a rare, life-threatening condition, with variability in access to existing pharmacological therapy for public drug plans. Based on the natural history of disease without treatment, the committee concluded that there is an unmet need. Additionally, the frequency of ravulizumab administration is less than eculizumab, resulting in a less burdensome administration, according to patient-reported outcomes. Based on the limited trial data, CDEC concluded that ravulizumab potentially met some needs identified by patients, such as tolerable side effects and less burdensome administration.

At the sponsor-submitted price for ravulizumab and publicly listed price for eculizumab, ravulizumab was less costly than eculizumab. As ravulizumab is considered no more effective as eculizumab, its total drug cost should not exceed that of eculizumab.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adult and pediatric patients 1 month of age and older must meet all 3 of the following criteria for initial treatment: 1.1. Confirmed diagnosis of aHUS at initial presentation, defined by presence of TMA: 1.1.1. ADAMTS-13 activity ≥ 10% on blood samples taken before PE/PI; and 1.1.2. STEC test negative in patients with a history of bloody diarrhea in the preceding 2 weeks.	Based on clinical expert opinion and/or evidence from 2 phase III studies that demonstrated clinically meaningful improvements in complete TMA response in adult patients with aHUS and pediatric patients with aHUS who are complement inhibitor-naive, and stable hematologic parameters for patients previously treated with eculizumab.	Based on clinical expert opinion, drug plans may consider treatment with ravulizumab for patients who do not respond or lost response to treatment with eculizumab on a case-by-case basis (e.g., when the biology of the complement activation clearly demonstrated C5 activation [by biochemical assessment of complement activation pathways

Reimbursement condition	Reason	Implementation guidance
1.1.3. TMA must be unexplained (not a secondary TMA). 1.2. Evidence of ongoing active TMA and progressing, defined by laboratory test abnormalities despite plasmapheresis, if appropriate. Patients must demonstrate: 1.2.1. Unexplained (not a secondary TMA) thrombocytopenia (platelet count < 150 × 10^9 /L); and hemolysis as indicated by the documentation of 2 of the following: schistocytes on the blood film; low or absent haptoglobin; or LDH above normal. OR 1.2.2. Tissue biopsy confirms TMA in patients who do not have evidence of platelet consumption and hemolysis. 1.3. Evidence of at least 1 of the following documented clinical features of active organ damage or impairment: 1.3.1. Kidney impairment, as demonstrated by one of the following: 1.3.1.1. A decline in eGFR of > 20% in a patient with pre-existing renal impairment; and/or 1.3.1.2. SCr > ULN for age or GFR < 60mL/min and renal function deteriorating despite prior PE/PI in patients who have no history of preexisting renal impairment (i.e., who have no baseline eGFR measurement); OR 1.3.1.3. SCr > the age-appropriate ULN in pediatric patients (as determined by or in consultation with a pediatric nephrologist) OR 1.3.2. The onset of neurological impairment related to TMA. 1.3.3. Other TMA-related manifestations, such as cardiac ischemia, bowel		and/or genetics] and as per clinical judgment, where C5 inhibition would be sensible to manage the condition). Based on clinical expert opinion, in pediatrics, where TTP is less common, clinicians would likely not first initiate plasmapheresis (i.e., not early initiation of plasmapheresis until the diagnosis is confirmed) since use of plasmapheresis is not recommended in this setting; however, they agree this would be prudent to do in older patients.

Reimbursement condition	Reason	Implementation guidance
ischemia, pancreatitis, and retinal vein occlusion.		
2. Transplant patients with a documented history of aHUS (i.e., history of TMA [not a secondary TMA only] with ADAMTS 13 > 10%) would be eligible for ravulizumab if they: 2.1. Develop TMA immediately (within hours to 1 month) following a kidney transplant; or 2.2. Previously lost a native or transplanted kidney due to the development of TMA; or 2.3. Have a history of proven aHUS and require prophylaxis with ravulizumab at the time of a kidney transplant	Based on clinical expert opinion. TMAs most commonly appear within 1 month of post-transplant, as such immediately could be considered within hours to 1 month. If a patient previously lost their native kidney to TMA/aHUS, and aHUS is now occurring in their transplanted kidney, they should be eligible to receive treatment with ravulizumab, as their current graft is similarly at risk with each subsequent transplant.	For 2.3, based on clinical expert opinion, if the genotype of the aHUS is tissue related (i.e., not present in the transplant), then ravulizumab should be given pretransplant and for at least 1-month post-transplant with monitoring closely after discontinuation for recurrence.
3. Patients should not have a history of ravulizumab treatment failure (i.e., treated with ravulizumab with a previous aHUS recurrence). 3.1. Treatment failure is defined as: 3.1.1. Dialysis-dependent at 6 months, and failed to demonstrate resolution or stabilization of neurological or extrarenal complications if these were originally present; OR 3.1.2. On dialysis for ≥ 4 of the previous 6 months while receiving ravulizumab and failed to demonstrate resolution or stabilization of neurological or extrarenal complications if these were originally present; OR 3.1.3. Worsening of kidney function with a reduction in eGFR or increase in SCr ≥ 25% from baseline.	Study 311 and Study 312 exclusion criteria included: • Identified drug exposure-related HUS. • Prior use of eculizumab or other complement inhibitors. Clinical experts stated they would not re-treat a patient with ravulizumab if they had a history of ravulizumab treatment failure.	—
Renewal		
4. Assessment of treatment response should be conducted at 6-months, at 12-months, then annually thereafter the following: 4.1. Treatment response is defined as, but not limited to, hematological normalization (e.g., platelet count, LDH), stabilization of end-organ damage (such as acute kidney injury and brain ischemia), transplant graft survival in susceptible individuals, and dialysis avoidance in patients who are pre-ESKD. 4.2. Treatment with ravulizumab can be renewed as long as the patient exhibits a	Based on clinical expert opinion, the outcomes indicating a favourable response include resolution of TMA (normalization of LDH and platelet count), and stabilization of end-organ damage such as acute kidney injury and brain ischemia, transplant graft survival in susceptible individuals, and dialysis avoidance in patients who are pre-ESKD. According to clinical experts, the required duration of treatment with C5 inhibition is unknown. It is possible to discontinue treatment	—

Reimbursement condition	Reason	Implementation guidance
response to treatment or as per physician discretion (e.g., long-term funding based on factors like limited organ reserve or high-risk genetic mutation such as Factor H deficiency). 4.3. At the 6-month assessment, treatment response and no treatment failure (defined in 3.1 above) is required. 4.4. At the 12-month and annual assessments, treatment response, no treatment failure (defined in 3.1 above), and the patient has limited organ reserve or high-risk genetic mutation are required. 4.4.1. Limited organ reserve is defined as significant cardiomyopathy, neurological, gastrointestinal, or pulmonary impairment related to TMA; or Grade 4 or 5 chronic kidney disease (eGFR < 30mL/min) is required.	with ravulizumab in patients with aHUS without a genetic mutation in complement 3 to 6 months after remission is achieved. Lifelong treatment may be considered for patients with high-risk complement genetic variations (such as, but not limited to, Factor H deficiency,) or limited organ reserve. Patients with DGKE mutations may discontinue if no response to treatment is observed.	
5. A patient previously diagnosed with aHUS and who responded to treatment with ravulizumab and has not failed ravulizumab is eligible to restart ravulizumab if the patient redevelops a TMA related to aHUS and meets the following clinical conditions: 5.1. Significant hemolysis as evidenced by presence of schistocytes on the blood film, or low or absent haptoglobin, or LDH above normal; AND 5.2. EITHER 5.2.1. Platelet consumption as measured by either ≥ 25% decline from patient baseline or thrombocytopenia (platelet count < 150,000 × 109/L); OR 5.2.2. TMA-related organ impairment (e.g., unexplained rise in serum creatinine with onset of urine dipstick positive for hemoglobin) including on recent biopsy.	Based on clinical expert opinion, if a patient redevelops a TMA related to aHUS, ravulizumab needs to be restarted to prevent end-organ damage.	—
Prescribing		
6. Ravulizumab should be prescribed by or in consultation with a pediatric nephrologist, a nephrologist, a pediatric hematologist or a hematologist.	Based on clinical expert input, ravulizumab can be given at home with nursing support or at an infusion centre. A specialist, such as a nephrologist or hematologist	—

Reimbursement condition	Reason	Implementation guidance
	with expertise in TMA, is needed to monitor the patients.	
Pricing		
7. Ravulizumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly complement inhibitor reimbursed for the treatment of aHUS.	No clear evidence of non-inferiority of ravulizumab relative to eculizumab was established through the submitted indirect treatment comparison. Additionally, the finding of no statistically significant difference for ravulizumab relative to eculizumab within the context of the submitted indirect treatment comparison is subject to substantial uncertainty owing to methodological challenges of the available data. As such, there is insufficient evidence to justify a cost premium for ravulizumab over the least expensive complement inhibitor reimbursed for aHUS.	—
Feasibility of adoption		
8. The feasibility of the adoption of ravulizumab must be addressed.	The magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption. Based on public list prices for eculizumab, ravulizumab is expected to lead to cost savings in plans that reimburse eculizumab in this population. However, there is uncertainty regarding the potential cost-savings across all participating plans, since not all plans currently reimburse eculizumab. The feasibility of adoption will be an issue in these jurisdictions.	—

ADAMTS-13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aHUS = atypical hemolytic uremic syndrome; DGKE = diacylglycerol kinase epsilon; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; LDH = lactate dehydrogenase; PE/PI = plasma exchange or plasma infusion; SCr = serum creatinine; STEC = Shiga toxin–producing *Escherichia coli*; TMA = thrombotic microangiopathy; TTP = thrombotic thrombocytopenic purpura; ULN = upper limit of normal.

Discussion Points

- The drug plans requested a reconsideration of the initial draft recommendation for ravulizumab for the treatment of adult and pediatric patients 1 month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA).

- The CDEC subpanel reviewed the sponsor's comments, the CADTH review team and clinical experts' responses to each item raised by the drug plans. The CDEC subpanel also noted similar items raised in the patient group feedback; for instance, clarity on the initiation condition regarding plasmapheresis or addressing restarting as a reimbursement condition rather than implementation guidance.
- During the reconsideration meeting, the CDEC subpanel discussed the drug plans' request for clarity and guidance related to initiation conditions, renewal conditions and implementation guidance. In particular, the CDEC subpanel discussed the initiation condition regarding plasmapheresis and acknowledged the feedback from the sponsor and patient group, input from the clinical experts, and noted that there was no minimum number of plasma exchange sessions in Study 311 and Study 312. The CDEC subpanel also discussed the guidance from the clinical experts regarding patients with high-risk complement genetic variations, such as Factor H deficiency, who would be potential candidates for lifelong treatment with ravulizumab. The CDEC subpanel also acknowledged that other high-risk genetic mutations exist. The CDEC subpanel discussed the feedback from the patient group regarding the initiation condition related to organ damage or impairment. While this initiation condition was not raised by the participating drug plans, sponsor or clinician group, the CDEC subpanel acknowledged the concerns raised by the patient group. As a result, the CDEC subpanel agreed to revisions to the ravulizumab recommendation conditions for clarity and offered guidance to jurisdictions.
- As there was uncertainty with the clinical evidence given the single-arm study design of Study 311 and Study 312, CDEC deliberated on ravulizumab considering the criteria for the significant unmet needs that are described in section 9.3.1 of the Procedures for CADTH Reimbursement Reviews. Considering the rarity and severity of the condition for which there is variability in access to existing pharmacological therapy among public drug plans, the committee concluded that the available evidence suggests that ravulizumab led to clinically meaningful improvements in complete TMA response.
- The sponsor submitted a propensity score weighted analysis comparing ravulizumab with eculizumab; however, no conclusion could be drawn on the comparative efficacy and safety of ravulizumab versus eculizumab due to several methodological limitations.
- CDEC discussed that the savings noted within the budget impact results assumed all patients in the reference case would be receiving eculizumab. Although ravulizumab may provide cost-savings relative to eculizumab based on publicly available list prices, CDEC noted ravulizumab is expected to be more costly than best supportive care (BSC) in terms of treatment acquisition costs. In jurisdictions that do not reimburse eculizumab, ravulizumab is expected to increase the budget.
- 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

Atypical hemolytic uremic syndrome (aHUS) is a life-threatening ultra-rare disease in which patients are susceptible to sudden and progressive episodes of complement-mediated

thrombotic microangiopathy (TMA) that most commonly damages the kidneys and also includes extrarenal multiorgan involvement. Patients typically present with signs and symptoms of the triad of thrombocytopenia, hemolysis, and acute kidney injury. aHUS is primarily caused by inherited or acquired dysregulation of complement regulatory proteins resulting in uncontrolled complement activation. In the majority of patients, aHUS may involve both genetic predisposition and a triggering condition in order for the clinical event of a TMA to occur. aHUS can occur at any age, although onset during childhood is more frequent than in adulthood (60% versus 40% respectively). Diagnosis of aHUS is based on exclusion of other causes of TMA. Therefore, the potential risk of misdiagnosis of aHUS may exist in clinical practice. Although a positive genetic test can help to confirm a previously clinically diagnosed case of aHUS, it is not required to make the diagnosis of aHUS or to commence treatment. A clinical differential diagnosis remains the primary method of establishing a diagnosis of aHUS.[6] According to the clinical experts consulted by CADTH for this review, 30% to 40% of patients with aHUS may have no known genetic predisposition. According to the clinical experts, aHUS patients with DGKE mutations are unlikely to benefit from C5 inhibitors (e.g., eculizumab and ravulizumab) treatment. The incidence and prevalence of aHUS varies widely. A 2020 systematic literature review of the global epidemiology of aHUS reported that, for all ages, the annual incidence ranged from 0.23 to 1.9 per million population.[14] It was also reported that, for all age groups, the annual incidence was 4.9 per million population. There is limited published prevalence data for aHUS specific to Canada and the US. A Canadian study published in 2004 reported an incidence of aHUS in children of 2 cases per million over a 4-year period. Most recently, a 2020 analysis of 37 Canadian patients (15 pediatric patients and 22 adult patients) enrolled in the aHUS Global Registry (i.e., an observational, noninterventional, multicentre study that prospectively and retrospectively collects data on patients with a clinical diagnosis of aHUS irrespective of treatment) estimated that there are potentially 74 patients with aHUS in Canada. Before ravulizumab approval, the terminal complement inhibitor eculizumab has been considered the standard of care for the treatment of patients with aHUS, in most jurisdictions, for over a decade. Eculizumab is the only Health Canada–approved drug indicated for the treatment of aHUS. However, eculizumab is not reimbursed across all Canadian jurisdictions. Furthermore, eculizumab imposes a substantial treatment burden on patients due to its shorter half-life and requirement for biweekly dosing. The frequent dosing schedule of eculizumab is burdensome to patients, potentially affecting health-related quality of life (HRQoL) and it is also health care resource-intensive, which also drives infusion-related costs with eculizumab. The clinical experts consulted by CADTH for this review indicated that there is an unmet need for alternative effective therapies with acceptable toxicity profiles that achieve TMA remission and improve HRQoL for patients with aHUS. The appropriate duration of treatment with anticomplement therapy is unknown.

Ravulizumab has been approved by Health Canada for the treatment of adult and pediatric patients 1 month of age and older with aHUS to inhibit complement-mediated TMA. Ravulizumab is a terminal complement inhibitor that specifically binds to the complement protein C5, inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex membrane attack complex (MAC) or C5b9. It is available as 10 mg/mL concentrate for solution for infusion and the dosage recommended in the product monograph is body weight based (for body weight greater than or equal to 5 kg) and consists of a single loading dose followed 2 weeks later by the first maintenance dose, and subsequent maintenance doses are administered every 8 weeks (q.8.w. for ≥ 20 kg or q.4.w. for 20 kg).

Sources of Information Used by the Committee

To make its recommendation, CDEC considered the following information:

- a review of 2 phase III, single-arm and open-label clinical studies in patients with aHUS (i.e., Study 311 for adult patients with aHUS and Study 312 for pediatric patients with aHUS)
- patient perspectives gathered by the patient group, aHUS Canada
- input from public drug plans that participate in the CADTH review process
- two clinical specialists with expertise in diagnosing and treating patients with aHUS
- a review of the pharmacoeconomic model and report, and indirect treatment comparison submitted by the sponsor.

Stakeholder Perspectives

Patient Input

One patient advocacy group, aHUS Canada, provided input for the treatment of aHUS. This group gathered information from 19 caregivers and 41 patients from inside and outside Canada through an online survey conducted in June 2022. Of these 60 respondents, 19 had experience with the drug under review.

Respondents identified anemia, low platelet count, and acute renal failure as the most difficult primary symptoms to control. Lack of quality of life, helplessness, post-traumatic stress disorder, fatigue or exhaustion, headache, high blood pressure, inability to travel, frequent hospital visits, and kidney issues and dialysis are some of the experiences that respondents go through while living with aHUS. According to aHUS Canada, aHUS dialysis patients needing a kidney transplant are not eligible for transplant in Canada, unless they receive eculizumab infusions at transplant. Caregivers to aHUS patients also face emotional and financial challenges, as the process to access eculizumab or other alternatives differ from province to province. Respondents described financial struggles, anxiety about access to treatment, protecting organs, exhaustion, and memory loss or brain fog as harder-to-control aspects of their disease.

Respondents identified plasma therapy (fresh frozen plasma or plasmapheresis), eculizumab infusions, and long-term dialysis as the currently available treatments for aHUS patients. Side effects reported by the respondents included nausea, headache, fatigue, anaphylactic reaction to plasma used, vein collapse, infection, anxiety, refractory to plasma therapy, kidney failure, uncontrolled blood pressure, migraines, exhaustion, memory loss or brain fog, central line issues, muscle crumps, insomnia, abdominal pain, fever and chills, and weight gain or loss.

While discussing their expectations about new drugs, patients believed that access to treatment and freedom for choice were critical components in managing the disease; whereas, quality of life was the most common outcome shared by the patients, which was affected by the choice in care, frequency of appointments, and affordability of the drug. The ability to travel, focus on family, and have more time between appointments were described as critical components for patients' mental health. Moreover, frequent blood tests and

IV therapies or ports were reported to be significant problems for many patients. While 1 caregiver pointed out the importance of maintaining "venous access for continuous access to eculizumab," other patients shared their ineligibility for ports due to damaged veins from the disease. Patient also expressed the importance of less frequent treatments.

While discussing the experience with the ravulizumab, patients listed more energy, less vein damage, less treatments, fewer symptom fluctuations, freedom of choice, less anxiety, and improve quality of life, as some of the common benefits. While patients reported experiencing headache, nausea, and body aches right after their infusion or during the month after the infusion, they said the overall benefits were worthwhile as these side effects were the same as or better than previous treatments.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Unmet Needs

The clinical experts consulted by CADTH for this review indicated that administration of eculizumab every 2 weeks interferes with a patient's quality of life by consuming time that could be spent working, travelling, or spending time with friends and family. Administration of eculizumab every 2 weeks can also be an issue when it comes to venous access fatigue; administration of eculizumab every 2 weeks also comes with the societal cost of nursing and allied health care support that is required. In addition, the biggest limitation to current treatment is prohibitive cost – most centres will fund an initial treatment or a few treatments, but very few centres have the resources to fund lifelong treatment. Provincial formulary inclusion is inconsistent and private insurance coverage is not common. Often, advocacy for subsidy or full payment is made for each patient by the health care team, but is not always successful. With respect to venous access fatigue, most patients should be candidates for portacaths or central lines, as it is normally offered to chemotherapy patients.

The clinical experts indicated that the mechanism of action of ravulizumab is the same as eculizumab. Ravulizumab would not be added to other treatments. Ravulizumab would replace eculizumab as the treatment of choice for aHUS. The clinical experts indicated that they believe that ravulizumab would have likely similar or equivalent efficacy as eculizumab, with the potential of a better therapeutic profile or reduced therapeutic burden. The reasons that they believed that ravulizumab would become the first-line treatment of choice were that they believed ravulizumab would result in improved in patient quality of life and improved cost-effectiveness compared to eculizumab. The clinical experts mentioned that, theoretically, as we have seen with other biologics that use the same target molecule, tachyphylaxis to 1 medication may open up options to treat with the second, so acquired non-response may be a consideration to switching therapies. Improvements in a patient's HRQoL is expected to be significant after switching from eculizumab to ravulizumab.

The clinical experts indicated that the patients most suitable for treatment with ravulizumab are patients diagnosed with aHUS. The patients least suitable are those with thrombotic microangiopathy that is clearly due to a secondary cause such as malignant hypertension, malignancy, or infection. There may be some benefit in using eculizumab in some autoimmune disease patients where there is histological evidence of TMA as well as evidence of complement dysregulation (e.g., some variants of lupus). According to the clinical experts, the patients with aHUS most in need of intervention are those with severe TMA with associated end-organ damage such as acute kidney injury or brain ischemia. The clinical

experts indicated that patients who qualify for treatment would be identified by physicians with expertise in thrombotic microangiopathies such as nephrologists and hematologists and internal medicine physicians based on clinical examination, lab investigations, genetic testing for complement dysregulation, and by excluding other causes of TMA. To make a diagnosis of aHUS, there needs to be evidence of thrombotic microangiopathy: schistocytes, elevated lactate dehydrogenase, decreased haptoglobin, decreased hemoglobin, and thrombocytopenia. These lab abnormalities should also coincide with 1 or more of the following: neurological symptoms, acute renal failure, or gastrointestinal symptoms, although any organ system can be involved (e.g., pancreas, heart). Diagnosis of aHUS can be very challenging as there is not 1 single diagnostic test that can confirm the diagnosis. In many situations, it is a diagnosis of exclusion. For this reason, misdiagnosis of this condition is a risk. One clinical expert indicated that testing has improved, and the difficulty in diagnosis has decreased — highlighting that this may have been more of an issue 10 to 15 years ago when available genetic and biochemical assessments of complement pathways were less accessible, but these tests are now more available and often on a quick turnaround, even when sent out of province for testing. One clinical expert indicated that haptoglobin is not the most reliable diagnostic indicator, and that LDH level is more reliable.

The clinical experts indicated that etiologies that mimic thrombotic microangiopathy need be excluded including infections, medications, malignancy, scleroderma, antiphospholipid antibody syndrome, systemic lupus erythematosus, malignant hypertension, disseminated intravascular coagulation, preeclampsia and hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome. Thrombotic thrombocytopenic purpura (TTP) can be distinguished from aHUS by measuring ADAMTS13 level. If ADAMTS13 is higher than 5% and the patient is resistant to plasma exchange, then the diagnosis is more likely to be aHUS than TTP. Screening for complement mutations and antibodies should be performed. More sophisticated testing is available as well, including sMAC levels (also known as soluble C5b-9) — this is elevated during aHUS and is reduced with treatment as it is generated as a product of complement activation. If initially low, most centres may also follow C3 and C4 levels to monitor for recovery.

The clinical experts indicated that the early initiation of plasmapheresis until diagnosis is confirmed is critical given the high mortality risk of untreated TTP. One clinical expert indicated that most centres have access to ADAMTS13 activity testing with a turnaround of 24 to 48 hours. The approach to treatment in adults, and particularly the older population, may include plasmapheresis before the result is known. One clinical expert specialized in pediatric nephrology indicated that if feasible, wait for the results for pediatric patients since the use of plasmapheresis is not recommended in this setting, but local resources dictate its use, and it can be dependent on whether they can procure C5 inhibitors quickly. In pediatrics, where TTP is less common, clinicians would likely not initiate plasmapheresis first, but tend to agree that this would be prudent to do in older patients. The clinical experts emphasized that once aHUS is diagnosed, C5 inhibition may be used as first-line therapy.

The clinical experts indicated that the treatment goals for aHUS are the resolution of the TMA with normal platelet and LDH counts as well as the resolution of acute kidney injury or neurological sequelae, or stabilization of end-organ damage. The required duration of treatment with C5 inhibition is unknown. Based on available data, if there are no high-risk complement genetic variants, then termination of treatment could be considered after 6 to 12 months. However, according to clinical experts, it is possible to discontinue treatment with ravulizumab in patients with aHUS without a genetic mutation in complement 3 to 6 months after remission is achieved. Lifelong treatment may be considered for patients with high-risk

complement genetic variations. The clinical experts mentioned that 30% to 40% of patients with aHUS may have no known genetic disposition. As noted previously, aHUS patients with DGKE mutations are unlikely to benefit from C5 inhibitors (e.g., eculizumab and ravulizumab) treatment. Clinical experts highlighted that patients with DGKE mutations can safely come off C5 inhibitors as it is unlikely to help if no response to treatment is observed. The outcomes indicating a favourable response include resolution of TMA (normalization of LDH and platelet count) and stabilization of end-organ damage such as acute kidney injury and brain ischemia, transplant graft survival in susceptible individuals, and dialysis avoidance in patients who are pre-ESKD.

Close monitoring of the patient for 1 year after discontinuing therapy is recommended to monitor for relapse. Treatment discontinuation in patients with a high-risk mutation in complement is associated with a 50% relapse rate, so discontinuing treatment in these patients is more challenging. Treatment discontinuation also needs to be considered in the setting of severe infections. However, 1 clinical expert indicated that this would entail restarting the medication either with reduced dosing or with prophylactic anti-infectives.

The clinical experts indicated that ravulizumab can be given at home with nursing support or at an infusion centre. A specialist such as a nephrologist or a hematologist with expertise in TMA needs to monitor the patients.

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 impact the implementation of a CADTH recommendation for ravulizumab:

- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for prescribing of therapy
- 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
Considerations for initiation of therapy	
Would patients who do not respond or lost response to treatment with eculizumab benefit from ravulizumab treatment?	The clinical experts noted that there is no evidence of this; however, ravulizumab does give an immediate, complete, and more sustained C5 inhibition when compared to eculizumab and therefore this may be considered in individual cases. There is also evidence that some patients develop tachyphylaxis to specific biologics and still retain some responsiveness to biosimilars. CDEC agreed with the clinical experts.

Implementation issues	Response
Can a patient restart ravulizumab if they responded to previous treatment? If so, under what clinical conditions?	The clinical experts stated that if a patient redevelops a TMA related to aHUS, ravulizumab needs to be restarted to prevent end-organ damage. Note that discontinuation of C5 inhibitors, when they have been maintaining remission and withdrawal has subsequently caused relapse, may cause irreversible damage resulting in progression of organ damage. Therefore, if a patient were in this situation and progressed to end-stage kidney disease with no history of other organ involvement, it may be futile to restart the medication as the patient would remain on dialysis - restarting the medication post-transplant would be necessary, if the patient were deemed a suitable transplant candidate. CDEC agreed with the clinical experts.
Consider alignment with current Canadian public drug plan initiation criteria for eculizumab.	CDEC discussed this input from public drug plans.
Considerations for continuation or renewal of therapy	
Consider alignment with renewal criteria for eculizumab.	CDEC discussed this input from public drug plans.
Considerations for prescribing of therapy	
Consider alignment with prescribing criteria for eculizumab (Soliris) — prescribed by or in consultation with a pediatric nephrologist, a nephrologist (for adults), a pediatric hematologist or a hematologist (for adults).	CDEC discussed this input from public drug plans. Based on clinical expert input, ravulizumab can be given at home with nursing support or at an infusion centre. A specialist, such as a nephrologist or hematologist with expertise in TMA, is needed to monitor the patients.
System and economic issues	
The submitted price for ravulizumab (Ultomiris) is $7,296.67/vial and the annual cost of treatment is expected to range from $94,857 to $569,140, depending on patient weight. The annual cost of treatment with eculizumab (Soliris) is expected to range from $116,861 to $701,168, depending on a patient's weight. It is expected that patients will transition from eculizumab to ravulizumab. The patent expiry for eculizumab is 2027 and for ravulizumab is 2035. If patients transition to the new, more convenient C5 inhibitor then savings that could be obtained by the entry of biosimilars may be lost.	CDEC acknowledged 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.

aHUS = atypical hemolytic uremic syndrome; TMA = thrombotic microangiopathy.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

Two manufacturer-sponsored studies were included in this review (Study 311 and Study 312).

Study 311 is an ongoing, phase III, prospective, multicentre, single-arm, open-label trial which included adult patients with aHUS. The key objective of Study 311 was to evaluate the safety and efficacy of ravulizumab (IV infusion) in complement inhibitor treatment-naive adult (18 years and older) patients with aHUS. The study consists of a screening period (up to 7 days), a 26-week Initial evaluation period, and an extension period until the product is registered or approved (in accordance with country-specific regulations) or for up to 4.5 years. The enrolment for this study started on March 18, 2017 and it is ongoing. The cut-off date for the data reported herein was July 2, 2019. As of the cut-off date, a total of 58 adult patients were included in this study and 56 patients received at least 1 dose of ravulizumab. The primary outcome was complete TMA (cTMA) response during the initial 26-week evaluation period, which was defined as normalization of hematologic parameters (platelet count and LDH) and at least a 25% improvement in serum creatinine from baseline. The secondary outcomes were hematologic normalization (platelet count and LDH), hematologic TMA parameters (platelet count, LDH, and hemoglobin), hemoglobin response (more than 2% increase), dialysis requirement status, eGFR, chronic kidney disease (CKD), fatigue (FACIT-Fatigue), HRQoL (EQ-5D-3L), and safety. Health care resource utilization, patient-reported aHUS symptoms, and extrarenal signs and symptoms of aHUS were reported as exploratory outcomes on a by-patient basis (no summary data provided).

Study 312 is an ongoing, phase III, prospective, multicentre, single-arm, open-label trial conducted in pediatric patients (less than 18 years old) with aHUS. Study 312 included 2 cohorts (cohort 1 and cohort 2). Cohort 1 included 21 complement inhibitor-naive children with aHUS. The key objective of the Study 312 cohort 1 was to evaluate the safety and efficacy of ravulizumab (IV infusion) in complement inhibitor treatment-naive children with aHUS. Cohort 2 included 10 eculizumab-treated children with aHUS. The key objective of Study 312 cohort 2 was to evaluate the safety and efficacy of ravulizumab (IV infusion) in children) with aHUS, with stable TMA parameters before a switch from eculizumab to ravulizumab treatment. The study consists of a screening period (up to 7 days), a 26-week Initial evaluation period, and an extension period until the product is registered or approved (in accordance with country-specific regulations) or for up to 4.5 years. The enrolment for this study started on September 1, 2017 and it is still ongoing. The cut-off date for the data reported herein was December 3, 2019. As of the cut-off date, a total of 21 pediatric patients were included in Study 312 cohort 1 and 18 patients received at least 1 dose of ravulizumab. In cohort 2, a total of 10 pediatric patients (were included and all 10 patients received at least 1 dose of ravulizumab. The primary outcome was cTMA response during the initial 26-week evaluation period, which was defined as by normalization of hematologic parameters (platelet count and LDH) and at least a 25% improvement in serum creatinine from baseline (cohort 1 only). The secondary outcomes were hematologic normalization (platelet count and LDH), hematologic TMA parameters (platelet count and LDH and hemoglobin, for cohort 1 only), hemoglobin response (great than 2% increase for cohort 1 only), dialysis requirement status, eGFR, CKD stage, fatigue (FACIT-Fatigue), and safety. Health care resource utilization, patient-reported aHUS symptoms, and extrarenal signs and symptoms of aHUS were reported as exploratory outcomes on a by-patient basis (no summary data provided).

Efficacy Results

Complete TMA Response

In Study 311: at week 26, complete TMA response was observed in 30 of the 56 patients in the Full analysis population (FAS) (53.6%; 95% CI, 39.6% to 67.5%). At the data cut-off (median follow-up time: 75.57 weeks), complete TMA response was observed in 34 of the 56 patients in the FAS (60.7%; 95% CI, 47.0% to 74.4%). In Study 312 cohort 1, at week 26,

Complete TMA response was observed in 14 of the 18 patients in the FAS (77.8%, 95% CI, 52.4% to 93.6%). At the data cut-off (median follow-up time: 82.43 weeks), complete TMA response was observed in 17 of the 18 patients in the FAS (94.4%; 95% CI, 72.7% to 99.9%).

Hematologic Normalization

In Study 311, hematologic normalization was defined as normalization of platelets and LDH. At week 26, hematologic normalization was observed in 41 of 56 patients in the FAS (73.2%, 95% CI, 60.7% to 85.7%). As of the data cut-off date, hematologic normalization was observed in 45 of the 56 patients in the FAS (80.4%, 95% CI, 69.1% to 91.7%). In Study 312 cohort 1, at week 26, hematologic normalization was observed in 16 of the 18 patients (88.9%, 95% CI, 65.3% to 98.6%). As of the data cut-off date, hematologic normalization was observed in 17 of the 18 patients in the FAS. (94.4%, 95% CI, 72.7% to 99.9%)

Individual Hematologic Parameters

In Study 311, mean (SD) platelet count improved to normal value after initiation of ravulizumab treatment and remained stable during the extension period at the data-cut-off date. Similarly, mean LDH value decreased from baseline, to within normal range at week 26 and was sustained during the extension period at the data-cut-off date. Mean hemoglobin value increased more gradually over time. The mean hemoglobin value was 120.27 (normal value: 130 g/L to 175 g/L) at week 26 and remained above 120 g/L during the extension period at the data cut-off date; At week 26, 40 of the 56 patients (71.4%, 95% CI, 58.7% to 84.2%) in the FAS achieved a hemoglobin response. As of the data cut-off date, 45 out of the 56 patients (80.4%, 95% CI, 69.1% to 91.7%) in the FAS achieved a hemoglobin response. In the Study 312 cohort 1, similar improvement was observed in platelet count, LDH, and hemoglobin at week 26 and at the data cut-off date. In Study 312 cohort 2, hematologic parameters (platelet count, LDH, and hemoglobin) remained stable for patients in cohort 2 during the initial 26 weeks as well as through the data cut-off date.

Time to Complete TMA Response

In Study 311, as of the data cut-off date, complete TMA response was achieved at a median time of 86 (range, 7 to 401) days. In Study 312 for pediatric patients, the median time to complete TMA response was 30 days (range: 15 to 351 days).

Fatigue (FACIT-Fatigue)

In Study 311, an improvement of at least 3 points in FACIT-Fatigue score, which is considered to be a clinically meaningful improvement, was observed in 37 (84.1%) of the 44 patients as per available data at week 26. During the extension period, 33 (82.5%) of the 40 patients as per available data had at least a 3-point improvement from baseline at the day 351 visit. In Study 312 cohort 1, 3 (33.3%) of 9 patients had at least a 3-point improvement in the FACIT-Fatigue total score from baseline at week 26. And all 9 patients had at least a 3-point improvement from baseline at day 351. In Study 312 cohort 2 there were no notable improvements or worsening compared to baseline in the Pediatric FACIT-Fatigue scores for all 8 patients during the initial 26 weeks through day 351 of the extension period.

HRQoL (EQ-5D-3L)

In Study 311, patients in the FAS showed improvement in EQ-5D-3L score at week 26 and continued into day 351 in the extension period.

Renal Function (eGFR, CKD stage shifting, dialysis status)

eGFR

In Study 311, the mean eGFR gradually improved during the initial 26 weeks. During the extension period, the mean eGFR remained stable above 50 mL/min/1.73 m^2 for the 43 patients that reached the day 407 visit. Overall, the mean eGFR value at baseline was 15.86 mL/min/1.73 m^2. The mean eGFR was 51.83 mL/min/1.73 m^2 at week 26 and 50.30 mL/min/1.73 m^2 at day 407, respectively. In Study 312 cohort 1, the mean eGFR value at baseline was 26.4 (SD, 21.17) mL/min/1.73m2.eGFR was 108.5 (SD, 56.87) mL/min/1.73 m^2 at week 26 and remained above 100 mL/min/1.73 m^2 for the 14 patients who reached the day 407 visit. In Study 312 cohort 2 eGFR remained generally stable for all 10 patients in cohort 2 at week 26 and through the data cut-off date.

CKD Stage

Study 311: in patients with available baseline and week 26 data, 32 (68.1%) of 47 patients in the FAS had improvement in CKD stage compared to baseline: Two patients experienced worsening CKD stage. During the extension Period: For the 42 patients with available baseline and day 407 data, 29 (69.0%) had improvement in CKD stage compared to baseline; the 2 patients who experienced worsening CKD stage at week 26 remained at stage 5 at the last available visit during the extension period. Study 312 cohort 1, with the exception of 2 patients, all patients improved their CKD stage at week 26; the shift was substantial as 14 patients improved by 2 or more stages. None of the patients worsened in CKD stage at week 26 nor during the extension period. Study 312 cohort 2, 8 out of 10 patients began at CKD stage I and were stable except for 2 patients who worsened during the initial 26 weeks. During the extension period, all 10 patients had no change in CKD stage at day 351 compared to baseline.

Dialysis Requirement Status

In Study 311, at baseline or within 5 days before the first dose of study drug, 29 (51.8%) patients in the FAS had received renal dialysis. During the initial 26 weeks, 17 of these 29 patients (58.6%) discontinued dialysis. As of the data cut-off date, 18 (62.1%) of these 29 patients discontinued dialysis during the study. Of the 27 patients who were not on dialysis at baseline, 7 (25.9%) initiated dialysis during the initial 26 weeks. As of the data cut-off date, 4 (14.8%) patients remained or started on dialysis. In Study 312 cohort 1, of the 6 patients in the FAS who were receiving kidney dialysis at baseline, 4 patients discontinued dialysis within the first 36 days of exposure to ravulizumab. All 6 patients had discontinued dialysis by day 193. For patients who were not on dialysis at baseline, there was no patient-initiated dialysis after starting treatment with ravulizumab. In Study 312 cohort, as of the data cut-off date, none of the 10 patients in cohort 2 initiated dialysis after starting treatment with the study drug.

Plasma-Therapy–Free Status

Plasma therapy was prohibited during the trials and was therefore not an outcome assessed in the pivotal studies. However, plasma therapy was reported in a section of the concomitant therapy. In Study 311, 3 (5.2%) patients received plasma therapy, which was considered a protocol violation. No patient received plasma therapy in Study 312 (cohort 1 or cohort 2).

Other Outcomes

Mortality, presence of bleeding, packed red blood cell transfusions, and soluble MAC levels, were not assessed as efficacy outcome in the 2 pivotal studies (Study 311 and Study 312). Symptoms (aside from fatigue) and hospitalization were reported on a by-patient bases in the

2 pivotal studies (CSRs) submitted by the sponsor; there were no summary data submitted. Therefore, symptom reduction and hospitalization have not been reported.

Harms Results

In both studies, as of the data cut-off date, all patients experienced at least 1 treatment-emergent AE (TEAE). In Study 311, the most common adverse events (occurred in at least 30% patients) were headache (n = 22; 37.9%), diarrhea (n = 19; 32.8%), vomiting (n = 18; 31.0%). In Study 312 cohort 1, the most common adverse events (occurred in at least 30% patients) were pyrexia (n = 10, 47.6%), and headache, diarrhea, vomiting, and nasopharyngitis (each of them occurred in 7 patients [33.3%]). In Study 312 cohort 2, the most common adverse event (occurred in at least 30% patients) was oropharyngeal pain (n = 3, 30%). In Study 311, a total of 33 (56.9%) patients experienced a serious adverse event (SAE). Each SAE was reported in 1 patient, except for pneumonia and hypertension, each of which occurred in 3 patients (5.2%); as well as septic shock, urinary tract infection, aHUS, and malignant hypertension, each of which occurred in 2 patients (3.4%). In Study 312 cohort 1, the SAEs that occurred in at least 2 patients were gastroenteritis viral infection and abdominal pain; each occurred in 2 patients (9.5%). In Study 312 cohort 2, no SAE was reported in more than 1 patient. In Study 311, a total of 3 (5.2%) of patients experienced adverse events leading to study drug discontinuation. In Study 312 cohort 1, a total of 1 (4.8%) of patients experienced adverse events leading to study drug discontinuation. In Study 312 cohort 2, no patients experienced adverse events leading to study drug discontinuation.

In Study 311, 4 patients died during the initial 26-week evaluation period. One of the 4 patients died due a pretreatment SAE (cerebral arterial thrombosis) and 3 patients (5.2%) died due to treatment-emergent SAEs that were not considered to be related to the study drug. In Study 312 cohort 1 and cohort 2, no patients died due to AE as of the data cut-off date. Regarding notable harms, as identified in the review protocol, no meningococcal disease was reported in either Study 311 or Study 312. In Study 311, sepsis and hypersensitivity to the drug, and antidrug antibodies were each reported in 1 patient (1.7%). Infusion-related reactions were not reported. In Study 312 cohort 1, 1 patient (5.6%) reported hypersensitivity; no other notable harms were reported. In Study 312 cohort 2, no notable harms were reported.

Critical Appraisal

The main limitation of the included 2 pivotal studies (Study 311 and Study 312) is the single-arm study design, which does not include a comparator arm. Due to the rare and severe nature of aHUS, a randomized control group was not likely to be feasible. Such a design, in addition to a lack of consideration of confounding variables, precludes causal inferences (i.e., the outcomes cannot be directly attributed to ravulizumab). Without an active comparator or standard of care, or any statistical hypothesis testing, it is not possible to confirm the relative therapeutic benefit or safety of ravulizumab against other available treatments (such as eculizumab in this population) or against standard care. In addition, both Study 311 and 312 were open-label trial and the study investigators and patients were aware of their treatment status, which increases the risk of detection and performance biases which have the potential to influence outcome reporting. However, the primary and most secondary outcomes (aside from fatigue and HRQoL) are objective end points, for which risk of bias due to the open-label design is low. The potential for bias is more of a concern for subjective end points such as safety, fatigue (FACIT-Fatigue), and HRQoL (EQ-5D-3L). The direction of anticipated bias related to these outcomes is unclear. It is possible that known harms and anticipated benefits would be overreported.

For the longer-term subjective end points (HRQoL and fatigue), there is a potential risk of bias because of a large number of patients did not have complete measures (especially for the extension period), leading to substantial missing data on these outcomes. there may have been differential recall bias, and/or those remaining in the study may have differed in some systematic way compared to those who remained in the study and provided responses. Overall, the magnitude and direction of the impact of these missing data and recall bias on the patient-reported and HRQoL outcomes is unknown. No minimal important difference was identified for HRQoL measures in the aHUS population,and overall the findings of HRQoL should be viewed as supportive evidence only.

One more potential limitation was that the efficacy assessment was not based on the intention-to-treat population (for Study 311 and Study 312 cohort 1), and instead included patients who received at least 1 dose of study intervention. A total of 2 (3.4%) patients in Study 311 and 3 (14.3%) patients in Study 312 cohort 1 were excluded from the primary FAS analysis. In addition, it is also noted that 43 (76.79%) patients in Study 311 and 14 (66.7%) patients in Study 312 cohort 1 experienced a major protocol violation, the majority (N = 25, 43.1% in Study 311 and N = 9, 42.9% in Study 312) of which were related to the eligibility criteria. Although the per-protocol analysis (N = 44, 75.9% for Study 311 and 18, 85.7% for Study 312 cohort 1) was performed and showed a consistent result with FAS analysis, not all those patients with the major protocol violation, especially those related to eligibility criteria, were excluded from the per-protocol analysis. Therefore, there is a potential impact on the results although the direction of the is unclear. The main limitation for Study 312 cohort 2 (pediatric patients with aHUS switched from eculizumab to ravulizumab) was that the sample size (N = 10) was small, which meant that the overall dataset was more sensitive to outliers and skewed distribution.

Overall, according to the clinical experts consulted by CADTH, the inclusion and exclusion criteria of 2 pivotal studies (Study 311 and Study 312) were reasonable and the baseline patient characteristics, concomitant medications, and prohibited medications were reflective of patients seen in clinical practice for the indication under review. Finally, it is unclear whether the magnitude of the treatment effect estimates observed in the relatively small study sample will be replicable in a larger study sample or generalizable to the target population in real-world clinical practice.

Indirect Comparisons

Direct comparisons between ravulizumab and eculizumab are likely to be infeasible due to the rare and severe nature of aHUS. Therefore, for this submission, a systematic literature review was conducted to identify any sources of indirect treatment comparisons between ravulizumab and eculizumab, or ravulizumab and BSC. No indirect treatment comparisons (ITCs) were identified in the CADTH search.

Description of Studies

Overall, 1 study, a sponsor-submitted ITC was available to assess the relative efficacy of ravulizumab relative to eculizumab utilizing a patient-level propensity-based primary analysis.

Efficacy Results

Among adult patients without kidney transplant with aHUS, the sponsor did not note any statistically significant differences between ravulizumab and eculizumab with respect to mortality, cTMA response, LDH, platelets, EQ-5D VAS, FACIT subscales, renal function or

dialysis status among adult patients with aHUS at 6 months when utilizing a stabilized weights model. Sensitivity analyses exploring pediatric patients without kidney transplant, adult patients with kidney transplant, and adult patients without kidney transplant utilizing propensity matching were broadly concordant with the primary analysis.

No data were available for the presence of severe bleeding, hemoglobin concentration change over time, plasma-therapy–free status, packed RBC transfusion, hospitalizations, or soluble MAC.

Harms Results

No evidence on relative safety or harms were presented for review.

Critical Appraisal

Overall, the submitted ITC was subject to several limitations, which add uncertainty to the conclusions presented. Principally, it is unclear whether all clinically meaningful covariates were accounted for within the sponsor's ITC, and as such residual confounding may occur from these characteristics not being accounted for within the primary analysis. Similarly, there remain potentially important unmeasured confounding characteristics, such as a 10- year gap between the studies of eculizumab and ravulizumab. During this period, there may have been changes to the standard of care, increased awareness or capacity to diagnose disease, and changes in health care system capacity, which are all confounding factors which cannot be excluded from the current analysis. Finally, a few reporting characteristics were absent, such as choice of exclusion for studies, specification of the estimands utilized in analysis and reporting units of outcomes and baseline covariates of interest.

Other Relevant Evidence

No other relevant evidence was identified.

Conclusions

The evidence of clinical benefits and harms of ravulizumab in the treatment of aHUS was based on the 2 sponsor-submitted pivotal multination, single-arm, open-label and prospective phase III trials (Study 311 for adults with aHUS, and Study 312 for pediatric patients with aHUS). For complement inhibitor treatment-naive patients, the majority of pediatric and adult patients experienced hematological normalization, improvement of renal function and HRQoL with the ravulizumab treatment. Despite uncertainty around the magnitude of the clinical benefit attributable to ravulizumab given the limitations inherent to the single-arm trial design, the lack of formal hypothesis testing and relatively small sample size, the clinical experts indicated that the benefits observed in the 2 trials appeared clinically meaningful considering the aHUS is an extremely rare, and life-threatening disease. For complement inhibitor experienced patients, no evidence was identified with the switching from eculizumab to ravulizumab in adult patients. The expected benefit of switching from eculizumab to ravulizumab lies in the reduced number of infusions required, related to the longer half-life of ravulizumab compared to eculizumab. Though the 10 patients who switched from eculizumab to ravulizumab in Study 312 appeared to have a maintained TMA response, due to the small sample size it remains unclear whether these findings are reflective of what would be observed in the larger population of aHUS patients. The sponsor also submitted a propensity score weighted analysis comparing ravulizumab with eculizumab; however, no robust conclusion could be drawn on the comparative efficacy and safety of

ravulizumab versus eculizumab due to several methodological limitations. The safety profile of ravulizumab observed in the 2 trials appeared consistent with the known safety profile of ravulizumab, and no additional safety signals were identified.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-minimization analysis
Target populations	Adult and pediatric patients with aHUS
Treatment	Ravulizumab
Dose regimen	In adult patients, ravulizumab is administered as a loading dose followed by a maintenance dose starting 2 weeks after, then administered every 8 weeks thereafter, based on weight as follows: • ≥ 40 kg to < 60 kg: 2,400 mg loading dose followed by 3,000 mg maintenance dosing • ≥ 60 kg to < 100 kg: 2,700 mg loading dose followed by 3,300 mg maintenance dosing • ≥ 100 kg: 3,000 mg loading dose followed by 3,600 maintenance dosing In pediatric patients, ravulizumab is administered as a loading dose followed by a maintenance dose starting 2 weeks after, then administered every 4 or 8 weeks thereafter, based on weight as follows: • ≥ 5 kg to < 10 kg: 600 mg loading dose followed by 300 mg maintenance dosing starting 2 weeks after, then every 4 weeks thereafter • ≥ 10 kg to < 20 kg: 600 mg loading dose followed by 600 mg maintenance dosing starting 2 weeks after, then every 4 weeks thereafter • ≥ 20 kg to < 30 kg: 900 mg loading dose followed by 2,100 maintenance dosing starting 2 weeks after, then every 8 weeks thereafter • ≥ 30 kg to < 40 kg: 1,200 mg loading dose followed by 2,700 maintenance dosing starting 2 weeks after, then every 8 weeks thereafter
Submitted price	Ravulizumab, 10 mg/mL, solution for IV infusion: $7,296.67 per 30 mL single-use vial
Treatment cost	Adult patients: • ≥ 40 kg to < 60 kg: $569,140 in year 1 and $474,284 in subsequent years • ≥ 60 kg to < 100 kg: $627,514 in year 1 and $521,712 in subsequent years • ≥ 100 kg: $685,887 in year 1 and $569,140 in subsequent years Pediatric patients: • ≥ 5 kg to < 10 kg: $116,747 in year 1 and $94,857 in subsequent years • ≥ 10 kg to < 20 kg: $218,900 in year 1 and $189,713 in subsequent years • ≥ 20 kg to < 30 kg: $379,427 in year 1 and $331,998 in subsequent years • ≥ 30 kg to < 40 kg: $488,877 in year 1 and $426,855 in subsequent years
Comparator	Eculizumab
Perspective	Canadian publicly funded health care payer
Time horizon	Undefined (year 1 and the subsequent year)

Component	Description
Key data source	A sponsor commissioned indirect treatment comparison to establish equivalent comparative efficacy and safety of ravulizumab compared to eculizumab based on Studies ALXN1210-aHUS-311 and ALXN1210-aHUS-312 (ravulizumab) and Studies aHUS-C08 to 002, aHUS-C10 to 003 and aHUS-C10 to 004 (eculizumab).[1,2]
Costs considered	Drug acquisition costs
Key limitations	• BSC (i.e., plasma exchange or infusion) is a relevant treatment comparator in clinical practice and was excluded by the sponsor in their analysis. As the ravulizumab trials were non-comparative, the effectiveness and cost-effectiveness of ravulizumab relative to BSC remains unknown. • The sponsor's assumption of clinical equivalence of ravulizumab and eculizumab to support the conduct of a CMA is uncertain as the CADTH clinical review determined no robust conclusion could be drawn on the comparative efficacy and safety of ravulizumab vs. eculizumab. Additionally, safety data and some clinical outcomes were not included in the sponsor's ITC. • There is considerable uncertainty surrounding the sponsor's assumption that the costs for doses of complement inhibitors administered in the acute hospital setting would be covered by the sponsor. No such program has been formally established for ravulizumab, [redacted]
CADTH reanalysis results	• CADTH conducted a reanalysis removing the assumption that costs for doses of complement inhibitors given in the acute hospital setting would be covered by the sponsor. • Based on the CADTH reanalysis, in the adult population, ravulizumab was associated with cost-savings of $106,752 in year 1 and $184,436 in subsequent years of treatment. In the pediatric population, ravulizumab was associated with cost-savings of $53,977 in year 1 and $90,876 in subsequent years of treatment. • Ravulizumab remained cost saving in all scenario analyses conducted by CADTH, including when free doses of complement inhibitors in the acute hospital setting were assumed and when administration costs were incorporated within the analysis. • As the confidentially negotiated price of eculizumab is unknown, CADTH conducted threshold analyses to determine the price of eculizumab, where ravulizumab would no longer be considered cost-savings. A price reduction of 15% for eculizumab is required for ravulizumab to be cost-neutral in the first year of treatment (26% for subsequent years) in the adult population. A price reduction of 11% for eculizumab is required for ravulizumab to be cost-neutral in the first year of treatment (20% in subsequent years) in the pediatric population. • BSC may be a relevant comparator in jurisdictions where eculizumab is not reimbursed for the aHUS indication. As the sponsor did not submit a cost-utility analysis comparing eculizumab with BSC, the cost-effectiveness of eculizumab compared with BSC is unknown.

aHUS = atypical hemolytic uremic syndrome; aSEAP = aHUS Soliris Emergency Access Program; BSC = best supportive care; CMA = cost-minimization analysis; ITC = indirect treatment comparison.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis, including uncertainty with the estimated target population given that the incidence rate of aHUS in Canada is unknown, the likely underestimation of the expected share of treatment-naive patients initiating with ravulizumab, and uncertainty with complement inhibitor treatment discontinuation and relapse rates. CADTH reanalyses increased the proportion of treatment-naive patients initiating ravulizumab to 100%. Based on CADTH reanalyses, the budget impact of reimbursing ravulizumab for the treatment of adult and pediatric patients with aHUS to inhibit complement-mediated TMA resulted in cost-savings to the drug plans of $9,837,687 in year 1, $18,220,135 in year 2, and $21,453,528 in year 3, for a 3-year total of $49,511,350. There is remaining uncertainty surrounding the confidential price of eculizumab, the incidence

rate of aHUS in Canada, the treatment discontinuation rate, and the relapse rate in these patients. The presence of confidential prices paid by the jurisdictions is likely to reduce or eliminate these savings, depending on the discounts in place.

Request for Reconsideration

The drug plans filed a Request for Reconsideration for the draft recommendation for ravulizumab for the treatment of adult and pediatric patients 1 month of age and older with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA) if certain conditions were met. In their request, the drug plans requested clarity and guidance on the following reimbursement conditions: initiation conditions, renewal conditions, and implementation guidance.

In the meeting to discuss the drug plan's Request for Reconsideration, the CDEC subpanel considered the following information:

- Feedback on the draft recommendation from the drug plans that participate in the CADTH review process, sponsor, 1 patient group (aHUS Canada), and 1 clinician group (Calgary Apheresis Group).
- Comments from the sponsor regarding the drug plans' feedback on the draft recommendation.
- Information from the initial submission and supplementary material (e.g., input from 2 clinical specialists with expertise in diagnosing and treating patients with aHUS, and input from the CADTH review team) related to the initiation conditions, renewal conditions, and implementation guidance.

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: October 26, 2022

Regrets: None

Conflicts of interest: None

Minor reconsideration CDEC subpanel meeting date: February 17, 2023